Cite this: RSC Adv., 2014, 4, 60785

Received 30th September 2014
Accepted 5th November 2014
DOI: 10.1039/c4ra11571f
www.rsc.org/advances

# An eco-friendly synthesis of novel 3,5-disubstituted-1,2-isoxazoles in PEG-400, employing the $\mathrm{Et}_{3} \mathrm{~N}$-promoted hydroamination of symmetric and unsymmetric 1,3-diyne-indole derivatives $\dagger$ 

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#### Abstract

A facile, efficient and atom-economic synthesis of 3,5-disubstituted 1,2-isoxazoles bearing indole moieties, is reported. The synthesis of these isoxazoles was carried out by the triethylamine-promoted reaction of symmetric and unsymmetric 1,3-diyne indole derivatives with hydroxylamine in PEG-400, as an ecofriendly solvent, under relatively mild conditions. The synthesis of the starting 1,3-diyne indole derivatives was performed by the aerobic self-coupling of diversely functionalized $N$-propargyl indoles and $N$ propargyl carbazole under copper catalysis, or by the reaction of the propargyl derivatives with phenylor $p$-tolyl-acetylene under combined nickel and copper catalysis. The isoxazolation reaction was optimized, its scope and limitations were studied and a detailed reaction mechanism was proposed.


## Introduction

Organic chemists are increasing their research efforts toward the development of new, efficient, sustainable and atomeconomic synthetic methodologies, with the aim of rapidly achieving high molecular complexity from simple building blocks, under convenient conditions.

The development of new protocols suitable for the synthesis of 1,2 -isoxazoles is of current interest ${ }^{1}$ because this structural motif is found in some natural products, such as the neurotoxin ibotenic acid and the CNS depressant muscimol. ${ }^{2}$ This heterocyclic ring is also part of many pharmaceutically relevant compounds, ${ }^{3}$ such as the non-steroidal anti-inflammatory agent valdecoxib, its prodrug parecoxib and the semisynthetic $\beta$-lactam antibiotics cloxacillin and dicloxacillin, being also found in the antibacterial sulfamethoxazole, the antiinflammatory isoxicam, and the antirheumatic and antiarthritic drug leflunomide. ${ }^{4}$

[^0]Therefore, the 1,2 -isoxazole moiety is highly regarded in Medicinal and Organic Chemistry, as a privileged heterocycle, a useful building block and a masked 1,3-dicarbonyl (an important synthetic functionality) scaffold, ${ }^{5}$ due to the easy cleavage of its $\mathrm{N}-\mathrm{O}$ bond. ${ }^{6}$

The 1,2 -isoxazole ring is generally constructed employing two main alternative methodologies, namely the condensation of hydroxylamine with 1,3-dicarbonyl derivatives and related compounds such as $\alpha, \beta$-unsaturated ketones and nitriles, or their synthetic equivalents, and the $[3+2]$ cycloaddition of alkynes with nitrile oxides. ${ }^{7}$

On the other hand, the 1,3-diynes are very interesting compounds, because they can participate in various reactions leading to heterocyclic compounds, including intramolecular cyclization, 1,3-dipolar addition and cyclization via two-fold attack at the acetylene bond, among others. ${ }^{8}$ Therefore, this structural moiety is an important building block, being found in synthetic intermediates and different products of biomedical ${ }^{9}$ or technological interest. ${ }^{10}$

Complex structures containing conjugated triple bonds are also found as natural products, often embodied with relevant biological activities. ${ }^{11}$ Examples of these are dipline D (Fig. 1), isolated from the sponge Diplastrella sp., ${ }^{11 a}$ which exhibits potent anti-HIV activity, as well as falcarinol and falcarindiol, obtained from Daucus carota (carrots) and Panax ginseng (red ginseng), which feature antibacterial, antifungal, anti-inflammatory and platelet anti-aggregation properties. ${ }^{12}$

Alkynes are usually considered carbonyl surrogates; ${ }^{13}$ this can be exemplified by the preparation of acetophenone oxime

Ibotenic acid

R=H, Valdecoxib
$\mathrm{R}=\mathrm{MeCH}_{2} \mathrm{CO}$, Parecoxib

Leflunomide

Isoxicam
R=H, Cloxacillin $\mathrm{R}=\mathrm{Cl}$, Dicloxacillin

Sulfamethoxazole


Falcarinol, $\mathrm{R}=\mathrm{OH}, \mathrm{R}_{1}=\mathrm{H}$; Falcaridiol, $\mathrm{R}=\mathrm{R}_{1}=\mathrm{OH}$
Fig. 1 Some relevant natural products containing 1,2-isoxazole and 1,3-diyne moieties, and pharmaceutical compounds bearing the 1,2isoxazole ring.
from phenylacetylene and hydroxylamine. ${ }^{14}$ In addition, in recent times $\alpha, \beta$-acetylenic oximes and oxime ethers have been used as precursors of 3,5-disubstituted 1,2-isoxazoles, accessed by copper, silver or gold-catalyzed cycloisomerization, ${ }^{15}$ and electrophilic cyclization. ${ }^{16}$

The related gold- or palladium-based annulations of arylpropargyl hydroxylamines and the $\mathrm{K}_{2} \mathrm{CO}_{3}$-mediated cyclization of propargyl oximes have also been employed for that purpose. ${ }^{17}$ Generally, however, these transformations involving alkynes have some drawbacks; they require either costly catalysts, stoichiometric amounts of special promoters and long reaction times, or proceed in moderate yields.

Despite these precedents, the use of 1,3-diynes as precursors for the synthesis of 3,5 -disubstituted 1,2 -isoxazole derivatives has only few and scattered precedents. ${ }^{18}$ Furthermore, several 1,3-diynes derived from different $N$-propargyl heterocycles have been synthesized for potential pharmaceutical and technological applications; ${ }^{19}$ however, their transformation into more complex structures has remained virtually unexplored.

We envisioned that 1,3-diynes, available through coppercatalyzed homo- and heterocoupling of terminal alkynes, could be regarded as synthetic equivalents of 1,3-dicarbonyl moieties. In this capacity, we speculated that 1,4-disubstituted 1,3-diynes could be suitable starting materials toward polyfunctionalized 1,2-isoxazoles (Scheme 1).


Scheme 1 Proposed synthesis of symmetric and unsymmetric 1,3diynes and their conversion into 3,5-disubstituted 1,2-isoxazoles.

Therefore, in view of the importance of the polysubstituted 1,2-isoxazoles, and in order to circumvent the limitations of the previous methods, here we report a convenient synthesis of 3,5disubstituted 1,2-isoxazoles from indole-derived 1,3-diynes employing polyethyleneglycol 400 (PEG-400) as solvent.

The proposed 1,2-isoxazole synthesis is part of our continuing interest in developing new synthetic methodologies toward indole-based heterocyclic compounds under mild and eco-friendly conditions, ${ }^{20}$ which include the use of sustainable, less conventional solvents such as PEG-400, as reaction medium. ${ }^{20 d}$

## Results and discussion

The precursor $N$-propargyl indole (2a-e) and carbazole (2f) derivatives were synthesized, in $70-80 \%$ yield (Table 1), by conventional propargylation of different indoles (1a-e) and carbazole (1f) with propargyl bromide and KOH in DMF. ${ }^{21}$

Table 1 Synthesis of symmetric 1,3-diynes 3a-f. N-Propargylation of indoles 1a-e and carbazole (1f), and their CuCl -catalyzed aerobic homocoupling

| Entry no. | $\mathrm{R}^{1}$ | $\mathrm{R}^{2}$ | $\mathrm{R}^{3}$ | Prod. no. <br> (yield, \%) | Prod. no. <br> (yield, \%) |
| :--- | :--- | :--- | :--- | :--- | :--- |
| $\mathbf{1}$ | H | H | H | $\mathbf{2 a}(76)$ | 3a (83) |
| 2 | H | H | OMe | $\mathbf{2 b}(71)$ | $\mathbf{3 b}(72)$ |
| 3 | H | H | Br | $\mathbf{2 c}(70)$ | $\mathbf{3 c}(76)$ |
| 4 | Me | H | H | $\mathbf{2 d}(72)$ | $\mathbf{3 d}(83)$ |
| 5 | H | H | $4-\mathrm{MeC}_{6} \mathrm{H}_{4}$ | $2 \mathrm{2e}(80)$ | $\mathbf{3 e}(72)$ |
| 6 | $\mathrm{CH}=\mathrm{CH}-\mathrm{CH}=\mathrm{CH}^{a}$ | H | $\mathbf{2 f}(78)$ | $\mathbf{3 f}(60)$ |  |
| Carbazole $(\mathbf{1 f})$ was used as starting material. |  |  |  |  |  |

In turn, the $N$-propargyl indoles and carbazole were subjected to a Glaser type coupling to afford the corresponding homodimerized 1,3-diynes 3a-f, employing $5 \mathrm{~mol} \% \mathrm{CuCl}$ as catalyst in DMSO ( $1 \mathrm{~mL} \mathrm{mmol}{ }^{-1}$ ) and air (atmospheric $\mathrm{O}_{2}$ ) as the stoichiometric oxidant. ${ }^{22}$ The product yields were satisfactory, ranging from 60 to $83 \%$, when the reaction was performed by heating 4 h at $90^{\circ} \mathrm{C}$.

Single crystal X-ray analysis of 3a (CCDC number is 1027013) confirmed the proposed structure and revealed some interesting features (Fig. 2). The 1,3-diyne unit is not linear and was found to be bent, with C2-C3-C4 and C3-C4-C5 angles of 177.2 $\pm 0.1^{\circ}$, and a torsion angle C2-C3-C4-C5 of $10.1^{\circ} ;^{18 d}$ on the other hand, the indole moieties are located on opposite sides of the plane drawn by the propargylic hydrogens, and exhibit a small torsion, with a N1-C1-C6-N2 dihedral angle of $146.9^{\circ}$.

In addition, their homocyclic rings are situated in the same hemispace, with observed $\mathrm{C} 14-\mathrm{N} 1-\mathrm{C} 1-\mathrm{C} 2$ and $\mathrm{C} 22-\mathrm{N} 2-\mathrm{C} 6-\mathrm{C} 5$ dihedral angles of $-79.0^{\circ}$ and $-65.3^{\circ}$, respectively, whereas the $\mathrm{N} 1-\mathrm{C} 1-\mathrm{C} 2$ and $\mathrm{N} 2-\mathrm{C} 6-\mathrm{C} 5$ angles are of similar values (112.8 and $112.6^{\circ}$, respectively). As a consequence, the indole moieties are not contained in parallel planes, but in ones tilted towards each other.

Next, in order to broaden the scope of the transformation, the synthesis of unsymmetric 1,3-diynes was approached. However, the Glaser-synthesis of these compounds mets with the problem of affording mixtures of homo- and hetero-coupled products, which often follow a statistical distribution. Therefore, unsymmetric 1,3-diynes are usually prepared by the copper-catalyzed Cadiot-Chodkiewicz cross-coupling between terminal alkynes and haloalkynes, and its modifications. ${ }^{23}$

An advantageous alternative has been recently reported by the group of Lei, as a variation of the Glaser-Hay coupling, and entails the addition of $\mathrm{NiCl}_{2} \cdot 6 \mathrm{H}_{2} \mathrm{O}$ as a co-catalyst to promote the oxidative heterocoupling process between aryl and propargyl acetylenes. The reaction is run under CuI catalysis in THF, with added TMEDA as ligand, and air (atmospheric oxygen) is used as the stoichiometric oxidant. ${ }^{24}$ The transformation, which proceeds at ambient temperature, requires a sacrificial excess of one of the starting alkynes.

Therefore, the propargyl derivatives $2 \mathbf{a}-\mathbf{c}$ and $2 f$ were coupled with excess phenylacetylene (4a) and $p$-tolylacetylene (4b), affording the corresponding unsymmetric 1,3-diynes (5a-f) in $60-85 \%$ yield, as shown in Table 2.


Fig. 2 ORTEP view of 1,3-diyne compound 3a, as determined by X-ray crystallography.

Table $2 \mathrm{NiCl}_{2} \cdot 6 \mathrm{H}_{2} \mathrm{O}$ and Cul co-catalyzed aerobic synthesis of unsymmetric 1,3-diynes 5a-f


| Entry no. | $\mathrm{R}^{1}$ | $\mathrm{R}^{2}$ | $\mathrm{R}^{3}$ | $\mathrm{R}^{4}$ | Prod. no. <br> (yield, \%) |
| :--- | :--- | :--- | :--- | :--- | :--- |
| $\mathbf{1}$ | H | H | H | H | $\mathbf{5 a}(\mathbf{7 6 )}$ |
| 2 | H | H | H | Me | $\mathbf{5 b}(70)$ |
| 3 | H | H | OMe | H | $\mathbf{5 c}(83)$ |
| 4 | H | H | Br | Me | $\mathbf{5 d}(60)$ |
| 5 | $\mathrm{CH}=\mathrm{CH}-\mathrm{CH}=\mathrm{CH}^{a}$ |  | H | H | $\mathbf{5 e}(80)$ |
| 6 | $\mathrm{CH}=\mathrm{CH}-\mathrm{CH}=\mathrm{CH}^{a}$ |  | H | Me | $\mathbf{5 f ( 8 5 )}$ |

${ }^{a} \mathrm{~N}$-Propargylcarbazole (2f) was used as starting material.

The symmetric 1,4-diphenyl- and 1,4-di-p-tolyl-1,3-butadiynes were concomitantly formed, but these were easily separated from their more polar nitrogen-containing congeners during the chromatographic purification stage.

Interestingly, except for 1,6-di(9H-carbazol-9-yl)hexa-2,4diyne (3f), ${ }^{25}$ both the symmetric and unsymmetric 1,3-diynes ( $3 \mathbf{a}-\mathbf{e}$ and $\mathbf{5 a - f}$ ) are novel, and their structures were unequivocally elucidated after exhaustive spectroscopic analyses (FTIR, ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR and MS).

With the set of required precursor 1,3-diynes in hands, the study of their transformation into 3,5-disubstituted 1,2-isoxazoles 6 was initiated, employing 1,6-di-(1H-indol-1-yl)hexa-2,4-diyne ( $3 \mathrm{a}, 0.3 \mathrm{mmol}$ ) as the starting material.

In the presence of $\mathrm{Et}_{3} \mathrm{~N}$ (4 equiv.), it was observed that the reaction with $\mathrm{NH}_{2} \mathrm{OH} \cdot \mathrm{HCl}$ ( 2.5 equiv.) was incomplete after heating 20 h in DMSO at $60{ }^{\circ} \mathrm{C}$ (Table 3, entry 1 ), ${ }^{18 c}$ affording only $43 \%$ yield of the expected 1,2 -isoxazole $6 \mathbf{a}$. Therefore, the transformation was tested at $80^{\circ} \mathrm{C}$, and $59 \%$ of the product was isolated (entry 2). Increasing the temperature to $110{ }^{\circ} \mathrm{C}$ resulted in a moderate decrease of the yield to $50 \%$ of $\mathbf{6 a}$ (entry 3 ), which was further reduced to $45 \%$ when the reaction was carried out at $120{ }^{\circ} \mathrm{C}$ (entry 4).

Consequently, aiming to attain better yields, the reaction was tested under different conditions. Initially, and in order to reduce the use of poorly friendly organic solvents, the performance of alternative reaction media was explored. However, the starting material was fully recovered and no product was observed when the reaction was carried out in glycerol (entry 5).

On the other hand, the transformation took place satisfactorily in monohydric alcohols such as ${ }^{t} \mathrm{BuOH}$ ( $75 \%$ yield, entry

Table 3 Isoxazolation of the symmetric 1,3-diyne 3a. Optimization of the synthesis of the 3,5-disubstituted 1,2-isoxazole $6 a^{a}$


6a

| Run no. | Solvent | $\mathrm{H}_{2} \mathrm{NOH} \cdot \mathrm{HCl}$ (equiv.) | $\mathrm{Et}_{3} \mathrm{~N}$ (equiv.) | Temp. $\left({ }^{\circ} \mathrm{C}\right)$ | Time (h) | Yield (\%) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | DMSO | 2.5 | 4 | 60 | 20 | 43 |
| 2 | DMSO | 2.5 | 4 | 80 | 20 | 59 |
| 3 | DMSO | 2.5 | 4 | 110 | 20 | 50 |
| 4 | DMSO | 2.5 | 4 | 120 | 20 | 45 |
| 5 | Glycerol | 2.5 | 2.5 | 80 | 12 | $-^{b}$ |
| 6 | ${ }^{t} \mathrm{BuOH}$ | 2.5 | 2.5 | 80 | 12 | 75 |
| 7 | 2-PrOH | 2.5 | 2.5 | 80 | 12 | 72 |
| 8 | PEG-400 | 2.5 | 4 | 80 | 12 | 89 |
| 9 | PEG-400 | 2.5 | 4 | 80 | 20 | 91 |
| 10 | PEG-400 | 2.5 | 4 | 80 | 8 | 72 |
| 11 | PEG-400 | 2.5 | 4 | 80 | $1{ }^{c}$ | 65 |
| 12 | PEG-400 | 2.5 | 2.5 | 80 | 12 | 89 |
| 13 | PEG-400 | 2.5 | $-{ }^{d}$ | 80 | 12 | 73 |
| 14 | PEG-400 | 1.5 | 1.5 | 80 | 12 | 61 |

${ }^{a}$ Reaction conditions: 1,3-diyne ( $3 \mathrm{a}, 0.3 \mathrm{mmol}$ ); solvent $(0.5 \mathrm{~mL}) .{ }^{b}$ Starting material was recovered. ${ }^{c}$ The reaction was carried out under microwave irradiation. ${ }^{d}$ The reaction was carried out in the presence of 2.5 equiv. $\mathrm{K}_{2} \mathrm{CO}_{3}$ as base.
6) and $2-\operatorname{PrOH}(72 \%$, entry 7). This was in marked contrast with previous observations on an analogous transformation (10-15\% yield). ${ }^{18 c}$

Continuing along this line and running the isoxazolation in PEG-400 afforded 6a in $89 \%$ yield (entry 8); however, the reaction performance remained essentially unmodified when the heating period was extended to 20 h (entry 9).

This was considered a very interesting result because PEG400, a polymeric, non-toxic, biodegradable, strongly hydrophilic and non-volatile solvent, qualifies as an eco-friendly reaction medium. ${ }^{26}$ Furthermore, use of PEG-400 represented a substantial improvement, since this solvent allowed the reaction to be advantageously carried out with great success under considerably milder conditions $\left(80^{\circ} \mathrm{C} v s .110{ }^{\circ} \mathrm{C}\right)$. In addition, similar results were achieved with less solvent consumption and in reaction times shorter ( $12 \mathrm{~h} v s .20 \mathrm{~h}$ ) than those reported for analogous processes, ${ }^{18 c, d}$ run in the more environmentally problematic DMSO. ${ }^{26 b}$

Therefore, the optimization of the transformation was pursued in PEG-400. Reducing the reaction time to 8 h afforded $72 \%$ of $\mathbf{6 a}$, a significantly lower yield (entry 10), whereas when the reaction was carried out under microwave irradiation, incomplete consumption of the starting material was observed after 1 h , resulting in a less satisfactory $65 \%$ yield of $\mathbf{6 a}$ (entry 11 ).

The nature and amount of base were next optimized, observing that reduction to 2.5 equivalents of $E t_{3} \mathrm{~N}$ did not affect
the performance of the reaction (entry 12), while employing $\mathrm{K}_{2} \mathrm{CO}_{3}$ instead of $\mathrm{Et}_{3} \mathrm{~N}$ resulted in diminished product yields (entry 13). Finally, simultaneous reduction of the amounts of $\mathrm{Et}_{3} \mathrm{~N}$ and $\mathrm{NH}_{2} \mathrm{OH} \cdot \mathrm{HCl}$ to 1.5 equiv. each caused a substantial deterioration of the performance of the reaction (entry 14), suggesting that both play significative roles in the transformation. Therefore, it was considered that the optimum conditions were those of entry 12 , which entail a lower consumption of added base.

The identity of 6a, which confirmed the Markovnikov selectivity of the reaction, ${ }^{14}$ was established after an exhaustive NMR analysis of the heterocyclic product. This included a revealing HMBC experiment, which exhibited a correlation between the protons of the methylene group attached to one of the indolyl moieties ( $\delta 5.18, \mathrm{~s}, 2 \mathrm{H}$ ) and the carbon atom attached to the isoxazolic nitrogen ( $\delta 160.8$ ) and two additional cross-peaks between the protons of both methylene groups associated to the other indolyl moiety $[\delta 3.05(\mathrm{t}, J=7.0,2 \mathrm{H})$ and $4.28(\mathrm{t}, J=7.0$, $2 \mathrm{H})$ ] and the carbon atom attached to the oxygen atom of the isoxazole ring ( $\delta 170.2$ ).

The group of Bao has found that DMSO was the best performing solvent in a similar transformation with 1,3-diaryl-1,3diynes, lacking a clear explanation for this serendipitous finding. ${ }^{18 c}$ In our hands, DMSO was clearly outperformed by PEG400. Notwithstanding, however, 1,4-diphenyl-1,3-butadiyne was refractory to undergo efficient isoxazolation in PEG-400, suggesting that the solvent should be playing some crucial role
during the reaction and that different kinds of substrates may require different solvents for a proper reaction. In this way, PEG400 and DMSO may be complementary relation media.

After this successful outcome, and in order to expand the scope of the transformation to the use of unsymmetrical 1,3diynes ( $\mathbf{5 a - f}$ ), the reaction conditions for the synthesis of 3,5disubstituted 1,2-isoxazoles 7 were optimized (Table 4).

Employing 1-(5-phenylpenta-2,4-diynyl)-1H-indole (5a) as model unsymmetric 1,3-diyne, it was observed that under the previously optimized conditions, the reaction took place rather sluggishly, providing 7 a in only $52 \%$ yield even after 24 h (entry 1). In addition, careful ${ }^{1} \mathrm{H}$ NMR analysis of the products of this initial test revealed the generation of two regioisomers ( $7 \mathbf{a}$ and $7^{\prime} \mathbf{a}$ ) resulting from attack at both ends of the 1,3-diyne moiety. The structures of the products were unequivocally established after a detailed NMR analysis, which confirmed a Markovnikov selectivity for the major product (7a). ${ }^{14}$ The outcome of the reaction forced to also evaluate the regioselectivity of the transformation under each new condition.

In order to speed up the reaction, its performance was tested at $100{ }^{\circ} \mathrm{C}$; this condition increased the regioselectivity, keeping the overall yield almost unaltered (entry 2). Therefore, the focus was placed on the study of the effect of the amounts of base and $\mathrm{NH}_{2} \mathrm{OH} \cdot \mathrm{HCl}$. Very good yields were attained in the presence of 4.0 equiv. $\mathrm{Et}_{3} \mathrm{~N}$ and 2.5 equiv. $\mathrm{NH}_{2} \mathrm{OH} \cdot \mathrm{HCl}$ (entry 3); however, the yield remained almost unchanged when the excess of $\mathrm{NH}_{2} \mathrm{OH} \cdot \mathrm{HCl}$ was raised to 4.0 equiv. (entry 4 ). In both 2 cases, the same good ( $7 \mathbf{a}: \mathbf{7}^{\prime} \mathbf{a}=10: 1$ ) selectivity was observed.

Speculating that the nature of the base may have impact on the yields of $7 \mathbf{a}$ and the selectivity of the reaction, various bases were tested. The use of $\mathrm{K}_{2} \mathrm{CO}_{3}$ was helpless, since lower yields and product regioselectivity were observed (entry 5), while employing the more hindered $N, N$-diisopropylethylamine (DIPEA) furnished only subtle improvements in both, reaction yield and regioselectivity (entry 6).

On the other side, the use of secondary amines such as ${ }^{i} \mathrm{Pr}_{2} \mathrm{NH}$ and $\mathrm{Et}_{2} \mathrm{NH}$ caused either diminished regioselectivity (entry 7) or lower yields (entry 8), respectively. These results underscored the role of the added base on the reaction outcome. Being the improvements induced by DIPEA minor in nature, the conditions of entry 3 were taken as optimal. These were still milder and more time-efficient conditions than those previously found for similar transformations. ${ }^{18 c, d}$

The two sets of optimized conditions were employed for the synthesis of 3,5-disubstituted 1,2-isoxazole derivatives 6 and 7 (Table 5). Under these conditions, the isoxazoles were isolated in moderate to excellent yields. The average yields of the products derived from unsymmetric 1,3-diynes (7a-f) were slightly higher and more consistent ( $75-89 \%$ ) than those arising from 6a-f, their symmetric counterparts (58-89\%). However, they could not be correlated with structural or electronic features of the starting heterocyles among both series of products.

In addition, in the case of the products resulting from isoxazolation of $\mathbf{5 a - f}$, mixtures of 1,2 -isoxazoles ( 7 and $7^{\prime}$ ) were invariably observed, being always $7^{\prime}$ their minor component. The latter resulted from attack of the hydroxylamine nitrogen to the more hindered benzylic position of the starting 1,3-diynes 5.

Interestingly, however, the use of PEG-400 seemed to afford highly selective reactions, resulting in mixtures with significantly lower amounts ( $<12.5 \%$ ) of the minor regioisomers $7^{\prime} \mathbf{a - f}$ than in a similar transformation employing DMSO (up to $42.6 \%) .{ }^{18 c}$

The structures of the isoxazoles 6a-f were also ascertained by NMR analysis, interpreting the effect of the heteroatoms of the 1,2-isoxazole ring on the shieldings of the hydrogens of the neighboring methylene groups. These were observed as a pair of coupled triplets resonating, at approximately $\delta 3.0$ and 4.2 (attached to the indolic nitrogen atom) and a singlet at approximately 5.2 ppm (displaced downfield to $\delta 5.6$ in the case of the carbazole derivatives). The latter was assigned to the protons of the methylene moiety attached to both, the indole nitrogen and the carbon of the isoxazole ring attached to the isoxazolic nitrogen.

The structures of the compounds 7a-f were easily differentiated from those of their $7^{\prime} \mathbf{a}-\mathbf{f}$ congeners. The former exhibited the resonances of their methylene protons as two singlets, at approximately $\delta 3.9$ and 5.2. The latter resonance was assigned to the methylene moiety attached to the indolic nitrogen atom; analogously to the cases of 6a-f, this signal appears deshielded at $\delta 5.67$ in the carbazole derivatives.

On the other side, compounds $7^{\prime} \mathbf{a}-\mathbf{f}$ displayed the pair of coupled methylene protons as triplets resonating at approximately $\delta 3.3$ and 4.5 ppm , the latter signal being attributed to the methylene group attached to the indole nitrogen.

Based on literature precedents, including the conclusions of a recently disclosed theoretical study of the isoxazolation of symmetric 1,4-diphenyl-1,3-butadiyne, ${ }^{27}$ a detailed reaction mechanism (Scheme 2) can be proposed.

Hydroxylamine is known to add efficiently to alkynes to give oximes, with the Markovnikov-type reactivity of this process being at the hearth of the selectivity of the transformation. ${ }^{14,28}$ Accordingly, it can be proposed that the reaction is initiated when one of the triple bonds of the 1,3-diyne conjugated system (5a) suffers a Cope-type intermolecular hydroamination (azaprotio transfer) reaction mediated by the hydroxylamine nitrogen, which is analogous to the reverse of the Cope elimination. ${ }^{29}$

Interestingly, unlike the copper-catalyzed 1,3-dipolar cycloaddition between nitrile oxides and alkynes to afford 1,2-isoxazoles, ${ }^{30}$ there is a mounting body of evidence that this noncatalyzed reaction, which should lead to the ene- $N$-oxide intermediate $\mathbf{i}$, is a concerted process when carried out under thermal and metal-free conditions. ${ }^{31}$

In turn, this intermediate should experience a proton transfer reaction from the nitrogen atom to the oxygen, furnishing the ene-hydroxylamine intermediate ii. Theoretical calculations have pointed out to this as the rate-determining step of the reaction; ${ }^{28}$ therefore, carrying out the transformation in the presence of an hydroxylic solvent like PEG-400 may be crucial for its success, since it can mediate a facile, bimolecular proton transfer within the generated amine oxide intermediate, through a 5-membered transition state, speeding up the process (Scheme 2). This proposal is supported by DFT studies. ${ }^{32}$


| Run no. | Base (equiv.) | $\mathrm{H}_{2} \mathrm{NOH} \cdot \mathrm{HCl}$ (equiv.) | Temp. $\left({ }^{\circ} \mathrm{C}\right)$ | Time (h) | Yield (\%) | Ratio 7a : 7'a |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | $\mathrm{Et}_{3} \mathrm{~N}$ (2.5) | 2.5 | $80^{\circ} \mathrm{C}$ | 24 | 52 | 7:1 |
| 2 | $\mathrm{Et}_{3} \mathrm{~N}$ (2.5) | 2.5 | $100{ }^{\circ} \mathrm{C}$ | 24 | 53 | 10: 1 |
| 3 | $\mathrm{Et}_{3} \mathrm{~N}$ (4.0) | 2.5 | $100{ }^{\circ} \mathrm{C}$ | 12 | 85 | 10: 1 |
| 4 | $\mathrm{Et}_{3} \mathrm{~N}$ (4.0) | 4.0 | $100{ }^{\circ} \mathrm{C}$ | 12 | 84 | 10: 1 |
| 5 | $\mathrm{K}_{2} \mathrm{CO}_{3}(4.0)$ | 2.5 | $100{ }^{\circ} \mathrm{C}$ | 12 | 50 | 7:1 |
| 6 | DIPEA (4.0) | 2.5 | $100{ }^{\circ} \mathrm{C}$ | 12 | 85 | 11:1 |
| 7 | ${ }^{\text {i }} \mathrm{Pr}_{2} \mathrm{NH}$ (4.0) | 2.5 | $100{ }^{\circ} \mathrm{C}$ | 12 | 85 | 8:1 |
| 8 | $\mathrm{Et}_{2} \mathrm{NH}$ (4.0) | 2.5 | $100{ }^{\circ} \mathrm{C}$ | 12 | 72 | 11:1 |

${ }^{a}$ Reaction conditions: 1,3-diyne (5a, 0.3 mmol$)$ and PEG-400 $(0.5 \mathrm{~mL})$.

Subsequent base-assisted N -oxide-oxime tautomerization of the intermediate ii, also involving the conjugated alkyne, ${ }^{33}$ could afford the allenic oxime iii. ${ }^{14}$ Rotation across the single bond would then place the oxime and allene moieties in position and have them with the correct geometry, ${ }^{34}$ suitable for undergoing an intramolecular electrophilic addition toward the final product (7a). ${ }^{35}$

This 5 -exo-dig cyclization would be formally arising from simple addition of the hydroxyl group across the distal double bond of the allene (iii). Theoretical studies have suggested that this step may involve a zwitterionic intermediate that undergoes a proton transfer reaction. ${ }^{28}$

Short and Ziegler demonstrated that $\mathrm{K}_{2} \mathrm{CO}_{3}$ is able to drive cyclization of homopropargyl oximes towards isoxazole derivatives. Interestingly, it seems likely that this process may involve the same kind of allenic intermediates and reaction mechanism. ${ }^{17 a}$

The group of Bao has recently proposed an analogous but less detailed mechanism for a similar transformation. ${ }^{18 c}$ However, in their proposal, the roles of the solvent, the added base and the rotation step are ignored, whereas no discussion about the reaction selectivity is included.

As an hydroxylic solvent, PEG-400 is here proposed to be involved in the formation of intermediate $\mathbf{i i}$, while it is evident that the added base is useful for freeing the hydroxylamine base from its hydrochloride and plays a crucial role in the tautomerization of ii into iii. On the other hand, geometric considerations should not be mechanistically neglected, since they turn
mandatory the rotation stage for a successful cyclization, which takes place with Markovnikov-type selectivity in both, symmetric and unsymmetric 1,3-diynes.

In conclusion, a regioselective, convenient and atomeconomic synthesis of 3,5 -disubstituted 1,2-isoxazoles bearing functionalized indolyl, aryl and carbazolyl substituents, is reported. The synthesis of the starting symmetric 1,3-diyne indole derivatives was performed employing an aerobic selfcoupling reaction of differently functionalized $N$-propargyl indoles and $N$-propargyl carbazole under copper catalysis. Analogously, the unsymmetric 1,3-diyne derivatives were synthesized by reaction of $N$-propargyl indoles and $N$-propargyl carbazole with phenylacetylene or p-tolylacetylene under combined $\mathrm{Ni}^{\mathrm{II}} / \mathrm{Cu}^{\mathrm{I}}$ catalysis and aerobic conditions.

The isoxazolation of the symmetric and unsymmetric 1,3diyne indole derivatives was carried out by reaction with hydroxylamine in PEG-400, as a superior and eco-friendly solvent, under relatively mild conditions and without the addition of acids or metal catalysts. The transformation was optimized relative to reaction temperature and time, as well as regarding the amounts of base and $\mathrm{NH}_{2} \mathrm{OH} \cdot \mathrm{HCl}$; its scope and limitations were studied and a reaction mechanism was proposed.

The operational simplicity of the described isoxazolation and the easy availability of the starting $N$-propargyl derivatives as well as their symmetric and unsymmetric 1,3-diynes should encourage the use of this approach in synthetic and medicinal chemistry.

Table 5 Synthesis of 3,5-disubstituted 1,2-isoxazoles 6a-f and 7a-f from symmetric (3a-f) and unsymmetric (5a-f) 1,3-diynes, in PEG-400


| Entry no. | $\mathrm{R}^{1}$ | $\mathrm{R}^{2}$ | $\mathrm{R}^{3}$ | $\mathrm{R}^{4}$ | Prod. no. (yield, \%) | Ratio 7: 7 ' |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | H | H | H | - | 6 a (89) | - |
| 2 | H | H | OMe | - | 6b (71) | - |
| 3 | H | H | Br | - | 6c (83) | - |
| 4 | Me | H | H | - | 6d (58) | - |
| 5 | H | H | $4-\mathrm{MeC}_{6} \mathrm{H}_{4}$ | - | 6 e (63) | - |
| 6 | $\mathrm{CH}=\mathrm{CH}-\mathrm{CH}=\mathrm{CH}^{a}$ |  | - | - | 6f (89) | - |
| 7 | H | H | H | H | 7 a (85) | $10: 1$ |
| 8 | H | H | H | Me | 7b (84) | 8:1 |
| 9 | H | H | OMe | H | 7c (75) | $10: 1$ |
| 10 | H | H | Br | Me | 7d (76) | 9.5:1 |
| 11 | $\mathrm{CH}=\mathrm{CH}-\mathrm{CH}=\mathrm{CH}^{a}$ |  | H | H | 7 e (84) | 9:1 |
| 12 | $\mathrm{CH}=\mathrm{CH}-\mathrm{CH}=\mathrm{CH}^{a}$ |  | H | Me | 7 f (89) | 7:1 |

## Experimental section

## General information

The solvents for the chemical reactions were purified according to the literature. Commercial reagents were used without further purification. In the conventional purification procedure, the crude material was submitted to flash column chromatography with silica gel 60 H (particle size $40-63 \mu \mathrm{~m}, 230-400$ mesh), eluting isocratically with hexane or mixtures of hexane : EtOAc and hexane : EtOAc : $\mathrm{CH}_{2} \mathrm{Cl}_{2}$.

All new compounds gave single spots when run on TLC plates of Kieselgel $60 \mathrm{GF}_{254}$, employing different hexane : EtOAc
and hexane : EtOAc : $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ solvent systems. Chromatographic spots were detected by irradiation of the plates with UV light ( 254 nm ), followed by exposure to iodine vapors of by spraying with ethanolic vanillin/sulfuric acid reagent and careful heating.

## Apparatus

The melting points were measured on an MQAPF-301 instrument (Microquímica) and are reported uncorrected. The infrared spectra were acquired on a Shimadzu Prestige-21 spectrometer, with the samples prepared as KBr pellets or thin films.


7a

Scheme 2 Proposed reaction mechanism for the synthesis of the 3,5disubstituted 1,2-isoxazoles.

The NMR spectra ( ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ ) were recorded in $\mathrm{CDCl}_{3}$ unless otherwise stated, on Bruker DPX-200 and Bruker DPX-400 spectrometers ( 200 and 400 MHz for ${ }^{1} \mathrm{H}$, respectively). Chemical shift data are reported in ppm downfield from TMS, employed as internal standard. Coupling constants ( $J$ ) are informed in Hertz.

Elemental analyses were recorded on a Perkin-Elmer CHN 2400 analyzer. Low resolution mass spectra were acquired on a Shimadzu QP2010 Plus CG-MS instrument. High-resolution mass spectral data were obtained in a Bruker microTOF-Q II instrument. Detection of the ions was performed with electrospray ionization in positive ion mode.

## General procedure for the synthesis of $N$-propargyl heterocycles (2a-f) ${ }^{21 b}$

A solution of the indole or carbazole ( $\mathbf{1 a - f}, 15 \mathrm{mmol}$ ) in DMF (30 mL ) was cooled to $0{ }^{\circ} \mathrm{C}$. Solid $\mathrm{KOH}(1.12 \mathrm{~g}, 20 \mathrm{mmol})$ was added and the reaction mixture was stirred for 15 minutes, when was treated with $80 \%$ propargyl bromide solution $(2.22 \mathrm{~mL}, 20$ mmol ). After further stirring for 6 h at room temperature, water $(50 \mathrm{~mL})$ was added, and the organic phase was extracted with EtOAc ( $4 \times 30 \mathrm{~mL}$ ). The combined organic layers were dried over $\mathrm{MgSO}_{4}$ and the solvent was evaporated under reduced pressure. The product was purified by column chromatography, eluting with hexane.

1-(Prop-2-ynyl)-1H-indole (2a). Yellowish crystalline solid, m.p.: 38-40 ${ }^{\circ} \mathrm{C}$ (lit.: ${ }^{36 a} 36-37^{\circ} \mathrm{C}$ ); yield: $76 \%{ }^{1}{ }^{1} \mathrm{H}$ NMR ( 200 MHz ) $\delta: 2.33(\mathrm{t}, J=2.5,1 \mathrm{H}), 4.76(\mathrm{~d}, J=2.5,2 \mathrm{H}), 6.51(\mathrm{~d}, J=3.1,1 \mathrm{H})$,
$7.08-7.26(\mathrm{~m}, 3 \mathrm{H}), 7.35(\mathrm{~d}, J=8.1,1 \mathrm{H})$ and $7.62(\mathrm{~d}, J=7.6,1 \mathrm{H})$. ${ }^{13} \mathrm{C}$ NMR ( 50 MHz ) $\delta: 35.6,73.4,77.7,102.0,109.3,119.8,121.0$, 121.8, 127.2, 128.8 and 135.7. MS ( $\mathrm{m} / \mathrm{z}$, rel. int., \%): 155 ( $66, \mathrm{M}^{+}$), 154 (100), 116 (30), 89 (32) and 63 (17).

5-Methoxy-1-(prop-2-ynyl)-1H-indole (2b). White solid, m.p.: $66-67{ }^{\circ} \mathrm{C}$ (lit.: ${ }^{36 b} 65-69{ }^{\circ} \mathrm{C}$ ); yield: $71 \% .{ }^{1} \mathrm{H}$ NMR ( 400 MHz ) $\delta$ : $2.35(\mathrm{t}, J=2.5,1 \mathrm{H}), 3.81(\mathrm{~s}, 3 \mathrm{H}), 4.75(\mathrm{~d}, J=2.5,2 \mathrm{H}), 6.42(\mathrm{~d}, J=$ $3.1,1 \mathrm{H}), 6.88(\mathrm{dd}, J=8.9$ and $2.4,1 \mathrm{H}), 7.07(\mathrm{~d}, J=2.4,1 \mathrm{H}), 7.12$ (d, $J=3.1,1 \mathrm{H})$ and $7.25(\mathrm{~d}, J=8.9,1 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR $(100 \mathrm{MHz}) \delta$ : 35.8, 55.8, 73.4, 77.8, 101.6, 102.9, 110.0, 112.1, 127.8, 129.3, 131.1 and 154.3. MS ( $\mathrm{m} / \mathrm{z}$, rel. int., \%): 186 [14, $\left.(\mathrm{M}+1)^{+}\right], 185$ ( $100, \mathrm{M}^{+}$), 171 (11), 170 (83), 146 (18), 142 (28), 115 (24), 103 (18) and 76 (16).

5-Bromo-1-(prop-2-ynyl)-1H-indole (2c). ${ }^{36 c}$ Brown oil; yield: $70 \% .{ }^{1} \mathrm{H}$ NMR ( 400 MHz ) $\delta: 2.38(\mathrm{t}, J=2.5,1 \mathrm{H}), 4.80(\mathrm{~d}, J=2.5$, $2 \mathrm{H}), 6.44(\mathrm{dd}, J=3.2$ and $0.8,1 \mathrm{H}), 7.16(\mathrm{~d}, J=3.2,1 \mathrm{H}), 7.23(\mathrm{~d}, J$ $=8.5,1 \mathrm{H}), 7.30(\mathrm{dd}, J=8.7$ and $1.8,1 \mathrm{H})$ and $7.73(\mathrm{~d}, J=1.8,1 \mathrm{H})$. ${ }^{13} \mathrm{C}$ NMR ( 100 MHz ) $\delta: 36.0,73.9,77.3,101.7,110.8,113.3,123.6$, 124.8, 128.4, 130.7 and 134.5. MS ( $\mathrm{m} / \mathrm{z}$, rel. int., \%): 235 [51, ( $\mathrm{M}+$ $\left.2)^{+}\right], 234\left[21,(\mathrm{M}+1)^{+}\right], 233\left(50, \mathrm{M}^{+}\right), 154(100), 153(22), 127(26)$, 126 (15), 115 (44), 114 (15), 88 (16) and 62 (14).

2-Methyl-1-(prop-2-ynyl)-1H-indole (2d). ${ }^{36 d}$ White solid, m.p.: $71-72{ }^{\circ} \mathrm{C}$; yield: $72 \% .{ }^{1} \mathrm{H}$ NMR ( 400 MHz ) $\delta: 2.21(\mathrm{t}, J=2.5,1 \mathrm{H})$, $2.44(\mathrm{~s}, 3 \mathrm{H}), 4.73(\mathrm{~d}, J=2.5,2 \mathrm{H}), 7.05-7.18(\mathrm{~m}, 3 \mathrm{H}), 7.30(\mathrm{~d}, J=$ 8.1, 1H) and $7.50(\mathrm{~d}, J=7.8,1 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR $(100 \mathrm{MHz}) \delta: 12.4$, 32.3, 72.1, 78.3, 100.9, 108.8, 119.8, 119.8, 120.9, 128.3, 135.9 and 136.5. MS ( $\mathrm{m} / \mathrm{z}$, rel. int., \%): $170\left[12,(\mathrm{M}+1)^{+}\right], 169\left(87, \mathrm{M}^{+}\right)$, 168 (100), 167 (40), 154 (22), 130 (31), 128 (13), 103 (27), 102 (13), 77 (28) and 63 (14).

1-(Prop-2-ynyl)-5-p-tolyl-1H-indole (2e). White crystalline solid, m.p.: 118-119 ${ }^{\circ} \mathrm{C}$; yield: $80 \%{ }^{1} \mathrm{H}$ NMR ( 400 MHz , DMSO$\left.d_{6}\right) \delta: 2.37(\mathrm{~s}, 3 \mathrm{H}), 3.39(\mathrm{t}, J=2.4,1 \mathrm{H}), 5.11(\mathrm{~d}, J=2.4,2 \mathrm{H}), 6.59$ (d, $J=3.1,1 \mathrm{H}$ ), 7.27 (d, $J=7.9,2 \mathrm{H}$ ), 7.46 (d, $J=3.1,1 \mathrm{H}), 7.51$ (dd, $J=8.5$ and $1.5,1 \mathrm{H}$ ), $7.59-7.63(\mathrm{~m}, 3 \mathrm{H})$ and $7.87(\mathrm{~d}, J=1.5$, $1 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 100 MHz , DMSO- $d_{6}$ ) $\delta: 20.4,35.1,75.2,78.9$, $101.6,110.1,118.2,120.5,126.4,128.7,128.8,129.2,131.9$, $134.9,135.2$ and 138.6. MS ( $\mathrm{m} / \mathrm{z}$, rel. int., \%): 246 [ $\left.20,(\mathrm{M}+1)^{+}\right]$, $245\left(100, \mathrm{M}^{+}\right), 230$ (16), 206 (26), 204 (12), 84 (10) and 66 (13).

9-(Prop-2-ynyl)-9H-carbazole (2f). White crystalline solid, m.p.: $104-105{ }^{\circ} \mathrm{C}$ (lit. $3^{36 e} 104-107{ }^{\circ} \mathrm{C}$ ); yield: $78 \%{ }^{1}{ }^{1} \mathrm{H}$ NMR (400 MHz, DMSO- $d_{6}$ ) $\delta: 3.24(\mathrm{t}, J=2.4,1 \mathrm{H}), 5.31(\mathrm{~d}, J=2.4,2 \mathrm{H}), 7.24-$ $7.28(\mathrm{~m}, 2 \mathrm{H}), 7.48-7.52(\mathrm{~m}, 2 \mathrm{H}), 7.69(\mathrm{~d}, J=8.2,2 \mathrm{H})$ and $8.17(\mathrm{~d}$, $J=7.8,2 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 100 MHz, DMSO- $d_{6}$ ) $\delta: 31.7,74.2,78.9$, 109.3, 119.2, 120.1, 122.3, 125.7 and 139.5. MS ( $\mathrm{m} / \mathrm{z}$, rel. int., \%): $206\left[11,(M+1)^{+}\right], 205\left(71, M^{+}\right), 204(100), 166(47), 140(23)$ and 139 (13).

General procedure for the synthesis of the symmetric 1,3diynes (3a-f) ${ }^{22 c}$
A stirred mixture of the heterocyclic $N$-propargyl derivative (2, 5 mmol ) and $\mathrm{CuCl}(25 \mathrm{mg}, 0.25 \mathrm{mmol}, 5 \mathrm{~mol} \%$ ) in DMSO ( 5 mL ) was heated to $90{ }^{\circ} \mathrm{C}$ for 4 h . Then, the reaction was cooled to room temperature and filtered through Celite. The filtrate was diluted with water ( 15 mL ) and extracted with EtOAc ( $4 \times 25$ mL ). The combined extracts were successively washed with water $(1 \times 10 \mathrm{~mL})$ and brine $(1 \times 10 \mathrm{~mL})$. The organic layer was
dried over $\mathrm{MgSO}_{4}$, and concentrated under reduced pressure. The product was purified by column chromatography using an hexane: EtOAc : $\mathrm{CH}_{2} \mathrm{Cl}_{2}(80: 10: 10)$ solvent mixture as eluent.

1,6-Bis(1H-indol-1-yl)hexa-2,4-diyne (3a). Light brown solid, m.p.: 147-149 ${ }^{\circ} \mathrm{C}$; yield: $83 \% .{ }^{1} \mathrm{H}$ NMR ( 400 MHz ) $\delta: 4.84(\mathrm{~s}, 4 \mathrm{H})$, $6.49(\mathrm{~d}, J=3.1,2 \mathrm{H}), 7.07(\mathrm{~d}, J=3.1,2 \mathrm{H}), 7.10-7.13(\mathrm{~m}, 2 \mathrm{H})$, $7.19-7.23(\mathrm{~m}, 2 \mathrm{H}), 7.31(\mathrm{~d}, J=8.2,2 \mathrm{H})$ and $7.60(\mathrm{~d}, J=7.9,2 \mathrm{H})$. ${ }^{13} \mathrm{C}$ NMR ( 100 MHz ) $\delta: 36.3,69.0,73.3,102.5,109.2,120.0,121.1$, 122.1, 127.2, 128.9 and 135.8. IR (KBr, $\nu)$ : 3104, 2904, 1614, 1463, 1333, 1315, 1185, 739 and $719 \mathrm{~cm}^{-1}$. MS ( $\mathrm{m} / \mathrm{z}$, rel. int., \%): 309 $\left[12,(M+1)^{+}\right], 308\left(51, M^{+}\right), 281(28), 253(17), 209(14), 208(21)$, 207 (100), 191 (100), 133 (15), 117 (38), 89 (24) and 73 (27). HRMS (ESI-TOF, $m / z$ ): obsd. 331.1208; $\mathrm{C}_{22} \mathrm{H}_{16} \mathrm{~N}_{2} \mathrm{Na}\left[(\mathrm{M}+\mathrm{Na})^{+}\right]$ requires 331.1211 .

1,6-Bis(5-methoxy-1H-indol-1-yl)hexa-2,4-diyne (3b). Beige solid, m.p.: $166-168{ }^{\circ} \mathrm{C}$; yield: $72 \%$. ${ }^{1} \mathrm{H}$ NMR ( 400 MHz ) $\delta: 3.82$ $(\mathrm{s}, 6 \mathrm{H}), 4.84(\mathrm{~s}, 4 \mathrm{H}), 6.42(\mathrm{dd}, J=3.2$ and $0.8,2 \mathrm{H}), 6.88(\mathrm{dd}, J=$ 8.9 and $2.4,2 \mathrm{H}), 7.06(\mathrm{~d}, J=3.2,2 \mathrm{H}), 7.07(\mathrm{~d}, J=2.4,2 \mathrm{H})$ and $7.21(\mathrm{~d}, J=8.9,2 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 100 MHz ) $\delta: 36.5,55.9,69.0,73.3$, 102.1, 103.0, 109.9, 112.3, 127.8, 129.3, 131.1 and 154.5. IR (KBr, ע): 3102, 2956, 2935, 2832, 1728, 1616, 1576, 1482, 1432, 1397, 1243, 1152, 1030, 802 and $726 \mathrm{~cm}^{-1}$. MS ( $\mathrm{m} / \mathrm{z}$, rel. int., \%): 368 $\left(3, \mathrm{M}^{+}\right), 78$ (99), 63 (100), 62 (13) and 61 (36). Anal. calc.: C, 78.24; H, 5.47; N, 7.60. Found: C, 77.86; H, 5.54; N, 7.25.

1,6-Bis(5-bromo-1H-indol-1-yl)hexa-2,4-diyne (3c). Beige solid, m.p.: $157-159{ }^{\circ} \mathrm{C}$; yield: $76 \%$. ${ }^{1} \mathrm{H}$ NMR ( 400 MHz , DMSO$\left.d_{6}\right) \delta: 5.26(\mathrm{~s}, 4 \mathrm{H}), 6.46(\mathrm{dd}, J=3.2$ and $0.7,2 \mathrm{H}), 7.29(\mathrm{dd}, J=8.7$ and $1.9,2 \mathrm{H}), 7.42(\mathrm{~d}, J=3.2,2 \mathrm{H}), 7.47(\mathrm{~d}, J=8.7,2 \mathrm{H})$ and 7.75 $(\mathrm{d}, J=1.9,2 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 100 MHz, DMSO- $d_{6}$ ) $\delta: 35.6,67.5,75.0$, 101.3, 111.8, 112.2, 122.7, 123.9, 129.8, 130.0 and 134.1. IR ( KBr , ע): 3106, 1705, 1604, 1562, 1507, 1463, 1333, 1208, 793, 754 and $581 \mathrm{~cm}^{-1} . \mathrm{MS}\left(\mathrm{m} / \mathrm{z}\right.$, rel. int., \%): $468\left[2,(\mathrm{M}+2)^{+}\right], 466\left(4, \mathrm{M}^{+}\right), 235$ (27), 233 (28), 197 (55), 195 (55), 154 (60), 127 (15), 116 (78) and 89 (39). Anal. calc.: C, 56.68; H, 3.03; N, 6.01. Found: C, 57.07; H, 3.13; N, 5.87.

1,6-Bis(2-methyl-1H-indol-1-yl)hexa-2,4-diyne (3d). Brown solid, m.p.: $218{ }^{\circ} \mathrm{C}$ (dec); yield: $83 \%{ }^{1}{ }^{1} \mathrm{H}$ NMR ( 400 MHz , DMSO$\left.d_{6}\right) \delta: 2.39(\mathrm{~s}, 6 \mathrm{H}), 5.13(\mathrm{~s}, 4 \mathrm{H}), 6.22(\mathrm{~s}, 2 \mathrm{H}), 6.98-7.09(\mathrm{~m}, 4 \mathrm{H})$ and 7.40-7.43 (m, 4H). ${ }^{13} \mathrm{C}$ NMR ( 100 MHz, DMSO- $d_{6}$ ) $\delta: 12.1$, 32.4, 66.7, 75.3, 100.5, 109.3, 119.3, 119.5, 120.6, 127.7, 136.2 and 136.3. IR (KBr, $\nu): 2916,1614,1552,1462,1337,787$ and 745 $\mathrm{cm}^{-1}$. MS ( $\mathrm{m} / \mathrm{z}$, rel. int., \%): 337 [17, (M+1) $\left.{ }^{+}\right], 336\left(60, \mathrm{M}^{+}\right), 205$ (100), 204 (88), 191 (28), 167 (18), 149 (12), 130 (44), 97 (18), 81 (26) and 69 (47). HRMS (ESI-TOF, $m / z$ ): obsd. 359.1507; $\mathrm{C}_{24} \mathrm{H}_{20} \mathrm{~N}_{2} \mathrm{Na}\left[(\mathrm{M}+\mathrm{Na})^{+}\right]$requires 359.1519.

1,6-Bis(5-p-tolyl-1H-indol-1-yl)hexa-2,4-diyne (3e). Brown solid, m.p.: $175-177^{\circ} \mathrm{C}$; yield: $72 \% .{ }^{1} \mathrm{H}$ NMR ( 400 MHz , DMSO$\left.d_{6}\right) \delta: 2.33(\mathrm{~s}, 6 \mathrm{H}), 5.27(\mathrm{~s}, 4 \mathrm{H}), 6.50(\mathrm{~d}, J=3.1,2 \mathrm{H}), 7.23(\mathrm{~d}, J=$ $7.9,4 \mathrm{H}), 7.38(\mathrm{~d}, J=3.1,2 \mathrm{H}), 7.44(\mathrm{dd}, J=8.6$ and $1.6,2 \mathrm{H}), 7.53-$ $7.55(\mathrm{~m}, 6 \mathrm{H})$ and $7.79-7.80(\mathrm{~m}, 2 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 100 MHz , DMSO$\left.d_{6}\right) \delta: 20.6,35.6,67.4,75.4,102.1,110.3,118.3,120.8,126.5$, 128.9, 129.1, 129.4, 132.1, 134.9, 135.5 and 138.5. IR (KBr, $\nu$ ): 2915, 1616, 1476, 1335, 799 and $720 \mathrm{~cm}^{-1}$. MS ( $\mathrm{m} / \mathrm{z}$, rel. int., \%): $489\left[20,(\mathrm{M}+1)^{+}\right], 488\left(50, \mathrm{M}^{+}\right), 282(22), 281$ (32), 267 (28), 266 (20), 244 (17), 208 (20), 207 (100), 206 (64), 204 (25), 97 (23) and 57 (46). HRMS (ESI-TOF, m/z): obsd. 511.2129; $\mathrm{C}_{36} \mathrm{H}_{28} \mathrm{~N}_{2} \mathrm{Na}$ $\left[(\mathrm{M}+\mathrm{Na})^{+}\right]$requires 511.2145.

1,6-Bis(9H-carbazol-9-yl)hexa-2,4-diyne (3f). White crystalline solid, m.p.: $204{ }^{\circ} \mathrm{C}$ (dec); yield: $60 \%{ }^{1} \mathrm{H}$ NMR ( 400 MHz , DMSO- $d_{6}$ ) $\delta: 5.39(\mathrm{~s}, 4 \mathrm{H}), 7.20-7.24(\mathrm{~m}, 4 \mathrm{H}), 7.42-7.46(\mathrm{~m}, 4 \mathrm{H})$, $7.59(\mathrm{~d}, J=8.1,4 \mathrm{H})$ and $8.12(\mathrm{~d}, J=7.6,4 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR $(100 \mathrm{MHz}$, DMSO- $d_{6}$ ) $\delta: 32.2,66.5,74.8,109.2,119.4,120.1,122.4,125.7$ and 139.3. IR (KBr, $\nu): 3050,2910,1625,1599,1485,1454,1325$, 747 and $720 \mathrm{~cm}^{-1}$. MS ( $\mathrm{m} / \mathrm{z}$, rel. int., \%): 409 [16, (M + 1) $\left.{ }^{+}\right], 408$ (50, M ${ }^{+}$), 242 (36), 241 (100), 167 (18), 166 (29) and 140 (16). HRMS (ESI-TOF, $m / z$ ): obsd. 431.1521; $\mathrm{C}_{30} \mathrm{H}_{20} \mathrm{~N}_{2} \mathrm{Na}\left[(\mathrm{M}+\mathrm{Na})^{+}\right]$ requires 431.1524 .

## General procedure for the preparation of unsymmetric 1,3diynes (5a-f) ${ }^{24}$

Solid $\mathrm{CuI}(10 \mathrm{mg}, 0.05 \mathrm{mmol}, 5 \mathrm{~mol} \%)$ and $\mathrm{NiCl}_{2} \cdot 6 \mathrm{H}_{2} \mathrm{O}(12 \mathrm{mg}$, $0.05 \mathrm{mmol}, 5 \mathrm{~mol} \%$ ) were added to a stirred solution of TMEDA ( $30 \mu \mathrm{~L}, 0.2 \mathrm{mmol}, 20 \mathrm{~mol} \%$ ) in THF ( 4 mL ). The aryl acetylene ( $\mathbf{4} \mathbf{a}$ and $\mathbf{b}, 5 \mathrm{mmol}$ ) and the $N$-propargyl indole or carbazole ( 1 mmol ) were successively added and the system was allowed to stir at room temperature for 6 h . Then, the volatiles were evaporated under reduced pressure and the residue was chromatographically purified, eluting with hexane.

1-(5-Phenylpenta-2,4-diynyl)-1H-indole (5a). Light brown solid, m.p.: $68-70^{\circ} \mathrm{C}$; yield: $76 \% .{ }^{1} \mathrm{H}$ NMR ( 400 MHz ) $\delta: 4.97$ (s, $2 \mathrm{H}), 6.53$ (dd, $J=3.2$ and $0.6,1 \mathrm{H}$ ), 7.12-7.19 (m, 2H), 7.23-7.34 $(\mathrm{m}, 4 \mathrm{H}), 7.38(\mathrm{~d}, J=8.2,1 \mathrm{H}), 7.43-7.45(\mathrm{~m}, 2 \mathrm{H})$ and $7.63(\mathrm{~d}, J=$ $7.8,1 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 100 MHz ) $\delta: 36.6,69.9,73.2,76.4,78.2,102.4$, 109.3, 120.0, 121.1, 121.2, 122.0, 127.2, 128.4, 128.9, 129.4, 132.6 and 135.8. IR (KBr, $\nu): 3045,2942,2240,1609,1573,1513,1483$, $1355,1304,1254,1192,752,732$ and $686 \mathrm{~cm}^{-1}$. MS ( $\mathrm{m} / \mathrm{z}$, rel. int., \%): $256\left[15,(\mathrm{M}+1)^{+}\right], 255\left(73, \mathrm{M}^{+}\right), 254$ (44), $140(12), 139(100)$, 113 (9) and 89 (14). HRMS (ESI-TOF, m/z): obsd. 278.0948; $\mathrm{C}_{19} \mathrm{H}_{13} \mathrm{NNa}\left[(\mathrm{M}+\mathrm{Na})^{+}\right]$requires 278.0946.

1-(5-p-Tolylpenta-2,4-diynyl)-1H-indole (5b). Light brown solid, m.p.: $83-85{ }^{\circ} \mathrm{C}$; yield: $70 \% .{ }^{1} \mathrm{H}$ NMR ( 400 MHz ) $\delta: 2.33$ (s, $3 \mathrm{H}), 4.99(\mathrm{~s}, 2 \mathrm{H}), 6.54(\mathrm{dd}, J=3.2$ and $0.5,1 \mathrm{H}), 7.09(\mathrm{~d}, J=8.0$, 2H), 7.12-7.16 (m, 1H), 7.18 (d, $J=3.2,1 \mathrm{H}), 7.24-7.27(\mathrm{~m}, 1 \mathrm{H})$, $7.35(\mathrm{~d}, J=8.1,2 \mathrm{H}), 7.40(\mathrm{~d}, J=8.3,1 \mathrm{H})$ and $7.64(\mathrm{~d}, J=7.9,1 \mathrm{H})$. ${ }^{13} \mathrm{C}$ NMR ( 100 MHz ) $\delta: 21.5,36.7,70.1,72.7,76.1,78.6,102.4$, 109.3, 118.2, 120.0, 121.1, 122.0, 127.2, 129.0, 129.2, 132.5, 135.9 and 139.8. IR (KBr, $\nu): 3028,2951,2239,1604,1508,1462,1336$, 1314, 1257, 1182, 811, 742 and $720 \mathrm{~cm}^{-1}$. MS ( $\mathrm{m} / \mathrm{z}$, rel. int., \%): $270\left[14,(\mathrm{M}+1)^{+}\right], 269\left(63, \mathrm{M}^{+}\right), 268(25), 207(13), 154(14), 153$ (100) and 152 (23). HRMS (ESI-TOF, $m / z$ ): obsd. 270.1255; $\mathrm{C}_{20} \mathrm{H}_{16} \mathrm{~N}\left[(\mathrm{M}+\mathrm{H})^{+}\right]$requires 270.1283.

5-Methoxy-1-(5-phenylpenta-2,4-diynyl)-1H-indole (5c). Beige solid, m.p: $105-107{ }^{\circ} \mathrm{C}$; yield: $83 \% .{ }^{1} \mathrm{H}$ NMR ( 400 MHz ) $\delta: 3.84$ (s, $3 \mathrm{H}), 4.95(\mathrm{~s}, 2 \mathrm{H}), 6.45(\mathrm{~d}, J=3.0,1 \mathrm{H}), 6.91(\mathrm{dd}, J=8.8$ and 2.3 , $1 \mathrm{H}), 7.09(\mathrm{~d}, J=2.3,1 \mathrm{H}), 7.14(\mathrm{~d}, J=3.0,1 \mathrm{H}), 7.26-7.35(\mathrm{~m}, 4 \mathrm{H})$ and 7.44-7.46 (m, 2H). ${ }^{13} \mathrm{C}$ NMR ( 100 MHz ) $\delta: 36.8,55.9,69.8$, 73.2, 76.5, 78.2, 102.0, 103.0, 110.0, 112.3, 121.2, 127.9, 128.4, 129.4, 131.2, 132.6 and 154.5. IR (KBr, $\nu$ ): 2943, 2901, 2244, 1619, 1574, 1486, 1451, 1423, 1347, 1237, 1152, 1026, 801, 757, 722 and $687 \mathrm{~cm}^{-1} . \mathrm{MS}\left(\mathrm{m} / \mathrm{z}\right.$, rel. int., \%): $286\left[16,(\mathrm{M}+1)^{+}\right], 285(69$, $\mathrm{M}^{+}$), 281 (11), 254 (11), 207 (29), 140 (13) and 139 (100). HRMS (ESI-TOF, $m / z$ ): obsd. 308.1039; $\mathrm{C}_{20} \mathrm{H}_{15} \mathrm{NNaO}\left[(\mathrm{M}+\mathrm{Na})^{+}\right]$ requires 308.1046 .

5-Bromo-1-(5-p-tolylpenta-2,4-diynyl)-1H-indole (5d). White solid, m.p.: $120-122{ }^{\circ} \mathrm{C}$; yield: $60 \%{ }^{1}{ }^{1} \mathrm{H}$ NMR ( 400 MHz ) $\delta: 2.33$ $(\mathrm{s}, 3 \mathrm{H}), 4.96(\mathrm{~s}, 2 \mathrm{H}), 6.46(\mathrm{~d}, J=3.1,1 \mathrm{H}), 7.09(\mathrm{~d}, J=8.0,2 \mathrm{H})$, $7.17(\mathrm{~d}, J=3.1,1 \mathrm{H}), 7.26(\mathrm{~d}, J=8.7,1 \mathrm{H}), 7.31-7.36(\mathrm{~m}, 3 \mathrm{H})$ and $7.74(\mathrm{~d}, J=1.6,1 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 100 MHz ) $\delta: 21.6,36.9,70.5,72.5$, 75.4, 78.9, 102.0, 110.8, 113.4, 118.0, 123.6, 124.9, 128.5, 129.2, 130.7, 132.6, 134.6 and 140.0. IR (KBr, $\nu$ ): 2916, 2891, 2247, 1650, 1560, 1508, 1463, 1433, 1400, 1344, 1268, 1242, 1210, 823, 794, 755 and $723 \mathrm{~cm}^{-1} . \mathrm{MS}\left(\mathrm{m} / \mathrm{z}\right.$, rel. int., \%): $349\left[8,(\mathrm{M}+2)^{+}\right], 347(9$, $\mathrm{M}^{+}$), 209 (12), 208 (21), 207 (100), 153 (44), 133 (15), 96 (17) and 73 (33). HRMS (ESI-TOF, $m / z$ ): obsd. $370.0190 ; \mathrm{C}_{20} \mathrm{H}_{14} \mathrm{BrNNa}[(\mathrm{M}$ $\left.+\mathrm{Na})^{+}\right]$requires 370.0202.

9-(5-Phenylpenta-2,4-diynyl)-9H-carbazole (5e). White crystalline solid, m.p: $154-155{ }^{\circ} \mathrm{C}$; yield: $80 \% .{ }^{1} \mathrm{H}$ NMR $(400 \mathrm{MHz}$, DMSO- $d_{6}$ ) $\delta: 5.58(\mathrm{~s}, 2 \mathrm{H}), 7.25-7.28(\mathrm{~m}, 2 \mathrm{H}), 7.34-7.44(\mathrm{~m}, 3 \mathrm{H})$, $7.47-7.53(\mathrm{~m}, 4 \mathrm{H}), 7.72(\mathrm{~d}, J=8.2,2 \mathrm{H})$ and $8.18(\mathrm{~d}, J=7.8,2 \mathrm{H})$. ${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{DMSO}-d_{6}$ ) $\delta: 32.6,67.0,72.9,77.2,79.4$, 109.4, 119.5, 119.9, 120.3, 122.5, 125.9, 128.6, 129.8, 132.3 and 139.5. IR (KBr, $\nu$ ): 3053, 2914, 2244, 1626, 1597, 1487, 1456, 1329, 748,720 and $684 \mathrm{~cm}^{-1} . \operatorname{MS}\left(\mathrm{m} / \mathrm{z}\right.$, rel. int., \%): $305\left(32, \mathrm{M}^{+}\right)$, 304 (24), 166 (10), 140 (21) and 139 (100). Anal. calc.: C, 90.46 ; H, 4.95; N, 4.59. Found: C, 90.10; H, 4.91; N, 4.29.

9-(5-p-Tolylpenta-2,4-diynyl)-9H-carbazole (5f). White crystalline solid, m.p: $155-156{ }^{\circ} \mathrm{C}$; yield: $85 \%$. ${ }^{1} \mathrm{H}$ NMR ( 400 MHz , DMSO- $d_{6}$ ) $\delta: 2.27(\mathrm{~s}, 3 \mathrm{H}), 5.57(\mathrm{~s}, 2 \mathrm{H}), 7.15(\mathrm{~d}, J=7.9,2 \mathrm{H}), 7.24-$ $7.28(\mathrm{~m}, 2 \mathrm{H}), 7.36(\mathrm{~d}, J=7.9,2 \mathrm{H}), 7.49-7.53(\mathrm{~m}, 2 \mathrm{H}), 7.72(\mathrm{~d}, J=$ $8.2,2 \mathrm{H})$ and $8.17(\mathrm{~d}, J=7.7,2 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 100 MHz , DMSO- $d_{6}$ ) $\delta: 20.9,32.6,67.2,72.4,77.5,78.9,109.4,116.8,119.5,120.2$, 122.5, 125.8, 129.2, 132.2, 139.5 and 139.9. IR (KBr, $\nu$ ): 3052, 2912, 2242, 1627, 1603, 1489, 1455, 1332, 812, 746 and 719 $\mathrm{cm}^{-1}$. MS ( $\mathrm{m} / \mathrm{z}$, rel. int., \%): 319 ( $5, \mathrm{M}^{+}$), 170 (65), 150 (12), 135 (22), 133 (57), 103 (21), 102 (29), 86 (100), 84 (100) and 66 (80). HRMS (ESI-TOF, m/z): obsd. 320.1420; $\mathrm{C}_{24} \mathrm{H}_{18} \mathrm{~N}\left[(\mathrm{M}+\mathrm{H})^{+}\right]$ requires 320.1434 .

## General procedure for the synthesis of 3,5-disubstituted 1,2isoxazoles ( $\mathbf{6 a - f}$ ) from the symmetric 1,3-diynes (3a-f)

A stirred mixture of the symmetric diyne ( $3,0.3 \mathrm{mmol}$ ), $\mathrm{H}_{2}{ }^{-}$ $\mathrm{NOH} \cdot \mathrm{HCl}\left(48 \mathrm{mg}, 0.75 \mathrm{mmol}, 2.5\right.$ equiv.) and $\mathrm{Et}_{3} \mathrm{~N}(0.1 \mathrm{~mL}, 0.75$ $\mathrm{mmol}, 2.5$ equiv.) in PEG-400 ( 0.5 mL ) was heated at $80^{\circ} \mathrm{C}$ for 12 h. After the reaction was completed, water ( 10 mL ) was added and the products were extracted with EtOAc ( $3 \times 15 \mathrm{~mL}$ ). The combined extracts were dried over $\mathrm{MgSO}_{4}$; the solvent was evaporated under reduced pressure and the oily residue was chromatographed using hexane: EtOAc $(85: 15)$ as eluent.

5-(2-(1H-Indol-1-yl)ethyl)-3-((1H-indol-1-yl)methyl)-1,2-isoxazole (6a). Beige solid, m.p.: $90-92{ }^{\circ} \mathrm{C}$; yield: $89 \% .{ }^{1} \mathrm{H}$ NMR ( 400 MHz ) $\delta: 3.05(\mathrm{t}, J=7.0,2 \mathrm{H}), 4.28(\mathrm{t}, J=7.0,2 \mathrm{H}), 5.18(\mathrm{~s}, 2 \mathrm{H}), 5.42(\mathrm{~s}$, $1 \mathrm{H}), 6.35(\mathrm{~d}, J=3.1,1 \mathrm{H}), 6.49(\mathrm{~d}, J=3.1,1 \mathrm{H}), 6.80(\mathrm{~d}, J=3.1$, $1 \mathrm{H}), 6.98(\mathrm{~d}, J=3.1,1 \mathrm{H}), 7.04-7.19(\mathrm{~m}, 5 \mathrm{H}), 7.26(\mathrm{~d}, J=8.2,1 \mathrm{H})$, $7.56(\mathrm{dd}, J=7.9$ and $0.6,1 \mathrm{H})$ and $7.60(\mathrm{dd}, J=7.9$ and $0.6,1 \mathrm{H})$. ${ }^{13} \mathrm{C}$ NMR ( 100 MHz ) $\delta: 27.7,41.7,43.8,101.3,101.9,102.5,108.8$, 109.3, 119.6, 119.9, 121.1, 121.1, 121.7, 122.0, 127.3, 127.6, 128.7, 128.8, 135.6, 136.1, 160.8 and 170.2. IR (KBr, $\nu$ ): 3099, 3051, 2924, 1709, 1610, 1513, 1477, 1461, 1429, 1338, 1314, 1257, 1213, 1180, 1011 and $739 \mathrm{~cm}^{-1}$. MS ( $\mathrm{m} / \mathrm{z}$, rel. int., \%): 341
( $14, \mathrm{M}^{+}$), 131 (10), 130 (100) and 103 (10). HRMS (ESI-TOF, $m / z$ ): obsd. 364.1425; $\mathrm{C}_{22} \mathrm{H}_{19} \mathrm{~N}_{3} \mathrm{NaO}\left[(\mathrm{M}+\mathrm{Na})^{+}\right]$requires 364.1426.

5-(2-(5-Methoxy-1H-indol-1-yl)ethyl)-3-((5-methoxy-1H-indol-1-yl)methyl)-1,2-isoxazole (6b). Beige solid, m.p.: 94-95 ${ }^{\circ} \mathrm{C}$; yield: $71 \% .{ }^{1} \mathrm{H}$ NMR $(400 \mathrm{MHz}) \delta: 3.09(\mathrm{t}, J=7.0,2 \mathrm{H}), 3.82(\mathrm{~s}$, $6 \mathrm{H}), 4.30(\mathrm{t}, J=7.0,2 \mathrm{H}), 5.19(\mathrm{~s}, 2 \mathrm{H}), 5.46(\mathrm{~s}, 1 \mathrm{H}), 6.29(\mathrm{~d}, J=3.0$, $1 \mathrm{H}), 6.42(\mathrm{~d}, J=3.0,1 \mathrm{H}), 6.81-6.87(\mathrm{~m}, 3 \mathrm{H}), 6.98(\mathrm{~d}, J=3.0,1 \mathrm{H})$, $7.04(\mathrm{~d}, J=2.4,1 \mathrm{H}), 7.07-7.09(\mathrm{~m}, 2 \mathrm{H})$ and $7.15(\mathrm{~d}, J=8.9,1 \mathrm{H})$. ${ }^{13} \mathrm{C}$ NMR ( 100 MHz ) $\delta: 28.0,42.0,44.1,55.9,101.4,101.5,102.1$, 103.1, 103.1, 109.5, 110.1, 112.1, 112.4, 127.9, 128.2, 129.1, 129.3, 131.0, 131.5, 154.3, 154.5, 161.0 and 170.2. IR (KBr, $\nu$ ): 3123, 2948, 2829, 1715, 1612, 1484, 1445, 1245, 1237, 1147, 1030, 802, 757 and $730 \mathrm{~cm}^{-1}$. MS ( $\mathrm{m} / \mathrm{z}$, rel. int., \%): $401\left(33, \mathrm{M}^{+}\right)$, 281 (36), 208 (18), 207 (83), 161 (11), 160 (100) and 117 (44). Anal. calc.: C, 71.80 ; H, 5.77 ; N, 10.47. Found: C, 71.53 ; H, 5.55 ; N, 10.06.

5-(2-(5-Bromo-1H-indol-1-yl)ethyl)-3-((5-bromo-1H-indol-1-yl)-methyl)-1,2-isoxazole (6c). Beige solid, m.p.: 99-101 ${ }^{\circ} \mathrm{C}$; yield: $83 \% .{ }^{1} \mathrm{H}$ NMR ( 400 MHz ) $\delta: 3.07(\mathrm{t}, J=6.8,2 \mathrm{H}), 4.30(\mathrm{t}, J=6.8$, $2 \mathrm{H}), 5.16(\mathrm{~s}, 2 \mathrm{H}), 5.36(\mathrm{~s}, 1 \mathrm{H}), 6.27(\mathrm{~d}, J=3.1,1 \mathrm{H}), 6.43(\mathrm{~d}, J=3.1$, $1 \mathrm{H}), 6.80(\mathrm{~d}, J=2.3,1 \mathrm{H}), 6.97-7.00(\mathrm{~m}, 2 \mathrm{H}), 7.09(\mathrm{~d}, J=8.7,1 \mathrm{H})$, $7.18(\mathrm{~d}, J=8.7,1 \mathrm{H}), 7.24(\mathrm{~d}, J=8.7,1 \mathrm{H}), 7.67(\mathrm{~s}, 1 \mathrm{H})$ and $7.72(\mathrm{~s}$, 1H). ${ }^{13} \mathrm{C}$ NMR ( 100 MHz ) $\delta: 27.8,41.9,44.0,101.4,101.4,102.0$, $110.2,110.7,112.8,113.2,123.5,123.5,124.5,124.8,128.4,128.8$, 130.1, 130.4, 134.1, 134.5, 160.4 and 170.0. IR (KBr, $\nu$ ): 3125, 3099, 2932, 1712, 1601, 1510, 1467, 1329, 1276, 1192, 1049, 870, 794, 754, and $718 \mathrm{~cm}^{-1} . \mathrm{MS}\left(\mathrm{m} / \mathrm{z}\right.$, rel. int., \%): 501 [11, $\left.(\mathrm{M}+2)^{+}\right]$, 499 (17, M ${ }^{+}$), 420 (36), 419 (15), 418 (37), 250 (11), 248 (11), 210 (97), 208 (100) and 129 (72). HRMS (ESI-TOF, m/z): obsd. 499.9775; $\mathrm{C}_{22} \mathrm{H}_{18} \mathrm{Br}_{2} \mathrm{~N}_{3} \mathrm{O}\left[(\mathrm{M}+\mathrm{H})^{+}\right]$requires 499.9796 .

5-(2-(2-Methyl-1H-indol-1-yl)ethyl)-3-((2-methyl-1H-indol-1-yl)-methyl)-1,2-isoxazole (6d). Brown solid, m.p: 112-114 ${ }^{\circ} \mathrm{C}$; yield: $58 \% .{ }^{1} \mathrm{H}$ NMR $(400 \mathrm{MHz}) \delta: 2.11(\mathrm{~s}, 3 \mathrm{H}), 2.33(\mathrm{~s}, 3 \mathrm{H}), 2.96(\mathrm{t}, J=$ $7.1,2 \mathrm{H}), 4.18(\mathrm{t}, J=7.1,2 \mathrm{H}), 5.14(\mathrm{~s}, 2 \mathrm{H}), 5.30(\mathrm{~s}, 1 \mathrm{H}), 6.07(\mathrm{~s}, 1 \mathrm{H})$, $6.24(\mathrm{~s}, 1 \mathrm{H}), 7.00-7.19(\mathrm{~m}, 6 \mathrm{H}), 7.44(\mathrm{~d}, J=7.7,1 \mathrm{H})$ and $7.49(\mathrm{~d}, J$ $=7.7,1 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 100 MHz ) $\delta: 12.2,12.5,27.2,38.4,40.7$, 100.5, 101.1, 101.3, 108.4, 108.7, 119.5, 119.8, 119.8, 119.8, 120.6, 121.0, 128.2, 128.3, 135.9, 136.1, 136.1, 136.7, 161.1 and 170.1. IR (KBr, $\nu$ ): 3050, 2916, 1603, 1553, 1462, 1397, 1341, 1312, 1166, 777,777 and $743 \mathrm{~cm}^{-1}$. MS ( $\mathrm{m} / \mathrm{z}$, rel. int., \%): $369\left(28, \mathrm{M}^{+}\right), 206$ (22), 145 (12), 144 (100), 143 (11) and 115 (12). HRMS (ESI-TOF, $\mathrm{m} / z$ ): obsd. 392.1720; $\mathrm{C}_{24} \mathrm{H}_{23} \mathrm{~N}_{3} \mathrm{NaO}\left[(\mathrm{M}+\mathrm{Na})^{+}\right]$requires 392.1733.

5-(2-(5-p-Tolyl-1H-indol-1-yl)ethyl)-3-((5-p-tolyl-1H-indol-1-yl)-methyl)-1,2-isoxazole (6e). Light brown solid, m.p.: $55-56{ }^{\circ} \mathrm{C}$; yield: $63 \% .{ }^{1} \mathrm{H}$ NMR ( 400 MHz ) $\delta: 2.34(\mathrm{~s}, 6 \mathrm{H}), 2.97(\mathrm{t}, J=6.7$, $2 \mathrm{H}), 4.19(\mathrm{t}, J=6.7,2 \mathrm{H}), 5.11(\mathrm{~s}, 2 \mathrm{H}), 5.38(\mathrm{~s}, 1 \mathrm{H}), 6.36(\mathrm{~d}, J=3.0$, $1 \mathrm{H}), 6.48(\mathrm{~d}, J=3.0,1 \mathrm{H}), 6.76(\mathrm{~d}, J=3.1,1 \mathrm{H}), 6.92(\mathrm{~d}, J=3.1$, $1 \mathrm{H}), 7.13(\mathrm{~d}, J=8.5,1 \mathrm{H}), 7.18(\mathrm{~d}, J=7.9,4 \mathrm{H}), 7.23(\mathrm{~d}, J=8.5$, $1 \mathrm{H}), 7.34-7.39(\mathrm{~m}, 2 \mathrm{H}), 7.48(\mathrm{~d}, J=7.9,4 \mathrm{H}), 7.74(\mathrm{~s}, 1 \mathrm{H})$ and 7.77 (s, 1H). ${ }^{13} \mathrm{C}$ NMR ( 100 MHz ) $\delta: 20.9,27.7,41.7,43.8,101.4,102.2$, $102.8,109.0,109.5,119.2,121.4,121.7,127.1,127.9,128.2,129.1$, 129.3, 129.3, 133.0, 133.4, 134.9, 135.4, 135.9, 135.9, 139.3, 139.3, 160.7 and 170.1. IR (KBr, $\nu$ ): 3098, 3020, 2919, 1602, 1516, 1477, $1450,1335,1260,1181,886,798,762$ and $722 \mathrm{~cm}^{-1} . \mathrm{MS}(\mathrm{m} / \mathrm{z}$, rel. int., \%): $521\left(22, \mathrm{M}^{+}\right), 260(13), 221(21), 220(100), 207(12)$ and

204 (15). HRMS (ESI-TOF, m/z): obsd. 544.2350; $\mathrm{C}_{36} \mathrm{H}_{31} \mathrm{~N}_{3} \mathrm{NaO}$ $\left[(\mathrm{M}+\mathrm{Na})^{+}\right]$requires 544.2359 .

5-(2-(9H-Carbazol-9-yl)ethyl)-3-((9H-carbazol-9-yl) methyl)-1,2-isoxazole (6f). White solid, m.p.: $167-168{ }^{\circ} \mathrm{C}$; yield: $89 \%{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{DMSO}-d_{6}$ ) $\delta: 3.13(\mathrm{t}, J=7.0,2 \mathrm{H}), 4.59(\mathrm{t}, J=7.0$, $2 \mathrm{H}), 5.60(\mathrm{~s}, 2 \mathrm{H}), 6.01(\mathrm{~s}, 1 \mathrm{H}), 7.14-7.18(\mathrm{~m}, 2 \mathrm{H}), 7.23-7.26(\mathrm{~m}$, $2 \mathrm{H}), 7.29-7.33$ (m, 2H), 7.43 (d, $J=8.2,2 \mathrm{H}), 7.45-7.49(\mathrm{~m}, 2 \mathrm{H})$, $7.59(\mathrm{~d}, J=8.2,2 \mathrm{H}), 8.08(\mathrm{~d}, J=7.7,2 \mathrm{H})$ and $8.16(\mathrm{~d}, J=7.7,2 \mathrm{H})$. ${ }^{13} \mathrm{C}$ NMR ( 100 MHz , DMSO- $d_{6}$ ) $\delta: 25.5,37.7,40.2,101.4,108.9$, $109.2,118.8,119.1,120.0,120.1,122.0,122.2,125.5,125.7$, 139.5, 139.7, 160.1 and 170.6. IR (KBr, $\nu$ ): 3051, 1599, 1486, 1456, 1329, 1232, 750 and 722. MS ( $\mathrm{m} / \mathrm{z}$, rel. int., \%): $441\left(17, \mathrm{M}^{+}\right), 181$ (19), 180 (100), 167 (77), 149 (40) and 105 (39). Anal. calc.: C, 81.61; H, 5.25; N, 9.52. Found: C, 81.58; H, 5.23; N, 9.25.

## General procedure for the synthesis of 3,5-disubstituted-1,2-

 isoxazoles ( $\mathbf{7 a - f}$ ) from the unsymmetric 1,3-diynes (5a-f)A stirred mixture of the unsymmetrical diyne ( $5,0.3 \mathrm{mmol}$ ), $\mathrm{H}_{2} \mathrm{NOH} \cdot \mathrm{HCl}\left(48 \mathrm{mg}, 0.75 \mathrm{mmol}, 2.5\right.$ equiv.) and $\mathrm{Et}_{3} \mathrm{~N}(0.17 \mathrm{~mL}$, $1.2 \mathrm{mmol}, 4.0$ equiv.) in PEG-400 ( 0.5 mL ) was heated at $100^{\circ} \mathrm{C}$ for 12 h . After the reaction was completed, water ( 10 mL ) was added and the products were extracted with EtOAc $(3 \times 15 \mathrm{~mL})$. The combined extracts were dried over $\mathrm{MgSO}_{4}$; the solvent was evaporated under reduced pressure and the oily residue was chromatographed using hexane : EtOAc $(90: 10)$ as eluent.

3-((1H-Indol-1-yl)methyl)-5-benzyl-1,2-isoxazole (7a). Beige waxy solid; yield: $85 \% .{ }^{1} \mathrm{H}$ NMR ( 400 MHz ) $\delta: 3.92$ (s, 2H), 5.24 (s, $2 \mathrm{H}), 5.60(\mathrm{~s}, 1 \mathrm{H}), 6.51(\mathrm{~d}, J=3.1,1 \mathrm{H}), 7.06(\mathrm{~d}, J=3.1,1 \mathrm{H}), 7.08-$ $7.13(\mathrm{~m}, 3 \mathrm{H}), 7.16-7.27(\mathrm{~m}, 4 \mathrm{H}), 7.33(\mathrm{~d}, J=8.2,1 \mathrm{H})$ and $7.60(\mathrm{~d}$, $J=7.8,1 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 100 MHz ) $\delta: 33.1,41.8,100.6,102.4$, 109.3, 119.8, 121.0, 122.0, 127.1, 127.7, 128.7, 128.7, 128.8, 135.5, 136.1, 160.7 and 172.9. IR (KBr, $\nu)$ : 3111, 3027, 2924, 2860, 1724, 1598, 1468, 1420, 1327, 1260, 1186, 1131, 996, 822, 746, 743 and 709. MS ( $\mathrm{m} / \mathrm{z}$, rel. int., \%): $289\left[10,(\mathrm{M}+1)^{+}\right], 288$ (49, $\mathrm{M}^{+}$), 197 (54), 169 (17), 131 (12), 130 (100), 103 (23) and 91 (17). HRMS (ESI-TOF, $m / z$ ): obsd. 311.1170; $\mathrm{C}_{19} \mathrm{H}_{16} \mathrm{~N}_{2} \mathrm{NaO}\left[(\mathrm{M}+\mathrm{Na})^{+}\right]$ requires 311.1160 .

3-((1H-Indol-1-yl)methyl)-5-(4-methylbenzyl)-1,2-isoxazole (7b). Beige waxy solid; yield: 84\%; ${ }^{1} \mathrm{H}$ NMR ( 400 MHz ) $\delta: 2.27$ (s, 3H), $3.88(\mathrm{~s}, 2 \mathrm{H}), 5.24(\mathrm{~s}, 2 \mathrm{H}), 5.59(\mathrm{~s}, 1 \mathrm{H}), 6.50(\mathrm{~d}, J=3.0$, 1 H ), $7.00-7.11$ (m, 6H), 7.17 (d, $J=8.1,1 \mathrm{H}), 7.33$ (d, $J=8.1$, 1 H ) and $7.60(\mathrm{~d}, J=7.8,1 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 100 MHz ) $\delta: 20.9,32.7$, $41.8,100.5,102.4,109.3,119.8,121.0$, 122.0, 127.6, 128.6, 128.7, 129.4, 132.4, 136.1, 136.7, 160.7 and 173.3. IR (KBr, $\nu$ ): 2924, 2860, 1728, 1603, 1468, 1460, 1268, 1226 and $751 \mathrm{~cm}^{-1}$. MS ( $\mathrm{m} / \mathrm{z}$, rel. int., \%): 303 [15, ( $\left.\mathrm{M}+1)^{+}\right], 302\left(60, \mathrm{M}^{+}\right), 207(14)$, 197 (29), 170 (40), 169 (53), 131 (13) and 130 (100). HRMS (ESI-TOF, m/z): obsd. 303.1543; $\mathrm{C}_{20} \mathrm{H}_{19} \mathrm{~N}_{2} \mathrm{O}\left[(\mathrm{M}+\mathrm{H})^{+}\right]$ requires 303.1492.

5-Benzyl-3-((5-methoxy-1H-indol-1-yl)methyl)-1,2-isoxazole (7c). Brown oil; yield: 75\%. ${ }^{1} \mathrm{H}$ NMR ( 400 MHz ) $\delta: 3.81$ (s, 3H), 3.93 (s, 2H), $5.20(\mathrm{~s}, 2 \mathrm{H}), 5.60(\mathrm{~s}, 1 \mathrm{H}), 6.42(\mathrm{~d}, J=3.0,1 \mathrm{H}), 6.85$ (dd, $J=8.9$ and $2.4,1 \mathrm{H}), 7.03(\mathrm{~d}, J=3.0,1 \mathrm{H}), 7.06(\mathrm{~d}, J=2.4$, $1 \mathrm{H}), 7.12-7.14(\mathrm{~m}, 2 \mathrm{H})$ and $7.19-7.28(\mathrm{~m}, 4 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR (100 $\mathrm{MHz}) \delta: 33.0,42.0,55.7,110.6,101.9,102.8,110.1,112.2$, $127.1,128.2,128.6,128.7,129.1,131.3,135.5,154.3,160.7$ and
172.9. IR (film, $\nu$ ): 2939, 2833, 1599, 1484, 1443, 1341, 1243, 1144, 1032, 801 and $715 \mathrm{~cm}^{-1}$. MS ( $\mathrm{m} / \mathrm{z}$, rel. int., \%): 319 [24, $\left.(\mathrm{M}+1)^{+}\right], 318\left(100, \mathrm{M}^{+}\right), 303$ (17), 227 (31), 160 (74), 117 (46) and 91 (32). HRMS (ESI-TOF, $m / z$ ): obsd. 341.1260; $\mathrm{C}_{20} \mathrm{H}_{18} \mathrm{~N}_{2} \mathrm{NaO}_{2}\left[(\mathrm{M}+\mathrm{Na})^{+}\right]$requires 341.1260 .

3-((5-Bromo-1H-indol-1-yl)methyl)-5-(4-methylbenzyl)-1,2isoxazole (7d). Brown oil; yield: 76\%. ${ }^{1} \mathrm{H}$ NMR ( 400 MHz ) $\delta: 2.29$ (s, 3H), $3.90(\mathrm{~s}, 2 \mathrm{H}), 5.23(\mathrm{~s}, 2 \mathrm{H}), 5.58(\mathrm{~s}, 1 \mathrm{H}), 6.44(\mathrm{dd}, J=3.2$ and $0.7,1 \mathrm{H}), 7.02-7.08(\mathrm{~m}, 5 \mathrm{H}), 7.19-7.25(\mathrm{~m}, 2 \mathrm{H})$ and $7.72(\mathrm{~d}, J$ $=1.8,1 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 100 MHz ) $\delta: 21.0,32.7,42.1,100.4,102.0$, 110.8, 113.2, 123.5, 124.8, 128.6, 128.9, 129.4, 130.4, 132.3, 134.7, 136.8, 160.2 and 173.5. IR (film, $\nu$ ): 2922, 1600, 1514, 1467, 1434, 1334, 1278, 1187, 792, 762 and $719 \mathrm{~cm}^{-1}$. MS (m/z, rel. int., \%): $382\left[84,(\mathrm{M}+2)^{+}\right], 380\left(85, \mathrm{M}^{+}\right), 277(26), 275(26)$, 210 (70), 208 (74), 196 (64), 130 (18), 129 (100), 128 (22) and 105 (31). HRMS (ESI-TOF, $m / z$ ): obsd. 403.0402; $\mathrm{C}_{20} \mathrm{H}_{17} \mathrm{BrN}_{2} \mathrm{NaO}[(\mathrm{M}$ $\left.+\mathrm{Na})^{+}\right]$requires 403.0416.

3-((9H-Carbazol-9-yl)methyl)-5-benzyl-1,2-isoxazole (7e). White solid, m.p.: $103-104{ }^{\circ} \mathrm{C}$; yield: $84 \%$. ${ }^{1} \mathrm{H}$ NMR ( 400 MHz , DMSO- $d_{6}$ ) $\delta: 4.02(\mathrm{~s}, 2 \mathrm{H}), 5.67(\mathrm{~s}, 2 \mathrm{H}), 5.93(\mathrm{~s}, 1 \mathrm{H}), 7.18-7.29(\mathrm{~m}$, $6 \mathrm{H}), 7.43-7.47(\mathrm{~m}, 3 \mathrm{H}), 7.66(\mathrm{~d}, J=8.2,2 \mathrm{H})$ and $8.15(\mathrm{~d}, J=7.4$, $2 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 100 MHz, DMSO- $d_{6}$ ) $\delta: 31.7,37.7,100.7,109.1$, 119.1, 120.0, 122.2, 125.6, 126.6, 128.3, 128.4, 135.9, 139.7, 160.2 and 172.3. IR (KBr, $\nu): 3113,3050,3030,2927,1598,1487,1456$, $1425,1329,1261,1207,751,725$ and $705 \mathrm{~cm}^{-1}$. MS ( $\mathrm{m} / \mathrm{z}$, rel. int., \%): 339 [11, ( $\left.\mathrm{M}+1)^{+}\right], 338\left(46, \mathrm{M}^{+}\right), 281$ (17), 247 (17), 207 (56), 180 (100) and 91 (31). Anal. calc.: C, 81.63; H, 5.36; N, 8.28. Found: C, 81.17; H, 5.28; N, 7.89.

3-((9H-Carbazol-9-yl)methyl)-5-(4-methylbenzyl)-1,2-isoxazole (7f). White solid, m.p.: $108-110{ }^{\circ} \mathrm{C}$; yield: $89 \%{ }^{1} \mathrm{H}$ NMR (400 MHz, DMSO- $d_{6}$ ) $\delta: 2.22(\mathrm{~s}, 3 \mathrm{H}), 3.95(\mathrm{~s}, 2 \mathrm{H}), 5.67(\mathrm{~s}, 2 \mathrm{H}), 5.90(\mathrm{~s}$, $1 \mathrm{H}), 7.06(\mathrm{~s}, 4 \mathrm{H}), 7.20-7.24(\mathrm{~m}, 2 \mathrm{H}), 7.43-7.47(\mathrm{~m}, 2 \mathrm{H}), 7.67(\mathrm{~d}, J$ $=8.2,2 \mathrm{H})$ and $8.15(\mathrm{~d}, J=7.7,2 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 100 MHz , DMSO$\left.d_{6}\right) \delta: 20.4,31.4,37.8,100.6,109.2,119.1,120.1,122.2,125.7$, 128.4, 129.0, 132.9, 135.8, 139.7, 160.2 and 172.7. IR ( $\mathrm{KBr}, \nu$ ): 3052, 2954, 2924, 2856, 1730, 1598, 1515, 1483, 1455, 1326, 1206, 1154, 775, 751 and $726 \mathrm{~cm}^{-1} . \mathrm{MS}\left(\mathrm{m} / \mathrm{z}\right.$, rel. int., \%): $352\left(18, \mathrm{M}^{+}\right)$, 180 (34), 84 (63) and 78 (100). HRMS (ESI-TOF, m/z): obsd. $353.1635 ; \mathrm{C}_{24} \mathrm{H}_{21} \mathrm{~N}_{2} \mathrm{O}\left[(\mathrm{M}+\mathrm{H})^{+}\right]$requires 353.1648.

## Acknowledgements

The authors are thankful to MCT/CNPq and CAPES, for financial support. TSK also thanks CONICET and ANPCyT.

## References and notes

1 (a) T. M. V. D. Pinho e Melo, Curr. Org. Chem., 2005, 9, 925958; (b) K. A. Kumar and P. Jayaroopa, Int. J. Pharm., Chem. Biol. Sci., 2013, 3, 294-304.
2 (a) K. Frydenvang, D. S. Pickering, J. R. Greenwood, N. Krogsgaard-Larsen, L. Brehm, B. Nielsen, S. B. Vogensen, H. Hald, J. S. Kastrup, P. KrogsgaardLarsen and R. P. Clausen, J. Med. Chem., 2010, 53, 83548361; (b) U. Madsen, H. Bräuner-Osborne, K. Frydenvang, L. Hvene, T. N. Johansen, B. Nielsen, C. Sánchez, T. B. Stensbøl, F. Bischoff and P. Krogsgaard-Larsen, J.

Med. Chem., 2001, 44, 1051-1059; (c) S. Sakuda and M. Kimura, Toxins of Microorganisms in Comprehensive Natural Products II, ed. L. Mander and H.-W. Liu, Elsevier, Amsterdam, 2010, vol. 4, pp. 411-455; (d) L. Rahbak and C. Christophersen, The Isoxazole Alkaloids, in The Alkaloids: Chemistry and Biology, ed. E. C. Taylor, Wiley, New York, 2001, vol. 57, pp. 185-233.
3 (a) J. J. Talley, D. L. Brown, J. S. Carter, M. J. Graneto, C. M. Koboldt, J. L. Masferrer, W. E. Perkins, R. S. Rogers, A. F. Shaffer, Y. Y. Zhang, B. S. Zweifel and K. Seibert, J. Med. Chem., 2000, 43, 775-777; (b) M. P. Giovannoni, C. Vergelli, C. Ghelardini, N. Galeotti, A. Bartolini and V. Dal Piaz, J. Med. Chem., 2003, 46, 1055-1059; (c) W.-T. Li, D.-R. Hwang, C.-P. Chen, C.-W. Shen, C.-L. Huang, T.-W. Chen, C.-H. Lin, Y.-L. Chang, Y.-Y. Chang, Y.-K. Lo, H.-Y. Tseng, C.-C. Lin, J.-S. Song, H.-C. Chen, S.-J. Chen, S.-H. Wu and C.-T. Chen, J. Med. Chem., 2003, 46, 1706-1715.
4 (a) The Chemistry of Heterocycles: Structures, Reactions, Synthesis, and Applications, ed. T. Eicher, S. Hauptmann and A. Speicher, Wiley, NY, 2013, p. 15; (b) The Isoxazoles: Leflunomide, Muscimol, Flucloxacillin, Sulfamethoxazole, Sitaxentan, Dicloxacillin, Abt-418, Valdecoxib, 5ia, Ibotenic Acid, LLC Books, 2010.
5 (a) F. Bendrath, A. Villinger and P. Langer, J. Organomet. Chem., 2011, 696, 1388-1393; (b) A. Schmidt, D. Michalik, S. Rotzoll, E. Ullah, C. Fischer, H. Reinke, H. Görls and P. Langer, Org. Biomol. Chem., 2008, 6, 2804-2814; (c) S. El Kharrat, P. Laurent and H. Blancou, Synlett, 2009, 9-22.
6 (a) T. M. Kaiser, J. Huang and J. Yang, J. Org. Chem., 2013, 78, 6297-6302; (b) J. B. Sperry and D. L. Wright, Curr. Opin. Drug Discovery Dev., 2005, 8, 723-740; (c) B. Heasley, Angew. Chem., Int. Ed., 2011, 50, 8474-8477.
7 (a) H. Pellisier, Tetrahedron, 2007, 63, 3235-3285; (b) V. Nair and T. D. Suja, Tetrahedron, 2007, 63, 12247-12275; (c) M. Pineiro and T. M. V. D. Pinto e Melo, Eur. J. Org. Chem., 2009, 5287-5307; (d) L. Johnson, J. Powers, F. Ma, K. Jendza, B. Wang, E. Meredith and N. Mainolfi, Synthesis, 2013, 45, 171-173; (e) H.-L. Liu, Z.-F. Geng, S. Y. Zhang and J. Han, Heterocycles, 2014, 89, 1221-1227.

8 (a) W. Shi and A. Lei, Tetrahedron Lett., 2014, 55, 2763-2772;
(b) I. A. Maretina and B. A. Trofimov, Adv. Heterocycl. Chem., 2002, 82, 157-259.
9 (a) X. Liang, C.-J. Lee, X. Chen, H.-S. Chung, D. Zeng, C. R. H. Raetz, Y. Li, P. Zhou and E. J. Toone, Bioorg. Med. Chem., 2011, 19, 852-860; (b) X. Liang, C.-J. Lee, J. Zhao, E. J. Toone and P. Zhou, J. Med. Chem., 2013, 56, 69546966; (c) S. Kyi, N. Wongkattiya, A. C. Warden, M. S. O'Shea, M. Deighton, I. Macreadie and F. H. M. Graichen, Bioorg. Med. Chem. Lett., 2010, 20, 45554557; (d) L. Manzoni, L. Belvisi, A. Bianchi, A. Conti, C. Drago, M. De Matteo, L. Ferrante, E. Mastrangelo, P. Perego, D. Potenza, C. Scolastico, F. Servida, G. Timpano, F. Vasile, V. Rizzo and P. Seneci, Bioorg. Med. Chem., 2012, 20, 6687-6708.
10 (a) L. Zhang, H. Gopee, D. L. Hughes and A. N. Cammidge, Chem. Commun., 2010, 46, 4255-4257; (b) G. Jeschke,
M. Sajid, M. Schulte, N. Ramezanian, A. Volkov, H. Zimmermann and A. Godt, J. Am. Chem. Soc., 2010, 132, 10107-10117; (c) M. Taniguchi and J. S. Lindsey, Tetrahedron, 2010, 66, 5549-5565; (d) G. Venkataramana, P. Dongare, L. N. Dawe, D. W. Thompson, Y. Zhao and G. J. Bodwell, Org. Lett., 2011, 13, 2240-2243.

11 (a) M. L. Lerch, M. K. Harper and D. J. Faulkner, J. Nat. Prod., 2003, 66, 667-670; (b) M. Ladika, T. E. Fisk, W. W. Wu and S. D. Jons, J. Am. Chem. Soc., 1994, 116, 12093-12094; (c) S. F. Mayer, A. Steinreiber, R. V. A. Orru and K. Faber, J. Org. Chem., 2002, 67, 9115-9121; (d) G. Zeni, R. B. Panatieri, E. Lissner, P. H. Menezes, A. L. Braga and H. A. Stefani, Org. Lett., 2001, 3, 819-821; (e) Y.-Z. Zhou, H.-Y. Ma, H. Chen, L. Qiao, Y. Yao, J.-Q. Cao and Y.-H. Pei, Chem. Pharm. Bull., 2006, 54, 1455-1456.
12 (a) D. Lechner, M. Stavri, M. Oluwatuyi, R. Pereda-Miranda and S. Gibbons, Phytochemistry, 2004, 65, 331-335; (b) M. Kobaisy, Z. Abramowski, L. Lermer, G. Saxena, R. E. W. Hancock, G. H. N. Towers, D. Doxsee and R. W. Stokes, J. Nat. Prod., 1997, 60, 1210-1213.

13 (a) W. E. Brenzovich Jr, Angew. Chem., Int. Ed., 2012, 51, 8933-8935; (b) B. Lu, C. Li and L. Zhang, J. Am. Chem. Soc., 2010, 132, 14070-14072; (c) B. M. Trost, Z. T. Ball and K. M. Laemmerhold, J. Am. Chem. Soc., 2005, 127, 1002810038.

14 J. Moran, S. I. Gorelsky, E. Dimitrijevic, M.-E. Lebrun, A.-C. Bédard, C. Séguin and A. M. Beauchemin, J. Am. Chem. Soc., 2008, 130, 17893-17906.
15 (a) C. Praveen, A. Kalyanasundaram and P. T. Perumal, Synlett, 2010, 777-781; (b) M. Ueda, A. Sato, Y. Ikeda, T. Miyoshi, T. Naito and O. Miyata, Org. Lett., 2010, 12, 2594-2597; (c) O. Debleds, E. Gayon, E. Ostaszuk, E. Vrancken and J. M. Campagne, Chem.-Eur. J., 2010, 16, 12207-12213; (d) M. Ueda, Y. Ikeda, A. Sato, Y. Ito, M. Kakiuchi, H. Shono, T. Miyoshi, T. Naito and O. Miyata, Tetrahedron, 2011, 67, 4612-4615; (e) Z. She, D. Niu, L. Chen, M. A. Gunawan, X. Shanja, W. H. Hersh and Y. Chen, J. Org. Chem., 2012, 77, 3627-3633; (f) M. Ueda, S. Sugita, A. Sato, T. Miyoshi and O. Miyata, J. Org. Chem., 2012, 77, 9344-9351.
16 (a) J. P. Waldo and R. C. Larock, Org. Lett., 2005, 7, 52035205; (b) J. P. Waldo and R. C. Larock, J. Org. Chem., 2007, 72, 9643-9647.
17 (a) K. M. Short and C. B. Ziegler Jr, Tetrahedron Lett., 1993, 34, 75-78; (b) E. Gayon, O. Quinonero, S. Lemouzy, E. Vrancken and J.-M. Campagne, Org. Lett., 2011, 13, 6418-6421; (c) P. A. Allegretti and E. M. Ferreira, Chem. Sci., 2013, 4, 1053-1058.
18 (a) G. Himbert, D. Faul and M. Barz, Z. Naturforsch., B: J. Chem. Sci., 1991, 46b, 955-968; (b) E. S. Turbanova, N. P. Stepanova, V. B. Lebedev, V. A. Galishev and A. A. Petrov, J. Org. Chem. USSR (Eng. Transl.), 1983, 19, 204; Z. Org. Khim., 1983, 19, 221; (c) L. Wang, X. Yu, X. Feng and M. Bao, Org. Lett., 2012, 14, 2418-2421; (d) N. S. A. Babu, G. Kaur, N. A. Aslam and M. Karanam, RSC Adv., 2014, 4, 18904-18916.

19 (a) C. Li, X. Liu, M. Yuan, J. Li, Y. Guo, J. Xu, M. Zhu, J. Lv, H. Liu and Y. Li, Langmuir, 2007, 23, 6754-6760; (b) H. E. Montenegro, P. Ramírez-López, M. C. de la Torre, M. Asenjo and M. A. Sierra, Chem.-Eur. J., 2010, 16, 37983814; (c) B. Alcaide, P. Almendros, C. Aragoncillo and G. Gómez-Campillos, Eur. J. Org. Chem., 2011, 364-370; (d) B. Alcaide, P. Almendros, R. Carrascosa, R. López and M. I. Menéndez, Tetrahedron, 2012, 68, 10748-10760; (e) H. Gan, H. Liu, Y. Li, Q. Zhao, Y. Li, S. Wang, T. Jiu, N. Wang, X. He, D. Yu and D. Zhu, J. Am. Chem. Soc., 2005, 127, 12452-12453.
20 (a) B. L. Kuhn, M. P. Fortes, T. S. Kaufman and C. C. Silveira, Tetrahedron Lett., 2014, 55, 1648-1652; (b) C. C. Silveira, S. R. Mendes, G. M. Martins, S. C. Schlösser and T. S. Kaufman, Tetrahedron, 2013, 69, 9076-9085; (c) C. C. Silveira, S. R. Mendes, M. A. Villetti, D. F. Back and T. S. Kaufman, Green Chem., 2012, 14, 2912-2921; (d) M. P. Fortes, M. M. Bassaco, T. S. Kaufman and C. C. Silveira, RSC Adv., 2014, 4, 34519-34530.

21 (a) Y. Kikugawa and Y. Miyake, Synthesis, 1981, 461-462; (b) H. Zhang, D. Liu, C. Chen, C. Liu and A. Lei, Chem.-Eur. J., 2011, 17, 9581-9585.
22 (a) Z. Ma, X. Wang, S. Wei, H. Yang, F. Zhang, P. Wang, M. Xie and J. Ma, Catal. Commun., 2013, 39, 24-29; (b) A. Narani, R. K. Marella, P. Ramudu, K. S. Rama Rao and D. R. Burri, RSC Adv., 2014, 4, 3774-3781; (c) K. Yin, C. Li, J. Li and X. Jia, Green Chem., 2011, 13, 591-593.

23 (a) L. Shu, M. Müri, R. Krupke and M. Mayor, Org. Biomol. Chem., 2009, 7, 1081-1092; (b) H.-F. Jiang and A.-Z. Wang, Synthesis, 2007, 1649-1654; (c) G. Kumaraswamy and K. Sadaiah, Tetrahedron, 2012, 68, 262-271; (d) M. Turlington, Y. Du, S. G. Ostrum, V. Santosh, K. Wren, T. Lin, M. Sabat and L. Pu, J. Am. Chem. Soc., 2011, 133, 11780-11794.
24 W. Yin, C. He, M. Chen, H. Zhang and A. Lei, Org. Lett., 2009, 11, 709-712.
25 (a) J.-A. He, K. Yang, J. Kumar, S. K. Tripathy, L. A. Samuelson, T. Oshikiri, H. Katagi, H. Kasai, S. Okada, H. Oikawa and H. Nakanashi, J. Phys. Chem. B, 1999, 103, 11050-11056; (b) T. Yaji, S. Isoda, N. Kawase, T. Kobayashi and K. Takeda, Mol. Cryst. Liq. Cryst., 2000, 349, 107-110; (c) M. Arai and S. Okada, Chem. Lett., 2006, 35, 1012-1013;
(d) Y. Miyazaki, K. Okamoto, K. Tsuchiya and K. Ogino, Chem. Lett., 2013, 42, 1217-1219; (e) K. C. Yee, Carbazolyl diacetylenic compounds, US Pat. 4,125,534, 1978.
26 (a) J. Chen, S. K. Spear, J. G. Huddleston and R. D. Rogers, Green Chem., 2005, 7, 64-82; (b) R. A. Sheldon, Green Chem., 2005, 7, 267-278; (c) Y.-N. Li, J.-L. Wang and L.-N. He, Tetrahedron Lett., 2011, 52, 3485-3488.

27 Y. Wang, D. Wei, W. Zhang, Y. Wang, Y. Zhu, Y. Jia and M. Tang, Org. Biomol. Chem., 2014, 12, 75037514.

28 (a) A. M. Beauchemin, Org. Biomol. Chem., 2013, 11, 70397050; (b) M.-E. Lebrun, J. Y. Pfeiffer and A. M. Beauchemin, Synlett, 2009, 1087-1090.
29 N. J. Cooper and D. W. Knight, Tetrahedron, 2004, 60, 243269.

30 F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless and V. V. Fokin, J. Am. Chem. Soc., 2005, 127, 210-216.
31 E. H. Krenske, E. C. Davison, I. T. Forbes, J. A. Warner, A. L. Smith, A. B. Holmes and K. N. Houk, J. Am. Chem. Soc., 2012, 134, 2434-2441.
32 (a) A. M. Beauchemin, J. Moran, M.-E. Lebrun, C. Séguin, E. Dimitrijevic, L. Zhang and S. I. Gorelsky, Angew. Chem., Int. Ed., 2008, 47, 1410-1413; (b) J. Moran, J. Y. Pfeiffer, S. I. Gorelsky and A. M. Beauchemin, Org. Lett., 2009, 11, 1895-1898.
33 (a) L. Antonov, Tautomerism: Methods and Theories, Wiley, NY, 2013, pp.128-129; (b) A. S. K. Hashmi, Synthesis of Allenes by Isomerization Reactions, in: Modern Allene Chemistry, ed. N. Krause and A. S. K. Hashmi, Wiley, Heidelberg, 2004, ch. 1.
34 F. Heaney and C. O'Mahony, J. Chem. Soc., Perkin Trans. 1, 1998, 341-350.
35 M. P. Muñoz, Chem. Soc. Rev., 2014, 43, 3164-3183.
36 (a) S. A. Samsoniya, N. A. Esakiya and N. N. Suvorov, Chem. Heterocycl. Compd., 1991, 27, 366-369; (b) N. Haider and J. Käferböck, Tetrahedron, 2004, 60, 6495-6507; (c) N. Haider, T. Kabicher, J. Käferböck and A. Plenk, Molecules, 2007, 12, 1900-1909; (d) R. Gibe, J. R. Green and G. Davidson, Org. Lett., 2003, 5, 1003-1005; (e) V. G. Lendel, B. I. Pak, I. M. Balog, M. V. Kiyak and Yu V. Migalina, Chem. Heterocycl. Compd., 1990, 26, 108-110.


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    $\dagger$ Electronic supplementary information (ESI) available: Selected spectra of intermediates and final products. CCDC 1027013. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ra11571f

