RSC Advances

PAPER

Cite this: *RSC Adv.*, 2014, **4**, 34519

A convenient eco-friendly system for the synthesis of 5-sulfenyl tetrazole derivatives of indoles and pyrroles employing $CeCl_3 \cdot 7H_2O$ in PEG-400†

Margiani P. Fortes,[a] Mariana M. Bassaco,[a] Teodoro S. Kaufman*[b] and Claudio C. Silveira*[a]

Received 11th June 2014
Accepted 29th July 2014

DOI: 10.1039/c4ra05625f

www.rsc.org/advances

The use of $CeCl_3 \cdot 7H_2O$ in polyethyleneglycol 400 (PEG-400), as an efficient and eco-friendly promoter system for the convenient synthesis of 5-sulfenyl tetrazoles derived from indoles and pyrroles, is reported. The synthesis entails the [3 + 2] cycloaddition reaction of NaN_3 with 3-thiocyanato indoles (including 3,3′-di-thiocyanato-1*H*,1*H*′,2,2′-biindoles) and 2-thiocyanato pyrroles. The thiocyanates were conveniently obtained by the oxone-mediated thiocyanation of differently substituted starting indoles, 1*H*,1*H*′,2,2′-biindoles and *N*-aryl pyrroles with NH_4SCN. The scope and limitations of the transformation were also studied.

Introduction

The tetrazoles are azapyrrole-type five-membered ring 6π-heterocycles, containing four contiguous nitrogen atoms,[1a] which have received much attention in recent years due to their diverse technological uses and numerous applications in biology. Tetrazoles are not found in Nature;[1b] however, due to their acidic character, metabolic stability and close structural similarity with carboxylic acids, they are considered isosteres of the latter.[2]

The 5-sulfenyl tetrazoles are a small and special group of tetrazoles that are progressively becoming more ubiquitous; they can be found as a distinguished motif in active pharmaceutical ingredients and other potentially bioactive molecules (Fig. 1).

Their derivatives have been shown to act as leukotriene antagonists (**A–C**)[3a–c] and acyl-CoA cholesterol acyltransferase (ACAT) inhibitors (**D**),[3d] being potentially useful in therapies for allergy and hypercholesterolemia, respectively.

Other compounds featuring a 5-sulfenyl tetrazole moiety, such as **D**, were also found to be selective agonists of the EP4 subtype of prostaglandin E2 receptors,[3e] with application in the treatment of glaucoma and other prostaglandin-mediated conditions, as in the case of indole derivative **F**.[3f]

On the other hand, the 5-sulfenyl tetrazole motif has also been included in antibiotics (**G**),[3g,h] antiviral (**H**),[3i] analgesic (**I**)[3j] and antitubercular (**J**)[3k] agents.

The technological applications of 5-sulfenyl tetrazoles include their use as 1*H*-tetrazole replacements in oligonucleotide synthesis,[4a,b] due to the improved solubility and acidity caused by the thioether moiety, which enhances their ability to act as activators[4c,d] and promoters of phosphate ester hydrolysis.[4e] They are also suitable capping agents for the stabilization of CdS and noble metal (Au, Ag, Pd, Pt) nanoparticles.[4f,g]

5-Thiotetrazoles have been employed as ligands,[5a] taking advantage of their relative stability to oxidation and high coordination ability.[5b] Their capacity to form stable complexes with various metal ions is widely used in photo processes and for protection of metals against corrosion.[5c]

Despite their usefulness, systematic research work devoted to the synthesis of 5-sulfenyl tetrazoles as a class of molecules has been rather scarce.[6] In fact, a critical analysis of the literature revealed that besides the pioneering work of Lieber and Enkoji,[4c] they have been mostly synthesized during studies on 5-aryl(alkyl) tetrazoles, and together with the latter.[7]

Approaches to the synthesis of 5-alkyl(aryl)thiotetrazoles include (a) the nucleophilic displacement of suitable leaving groups with 5-tetrazoyl mercaptan or its tautomer;[8a–e] (b) the reaction of isothiocyanates and azides, which yields tetrazole-thiols/thiones, that can exist in different tautomeric forms;[8e,f] (c) the reaction of substituted thiosemicarbazides with aralkyl chlorides, followed by diazotization and reaction of the product with a Friedel Crafts catalyst;[8g] (d) the S_NAr reaction of arylsulfonyl tetrazoles with thiophenols,[8h] and (e) the [3 + 2] cycloaddition reaction between thiocyanates and sources of hydrazoic acid, such as azides.

[a]*Departamento de Química, Universidade Federal de Santa Maria 97105-900, Santa Maria, RS, Brazil. E-mail: silveira@quimica.ufsm.br; margiani.fortes@ufsm.br; mariquimica@gmail.com; Fax: +55-55-3220-8754; Tel: +55-55-3220-8754*

[b]*Instituto de Química Rosario (CONICET-UNR), Suipacha 531, S2002LRK, Rosario, SF, Argentina. E-mail: kaufman@iquir-conicet.gov.ar; Fax: +54-341-4370477; Tel: +54-341-4370477*

† Electronic supplementary information (ESI) available: Selected spectra of intermediates and final product. See DOI: 10.1039/c4ra05625f

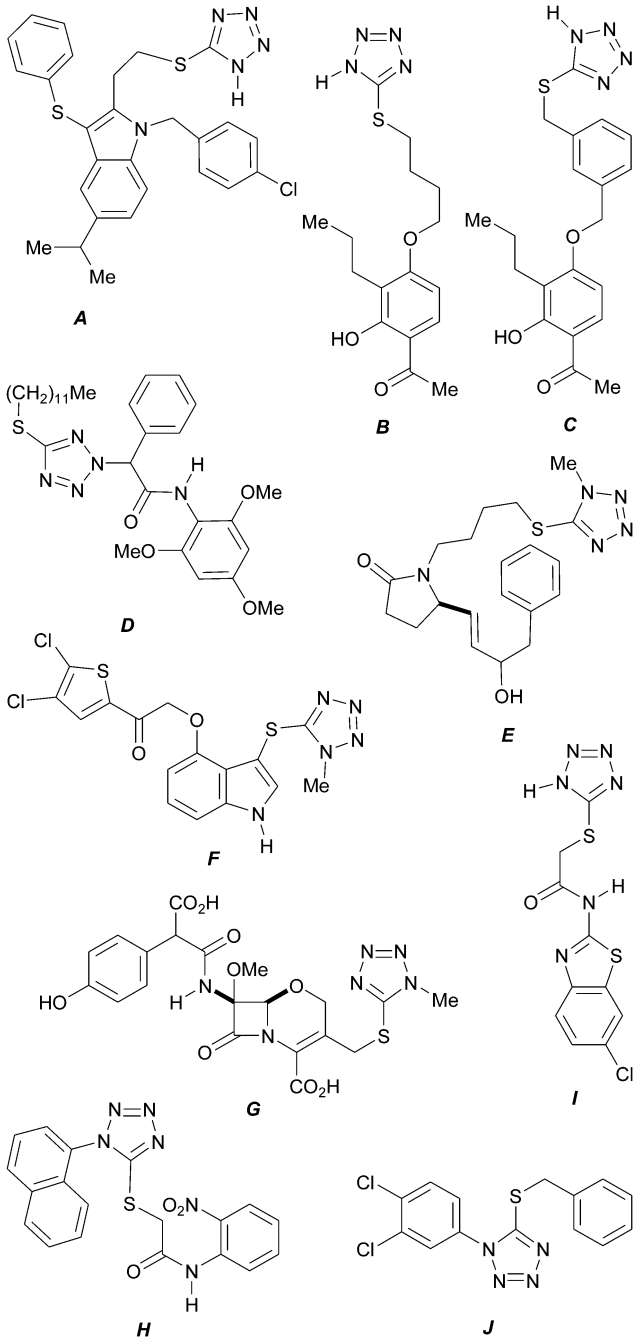


Fig. 1 Some selected examples of bioactive 5-sulfenyl tetrazole derivatives.

Unfortunately, each one of these approaches suffers from some disadvantage, including long reaction times, the use of toxic metals, polar aprotic solvents, expensive reagents, harsh reaction conditions, water sensitivity or the use of stoichiometric amounts of promoters.

The [3 + 2] cycloaddition between thiocyanates and hydrazoic acid is the most widely employed approach towards tetrazoles. The reaction is promoted by protic and Lewis acids, including $Et_3N{\cdot}HCl$,[9a] NH_4Cl,[6d] magnetic Fe_3O_4 nanoparticles[6e] and ionic liquids,[9b] while the main source of hydrazoic acid is NaN_3;[3i,6b,c] however, Et_2AlN_3,[9c] aluminium azide[9d] and Bu_3SnN_3 (ref. 9e) have also been employed.

The discovery of $ZnBr_2$ as a stoichiometric promoter in aqueous or hydroalcoholic medium, was a major breakthrough in the synthesis tetrazoles in general,[7c,10a,b] which also impacted on 5-sulfenyl tetrazole chemistry.[9e,10c] Since then, different zinc derivatives, including $ZnCl_2$, mesoporous ZnS nanospheres and Zn/Al hydrotalcite have also been disclosed as suitable alternative promoters.[11]

Based on computational and experimental studies, Himo *et al.*[12a] proved the role of Zn in the reaction between MeCN, MeN_3 and $ZnBr_2$, demonstrating that the activation energy of the reaction experiences a significant decrease (4–11 kcal mol^{-1}) when the nitrogen of the nitrile group is coordinated to the metal ion. Furthermore, a recently reported organocatalyst for the synthesis of tetrazoles also acts through nitrile activation.[12b]

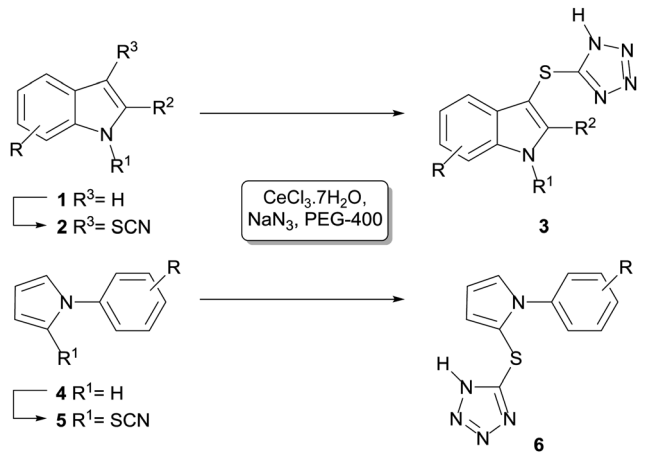
On the other hand, lanthanide salts are useful as promoters and catalysts in organic synthesis.[13] Some of them are interesting because of their ready availability, ease of handling and low toxicity, as well as for their air and water stability.[14] Among them, cerium compounds have found extensive use in organic synthesis.[15]

During the past decade, $CeCl_3$ has been continuously fascinating the scientific community with regards to its exploitation as promoter of a growing array of organic reactions.[16a] The salt, which qualifies as a "3E-catalyst" (eco-friendly, efficient and economical),[6e] is a safe, non-toxic, inexpensive and water-tolerant compound, which has been used in its anhydrous and heptahydrate forms, associated with NaI[16b–d] and as a solid-supported reagent.[16e–h]

We have focused our recent research in trying to develop new applications for $CeCl_3{\cdot}7H_2O$ and related compounds, as a means to find cleaner and more efficient methodologies for carrying out classical reactions. One of the keys to waste minimization and environmental friendliness is the substitution of stoichiometric amounts of reagents in these classical transformations with lower loads of reagents, as well as the use of cleaner or catalytic alternatives.

Aiming to extend this research to other important organic processes such as addition and cycloaddition reactions, we have recently reported several $CeCl_3$-mediated useful transformations.[13c,17,18] We have also developed a study focused on the synthesis of 5-sulfenyl tetrazoles and became interested in these heterocycles.[6a]

Being important structural motifs, the synthesis of 5-sulfenyl tetrazole derivatives has been arousing continued attention during the last decade. Therefore, we inquired into the application of Ce^{III} for the tetrazoylation of thiocyanates and herein we report the use of $CeCl_3{\cdot}7H_2O$ in polyethyleneglycol 400 (PEG-400) as a promoting system for the development of a mild, efficient and eco-friendly synthesis of 5-sulfenyl tetrazole derivatives (**3**, **6**) of indoles (**1**) and pyrroles (**4**), based on the [3 + 2] cycloaddition reaction of their corresponding thiocyanates (**2**, **5**) with NaN_3 (Scheme 1).



Scheme 1 Proposed reaction sequence towards 5-sulfenyl tetrazoles.

Results and discussion

Employing 1-methyl-3-thiocyanato-1*H*-indole (**2a**, 0.5 mmol) as model heterocycle, the establishment of the optimum conditions was performed, by reacting the latter with NaN_3 (0.6 mmol, 1.2 equiv.) under promotion by $CeCl_3 \cdot 7H_2O$. The efficiency of the transformation was evaluated in different solvents and under various reaction temperatures and amounts of promoter (Table 1).

The 2-PrOH : H_2O (1 : 1) system was chosen as a starting point, for its efficiency as reaction medium for the synthesis of 5-sulfenyl tetrazoles under zinc assistance.[6a,f]

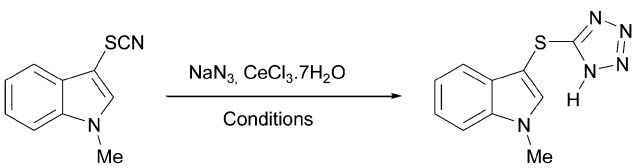
Using 0.5 equiv. of $CeCl_3 \cdot 7H_2O$ under reflux for 8 h, there was a limited conversion of the starting material and the product (**3a**) was isolated in only 18% yield (entry 1). When H_2O was used as solvent, the reaction also proceeded very slowly; however, 25% of **3a** was obtained after a reflux period of 8 h (entry 2). In MeCN, which is effective for carrying out [3 + 2] cycloadditions leading to pyrroles,[18] no product was detected (entry 3).

Considering our interest in developing environmentally friendly processes, the transformation was next attempted in glycerol[19] and PEG-400.[20] These solvents showed up as great alternative reaction media to those commonly used in synthesis, because they are miscible with water, easily accessible, biodegradable, and of low toxicity.

When run in glycerol, the solvent of choice for the Ce^{III}-promoted synthesis of 3,3′-bis(indolyl)methanes,[21] a 70% yield of **3a** was realized after heating for 3 h at 110 °C (entry 4). A parallel blank reaction carried out in the absence of $CeCl_3$ demonstrated the requirement of the salt to promote the transformation (entry 5), since no product was observed after 8 h.[22] On the other side, the use of PEG-400 as solvent produced 77% of **3a** after heating for 3 h at 110 °C (entry 7).

The 5-sulfenyl tetrazoles are known to decompose at high temperatures, reverting to the thiocyanates and hydrazoic acid; this explains the low yields attained at high temperatures and/or after prolonged heating.[4c] Therefore, lowering the reaction

Table 1 Optimization of the synthesis of the 5-sulfenyl tetrazoles



2a **3a**

Entry no.	Solvent	Promoter (equiv.)	Temp. (°C)	Time (h)	Yield[a] (%)
1	2-PrOH : H_2O (1 : 1)	0.5	Reflux	8	18
2	H_2O	0.5	Reflux	8	25
3	MeCN	0.5	Reflux	8	—
4	Glycerol	0.5	110	3	70
5	Glycerol	—	110	8	—
6	Glycerol	0.5	95	3	69
7	PEG-400	0.5	110	3	77
8	PEG-400	0.5	95	3	89
9	PEG-400	0.3	95	3	89
10	PEG-400	0.2	95	3	90
11	PEG-400	0.1	95	8	78
12	PEG-400	0.2	80	3	92
13	PEG-400	0.2	65	3	71
14	PEG-400	0.2	80	3.5	76[b]
15	PEG-400 : H_2O (10 : 1)	0.2	80	3.5	29[c]

[a] Isolated yields after column chromatography. [b] Carried out with anhydrous $CeCl_3$; 18% of starting material was recovered (92% yield based on recovered starting material). [c] Starting material (65%) was recovered.

temperature to 95 °C avoided some decomposition[6d] and afforded the product in an improved 89% yield (entry 8). Interestingly, under the same conditions, glycerol furnished only 69% of **3a** (entry 6). This result confirmed PEG-400 as the solvent of choice for this transformation (entry 8 *vs.* entry 6).

PEG-400 has emerged as one of the suitable solutions in the global chemical strategy to avoid volatile organic solvents, especially chlorinated ones, which may create environmental problems. PEG-400 is an affordable, recyclable and eco-friendly solvent for metal-mediated transformations.[23] It is miscible with water and many different organic solvents, and has successfully been utilized in different $CeCl_3 \cdot 7H_2O$-promoted reactions.[23d,e]

The amount of promoter was next optimized. Lowering the quantity of added $CeCl_3 \cdot 7H_2O$ to 0.3 equiv. afforded 89% of **3a** (entry 9). The yield of **3a** was 90% in the presence of 0.2 equiv. of the salt (entry 10) and dropped to 78% when the promoter was present at a 0.1 equiv. level; the latter process also required 8 h of reaction time (entry 11).

Using the optimum amount of promoter, the transformation was further fine-tuned. When the reaction was performed at 80 °C, the product was obtained in 92% yield (entry 12) while additional reduction of the temperature to 65 °C, exhibited a decrease in efficiency, reaching 71% yield after 3 hours of reaction (entry 13). Finally, the effects of adding water and using anhydrous $CeCl_3$ were explored. It was concluded that drying the salt reduces the reaction rate, but has no marked incidence on the yield of the transformation (entry 14). On the other side, addition of 10% water to PEG-400 furnished only 29% of **3a** after 3.5 h and most of the starting material (65%) was recovered (entry 15).

From these results it was concluded that, opposite to the use of $ZnBr_2$,[6a] there is no need of stoichiometric amounts of the Ce^{III} promoter or high reaction temperatures for satisfactory outcomes. The conditions employed in entry 12 (heating at 80 °C for 3 h in PEG-400, in the presence of 0.2 equiv. $CeCl_3 \cdot 7H_2O$), were considered optimum. Interestingly, the transformation was efficient, without requiring special protection against atmospheric oxygen or humidity.

With the optimized reaction conditions for the synthesis of **3a** in hand, the scope and limitations of the transformation were studied next, employing various thiocyanates derived from indoles and *N*-phenyl pyrroles.

The starting indoles (**1a–n**) and the pyrroles employed (**4a–c**) were synthesized according to the literature[18,24] and properly characterized before use.[25] Their corresponding thiocyanates **2a–n** and **5a–c** were prepared in high yields by reaction of the heterocycles with NH_4SCN, using oxone as oxidizing agent. Based on our previous results,[18] and adapting the work of Wu,[26] a limited excess of NH_4SCN was employed in order to avoid formation of poly-thiocyanated compounds. When the thiocyanates **2** and **5** were submitted to the Ce^{III}-promoted [3 + 2] cycloaddition reaction towards 5-sulfenyl tetrazoles, it was observed that, in general, the products were obtained in good to excellent yields and in short reaction times (Table 2).

The *N*-substituted indole derivatives carrying alkyl and aryl groups (**2a–h**) afforded the expected products in excellent yields (88–93%) after 3–4 h (entries 1–8). In addition, the nature of the substituents did not show any marked influence on the reactivity.

On the other hand, the *N*-unsubstituted indoles furnished slightly lower yields of product than the corresponding *N*-substituted counterparts. This was ascribed in part to the lower solubility of the starting materials **2i–l** in PEG-400. For instance, compound **2i** gave only 74% of **3i** after heating for 4 hours, exhibiting the presence of insoluble material in the reaction mixture (entry 9).

The use of glycerol as an alternative solvent overcame the low solubility obstacle, affording 93% yield of **3i** in 3 h (entry 10), and improved the yields of the corresponding 5-sulfenyl tetrazoles derived from other *N*-unsubstituted indole thiocyanates (entries 12 and 14).

Not unexpectedly, the reaction with the 5-methoxy derivative **2k** required 8 h. On the other hand, the outcome with the 5-(*p*-tolyl) example **2l** was better in PEG-400 than in glycerol (entries 15–16), while despite the lack of an *N*-substituent, the 2-methyl substituted compound **2m** did not exhibit solubility problems in PEG-400, affording 82% yield of **3m** after 4 h (entry 17).

Interestingly, thiocyanato-nitrile **2n**, prepared by cyanation of 5-bromoindole (**1j**) followed by the usual thiocyanation conditions,[27] yielded exclusively 87% of the tetrazole derivative **3n** (entry 18). The yield of **3n** increased to 91% when the amounts of $CeCl_3 \cdot 7H_2O$ and NaN_3 were doubled, suggesting the relative unability of the Cerium-based system to tetrazoylate these benzonitriles.

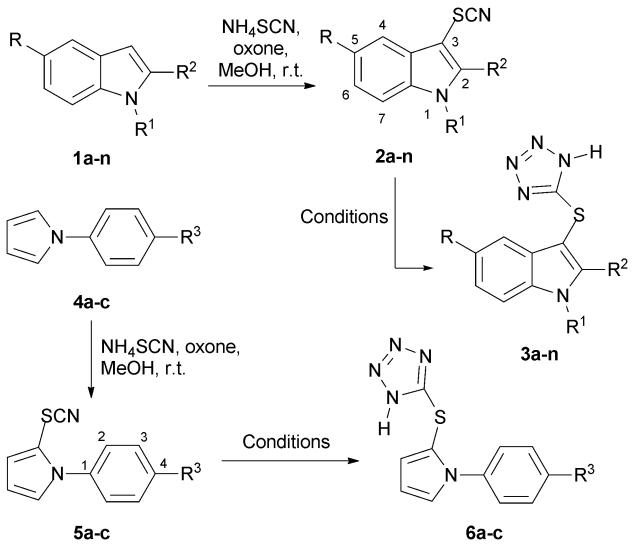
A competition experiment between thiocyanate **2a** and benzonitrile afforded 77% of **3a** and none of 5-phenyltetrazole (entry 19), confirming that thiocyanates are much more easily converted into the corresponding tetrazoles than the nitriles, in agreement with the observation that the related cyanates (nitriles attached to oxygen), react with NaN_3 in H_2O at room temperature, in the absence of a catalyst.[28] In addition, another experiment proved that the Ce^{III} in PEG-400 reagent system is more selective than the traditional $ZnBr_2$ in refluxing H_2O, which gave a 6.6 : 1 mixture of **3a** and 5-phenylsulfenyl tetrazole (91% global yield) after 24 h.

The $CeCl_3 \cdot 7H_2O$ in PEG-400 reagent combination also proved to be an effective promoting system for the synthesis of 5-sulfenyl tetrazole derivatives of *N*-aryl pyrroles (**6a–c**), which were obtained in more than 90% yields from their corresponding thiocyanates **5a–c** after 3 h (entries 20–22).

The structures of the products were confirmed by spectroscopic means, especially employing exhaustive ^1H and ^{13}C NMR data analysis. The main evidence of the formation of the tetrazoles was found in their ^{13}C NMR spectra, where a deshielding effect of the representative thiocyanate carbon (originally resonating at 110–112 ppm) was observed after the [3 + 2] cycloaddition. This resulted in a low intensity signal resonating at approximately δ = 154–156 ppm, characteristic of the tetrazole ring carbon atom. The other carbons exhibited only minor variations in their resonances.

On the other hand, the low resolution electron impact mass spectra of the 5-sulfenyl tetrazolic compounds in the series **3a–n** and **6a–c** also exhibited some common fragmentation patterns.

Table 2 Synthesis of 3-indolyl (**2**) and 2-pyrrolyl (**5**) thiocyanates and their transformation into 5-sulfenyl tetrazoles **3** and **6** mediated by $CeCl_3 \cdot 7H_2O$ in PEG-400



Entry no.	R	R^1	R^2	R^3	St. mat./prod. no.	Time[a] (h)	Yield[b] (%) 2/5	3/6
1	H	Me	H	—	**2a/3a**	3	96	92
2	Br	Me	H	—	**2b/3b**	3	95	90
3	MeO	Me	H	—	**2c/3c**	3	82	88
4	*p*-Tolyl	Me	H	—	**2d/3d**	3	89	92
5	H	Ph	H	—	**2e/3e**	3	90	89
6	H	4-ClC_6H_4	H	—	**2f/3f**	3.5	88	93
7	H	4-$MeOC_6H_4$	H	—	**2g/3g**	4	85	91
8	H	*n*-C_8H_{17}	H	—	**2h/3h**	3.5	95	91
9	H	H	H	—	**2i/3i**	4	93	74
10	H	H	H	—	**2i/3i**	3		93[c]
11	Br	H	H	—	**2j/3j**	3	87	80
12	Br	H	H	—	**2j/3j**	3		96[c]
13	MeO	H	H	—	**2k/3k**	8	83	47
14	MeO	H	H	—	**2k/3k**	8		63[c]
15	*p*-Tolyl	H	H	—	**2l/3l**	8	84	78
16	*p*-Tolyl	H	H	—	**2l/3l**	8		52[c]
17	H	H	Me	—	**2m/3m**	4	90	82
18	CN	H	H	—	**2n/3n**	2	95	87
19	H	Me	H	—	**2a/3a**	3		77[d]
20	—	—	—	H	**5a/6a**	3	89	90
21	—	—	—	MeO	**5b/6b**	3	92	92
22	—	—	—	Cl	**5c/6c**	3	92	94

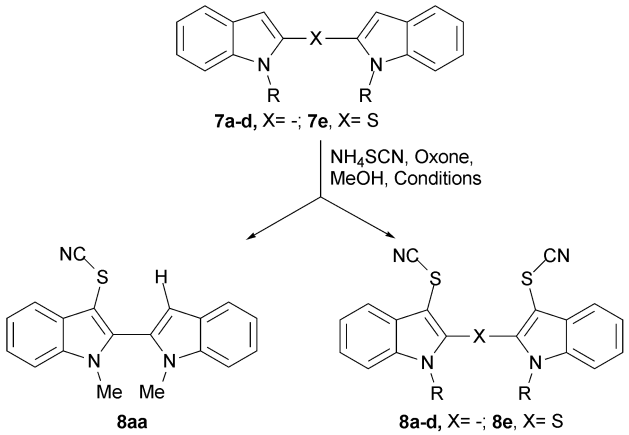
[a] Conditions: thiocyanate (0.5 mmol), NaN_3 (0.6 mmol), $CeCl_3 \cdot 7H_2O$ (0.1 mmol), PEG-400 (0.5 mL), 80 °C. [b] Isolated yields after column chromatography. [c] In glycerol (0.5 mL). [d] Competition experiment in the presence of 1 equivalent of benzonitrile.

Besides the signal of the molecular ion M^+, a characteristic $[(M - 69)^+$ fragment was observed (commonly the base peak), representing the loss of the tetrazole ring.

In order to further explore the scope and limitations of this Ce^{III}-assisted 5-sulfenyltetrazole synthesis, the transformation was extended to the more complex 1,1′-dimethyl-1*H*,1′*H*-2,2′-biindole (**7a**).[29] However, reaction of the latter with 3 equiv. of both, NH_4SCN and oxone, in MeOH at room temperature led to the formation of two products after 3 h (Table 3, entry 1). These were unequivocally identified as the expected di-thiocyanate **8a** (71% yield) and the mono-substituted product (**8a′**, 19%), which can be considered a reaction intermediate.

According to the above observation, the reaction time was increased to 18 h, which allowed the isolation of 89% of **8a** (entry 2). Increasing the temperature to 45 °C reduced the reaction time to 6 h, while keeping high the product yield (entry 3, 91%). Therefore, in view of the cleanliness of the transformation, its slow pace was overcome by submitting the reaction mixture to reflux during 1 h, which afforded 91% of the required di-thiocyanate (entry 4).

Table 3 Optimization of the thiocyanation of 1*H*,1′*H*-2,2′-bisindoles (**7**)[a]



Entry no.	R	Temp. (°C)	Time (h)	St. mat./prod. no.	Product yield[b] (%)
1	Me	Ambient	3	**7a**/**8a**	71 (+**8a′**, 19%)
2	Me	Ambient	18	**7a**/**8a**	89
3	Me	45	6	**7a**/**8a**	91
4	Me	Reflux	1	**7a**/**8a**	91
5	H	Reflux	1	**7b**/**8b**	87
6	Ph	Reflux	1	**7c**/**8c**	81
7	Bu	Reflux	1	**7d**/**8d**	94
8	H	Reflux	1	**7e**/**8e**	<10
9	H	Ambient	0.5	**7e**/**8e**	95[c]

[a] Conditions: indole derivative (0.5 mmol), oxone (3 equiv.), NH_4SCN (3 equiv.), MeOH (5 mL). [b] Isolated yields after column chromatography. [c] Carried out with CAN (6 equiv.) and NH_4SCN (6 equiv.).

These optimized conditions were employed for the synthesis of 1*H*,1′*H*-2,2′-biindole 3,3′-di-thiocyanates **8b–d** from the corresponding 1*H*,1′*H*-2,2′-biindoles **7b–d**,[30] bearing different substituents on the nitrogen atom.

Unfortunately, the attempted di-thiocyanation of the related di(1*H*-indol-2-yl)sulfide (**7e**)[30e] under the optimized conditions met with failure and a complex mixture of products was obtained, which included a minor amount of the expected **8e**. This outcome may be a result of the oxone-mediated oxidation of the sulfur bridge to the sulfoxide and sulfone derivatives.[31a]

Therefore, a milder and more selective approach was selected, which employs ceric ammonium nitrate (CAN) as an environmentally friendly oxidant; this cleanly furnished 95% of **8e** after 30 min. at room temperature.[31b]

The ^1H and ^{13}C NMR spectra of the symmetric compounds **8a–e** were relatively simple, exhibiting a single set of signals corresponding to both indole nuclei, consistent with the free rotation of these heterocyclic moieties around both, the indole–indole and the indole–S bonds.

On the other hand, besides the molecular ion peaks (M^+) of the di-thiocyanates, the major fragments observed in their mass spectra were those related to the loss of one or both SCN moieties [$(M - 58)^+$ and $(M - 116)^+$, respectively], the deprivation of both SCN and CN groups [$(M - 85)^+$] or the loss of SCN together with S [$(M - 91)^+$]. The heterocycles exhibited the typical C≡N stretching band of the SCN moiety at 2100–2200 cm^{-1} in their infrared spectra.

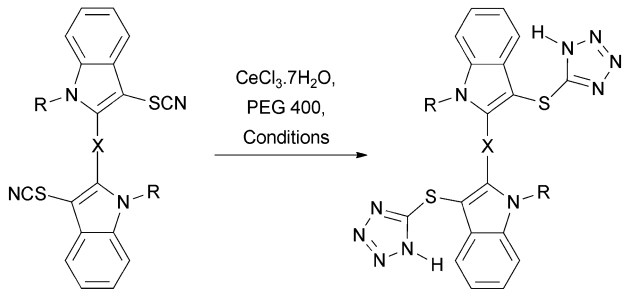
With convenient routes towards the 3,3′-di-thiocyanates **8a–e** in hands, the effectiveness of the Ce^{III}-assisted 5-sulfenyltetrazole synthesis was further tested with these heterocycles. The results (Table 4) indicated that good to excellent yields could be attained in 3 h under the optimized reaction conditions.

Interestingly, however, the *N*-unsubstituted biindole **8b** afforded 49% of **9b** (entry 2) in mixture with side products that exhibited low solubility in PEG-400, which precluded access of good yields of the heterocycle under the standardized conditions. This seems to be a drawback of the proposed tetrazoylating system, since **9b** could be obtained employing $ZnBr_2$ in 2-PrOH : H_2O (1 : 1, v/v)[6f] in more satisfactory yield (entry 3).

Although the exact intimate details remain unknown, from the mechanistic point of view, one can speculate that the Ce^{III} salt coordinates with the nitrogen of the thiocyanate group in **2** or **5**, increasing the polarization of the C≡N moiety and turning it prone to a nucleophilic attack by the azide anion (**i**) to furnish **ii**. This should give way to formation of the intermediate Cerium^{III} tetrazolate (**iii**), as shown in Scheme 2. The formation of Cerium^{III} azide, that may drive the reaction, cannot be ruled out. This has been included in the list of reagents capable of furnishing tetrazoles, under Zinc promotion.[32]

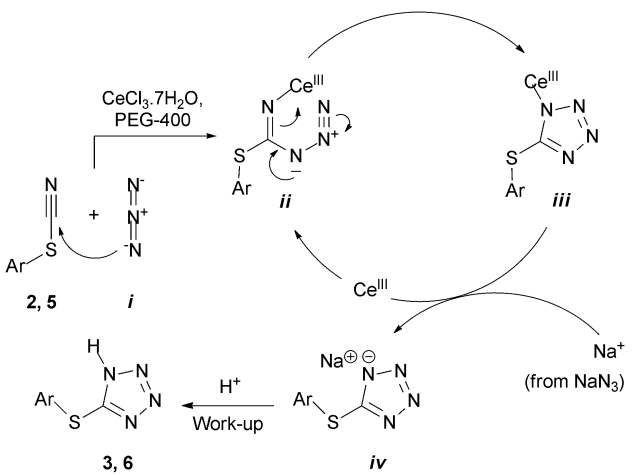
In turn, **iii** may attract a proton from the reaction medium or, most probably exchange with Na^+, furnishing **iv** and

Table 4 Synthesis of bis-(5-sulfenyl tetrazoles) **9a–e** derived from 3,3′-di-thiocyanates of 1*H*,1′*H*-2,2′-bis and di-indoles (**8a–e**)[a]



Entry no.	R	X	Time (h)	St. mat./prod. no.	Yield[b] (%)
1	Me	—	3	**8a**/**9a**	93
2	H	—	3	**8b**/**9b**	49
3	H	—	2	**8b**/**9b**	90[c]
4	Ph	—	3.5	**8c**/**9c**	85
5	Bu	—	3.5	**8d**/**9d**	96
6	H	S	3	**8e**/**9e**	80

[a] Conditions: substrate (0.25 mmol), NaN_3 (0.6 mmol), $CeCl_3 \cdot 7H_2O$ (0.1 mmol), PEG-400 (1 mL), heated at 80 °C. [b] Isolated yields after column chromatography. [c] Carried out using substrate (0.25 mmol), NaN_3 (0.6 mmol) and $ZnBr_2$ (0.5 mmol) in 2-PrOH : H_2O (1 : 1, 5 mL), at reflux.



Scheme 2 Proposed reaction mechanism for the Ce^{III}-promoted synthesis of 5-sulfenyl tetrazoles.

regenerating the Ce^{III}, which reenters into the cycle. Final addition of HCl during the work-up frees the 5-sulfenyl tetrazole (**3**, **6**). That the reaction seems to run at a slower pace when anhydrous $CeCl_3$ is employed, probably reflects that H_2O also plays a key role in the transformation, probably during the stages of formation of **ii** or when **iii** is converted into **iv**.[33]

Interestingly enough, in some $CeCl_3$-promoted reactions, the presence of small amounts of water is essential for success,[33b] and it has been speculated that this is related to the H_2O-mediated increase in Lewis acidity of the Ce^{III}.[33c]

In conclusion, a facile and efficient synthesis of 5-sulfenyl-tetrazoles (**3a–m** and **6a–c**) from thiocyanates derived from 1*H*-indoles, and 1-phenyl pyrroles, under environmentally friendly conditions, is reported. The transformation, which was also successfully applied to bi- and di-indolyl di-thiocyanate derivatives, yielding **9a–e**, entailed a [3 + 2] cycloaddition reaction with NaN_3 in PEG-400 containing 20 mol% $CeCl_3 \cdot 7H_2O$, as a novel tetrazoylation promoter system.

The cycloaddition was optimized with regards to the reaction time, temperature, concentration of the reactants and amount of the promoter. Under the optimized conditions, the process furnished good to excellent yields of the target heterocycles and exhibited satisfactory level of generality. Access to the products was accomplished cleanly and in short time, after a simple acidic workup to free the sodium tetrazolates. No special protection against humidity was required, turning the procedure amenable to use in synthetic organic chemistry.

Experimental section

General information

THF was refluxed over sodium metal utilizing benzophenone as an indicator and distilled immediately before use. Acetonitrile was distilled from CaH_2 under argon and kept over molecular sieves. The alcohols used as solvents were previously distilled. DMF and DMSO were dried over molecular sieves. All other reagents were used as received.

Column chromatography was performed with silica gel 60 H (40–63 μm particle size, 230–400 mesh). Elution was carried out with hexanes or hexanes–EtOAc mixtures. All new compounds gave single spots on TLC plates (Whatman – AL SIL G/UV) run in different solvent systems (hexanes or hexanes–EtOAc). Chromatographic spots were detected by exposure to 254 nm UV light, as well as by treatment with iodine or with an acid solution of vanillin.

Apparatus

Melting points were measured on an MQAPF-301 (Microquímica) instrument and are reported uncorrected. IR spectra were recorded with a Shimadzu Prestige 21 spectrophotometer, as thin films held between NaCl cells or as solid dispersions in KBr disks. The ^1H NMR spectra were acquired at 200 or 400 MHz on Bruker DPX 200 or DPX 400 spectrometers. The peak for $CHCl_3$ in $CDCl_3$ (δ 7.26) was used as the internal standard. Chemical shifts are reported in parts per million on the δ scale and *J*-values are given in Hertz. The ^{13}C NMR spectra were recorded at 50 or 100 MHz on Bruker DPX 200 or DPX 400 spectrometers. The central peaks of DMSO-d_6 and $CDCl_3$ (δ 40.5 and 77.0, respectively) were used as internal standards.

The low resolution mass spectra were obtained in a Shimadzu QP2010 Plus GC-MS instrument. Fragments are described with regards to their *m*/*z* ratios, in terms of relative intensity (%) of their signals. The high resolution mass spectra were obtained with a Bruker MicroTOF-Q II instrument (Bruker Daltonics, Billerica, MA), using sodium formate. Detection of the ions was performed in the electrospray ionization, positive

ion mode. Elemental analyses were performed using a Perkin-Elmer analyzer model 2400 (Analytical Center; IQ-USP, SP, Brazil).

General procedure for the syntheses of the 5-sulfenyl tetrazole derivatives 3a–m, 6a–c, and 9a–e

A stirred mixture of thiocyanate (**2** or **5**, 0.5 mmol), NaN_3 (0.39 g, 0.6 mmol) and $CeCl_3 \cdot 7H_2O$ (0.037 g, 0.1 mmol) in PEG-400 (0.5 mL) was heated to 80 °C (0.25 mmol thiocyanate and 1 mL PEG-400 were employed for the bi- and di-indole derivatives) in a test tube, without special protection against moisture or atmospheric oxygen. The progress of the reaction was monitored by TLC. After completion, a 2 M HCl solution (10 mL) was added and the product was extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by precipitation with Et_2O from an EtOAc solution or by column chromatography, eluting with mixtures of hexanes and EtOAc. For products **9b** and **9e**, the precipitate formed after addition of 2 M HCl solution was filtered, washed with water (3 × 10 mL) and dried under vacuum.

3-((1*H*-Tetrazol-5-yl)thio)-1-methyl-1*H*-indole (3a). Beige solid, m.p.: 179.5–180.5 °C (Lit.:[6a] 179.9–181.4 °C); yield: 92%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.90 (s, 1H), 7.57 (d, J = 8.2, 1H), 7.48 (d, J = 7.9, 1H), 7.30–7.27 (m, 1H), 7.19–7.15 (m, 1H) and 3.87 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 155.3, 137.1, 136.7, 128.6, 122.3, 120.5, 118.0, 110.6, 92.7 and 32.8. IR (KBr, ν): 3393, 3110, 2672, 2481, 1517, 1501, 1372, 1243, 1028 and 743 cm^{-1}. EI-MS (*m*/*z*, rel. int., %): 232 [(M + 1)$^+$, 5], 231 (M$^+$, 33), 188 (10), 174 (27), 162 (100), 130 (11), 77 (17) and 45 (5).

3-((1*H*-Tetrazol-5-yl)thio)-5-bromo-1-methyl-1*H*-indole (3b). Beige solid, m.p.: 203.6–204.6 °C (Lit.:[6a] 205.5–207.0 °C); yield: 90%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.94 (s, 1H), 7.62 (d, J = 1.8, 1H), 7.56 (d, J = 8.7, 1H), 7.40 (dd, J = 8.7 and 1.8, 1H) and 3.86 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 154.9, 138.0, 135.9, 130.5, 124.8, 120.2, 113.4, 112.8, 92.8, 33.0. IR (KBr, ν): 3274, 1734, 1496, 1308, 1217, 1109, 1032, 883 and 608 cm^{-1}. EI-MS (*m*/*z*, rel. int., %): 311 [(M + 2)$^+$, 35], 310 [(M + 1)$^+$, 5], 309 (M$^+$, 36), 254 (48), 253 (7), 252 (47), 242 (98), 241 (17), 240 (100), 162 (25), 117 (32), 77 (7). Anal. calc.: C, 51.93; H, 3.92. Found: C, 51.99; H, 3.99%.

3-((1*H*-Tetrazol-5-yl)thio)-5-methoxy-1-methyl-1*H*-indole (3c). White solid, m.p.: 165.1–165.7 °C; yield: 88%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.82 (s, 1H), 7.47 (d, J = 8.5, 1H), 6.93–6.90 (m, 2H), 3.82 (s, 3H) and 3.74 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 155.2, 154.7, 137.0, 132.2, 129.4, 112.3, 111.5, 99.7, 92.0, 55.3 and 32.9. IR (KBr, ν): 3565, 3522, 3447, 3111, 3035, 2999, 2915, 2712, 2533, 1622, 1513, 1490, 1424, 1370, 1221, 1037, 870, 793, and 629 cm^{-1}. EI-MS (*m*/*z*, rel. int., %): 262 [(M + 1)$^+$, 5], 261 (M$^+$, 31), 218 (15), 204 (30) and 192 (100). HRMS obsd. *m*/*z*: 262.0731; $C_{11}H_{12}N_5OS$ [(M + H)$^+$] requires *m*/*z*: 262.0763.

3-((1*H*-Tetrazol-5-yl)thio)-1-methyl-5-(*p*-tolyl)-1*H*-indole (3d). Beige solid, m.p.: 198.5–199 °C; yield: 92%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.92 (s, 1H), 7.68 (s, 1H), 7.63 (d, J = 8.6, 1H), 7.57–7.52 (m, 3H), 7.24 (d, J = 8.0, 2H), 3.88 (s, 3H) and 2.32 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 155.0, 138.0, 137.2, 136.5, 135.7, 133.1, 129.2, 129.1, 126.4, 121.5, 115.5, 111.0, 93.3, 32.8 and 20.3. IR (KBr, ν): 3446, 3102, 2915, 2857, 2695, 2667, 1617, 1513, 1476, 1448, 1364, 1304, 1239, 1150, 1117, 1035 and 801 cm^{-1}. EI-MS (*m*/*z*, rel. int., %): 322 [(M + 1)$^+$, 8], 321 (M$^+$, 38), 278 (36), 264 (48), 252 (100) and 43 (39). Anal. calc.: C, 63.53; H, 4.70. Found: C, 63.56; H, 4.70%.

3-((1*H*-Tetrazol-5-yl)thio)-1-phenyl-1*H*-indole (3e). Yellow solid, m.p.: 151.5–152.5 °C (Lit.:[6a] 153.1–154.3 °C); yield: 89%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.21 (s, 1H), 7.64–7.58 (m, 6H), 7.50–7.47 (m, 1H) and 7.34–7.23 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 154.7, 137.9, 136.0, 135.3, 129.7, 129.1, 127.2, 124.2, 123.4, 121.5, 118.5, 111.0 and 96.9. IR (KBr, ν): 3447, 3033, 2885, 2531, 2331, 1598, 1517, 1498, 1457, 1230, 1016, 745 and 695 cm^{-1}. EI-MS (*m*/*z*, rel. int., %): 293 (M$^+$, 30), 236 (36), 224 (100), 121 (21), 77 (41) and 51 (22).

3-((1*H*-Tetrazol-5-yl)thio)-1-(4-chlorophenyl)-1*H*-indole (3f). White solid, m.p.: 176–177 °C; yield: 93%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.25 (s, 1H), 7.70–7.66 (m, 4H), 7.61 (d, J = 8.1, 1H), 7.56 (d, J = 7.8, 1H), 7.34–7.31 (m, 1H) and 7.27–7.24 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 154.7, 136.7, 135.9, 135.4, 131.6, 129.7, 129.1, 126.0, 123.6, 121.7, 118.7, 111.1 and 97.4. IR (KBr, ν): 3437, 1627, 1614, 1594, 1514, 1493, 1454, 1226, 1091, 1011, 832, and 743 cm^{-1}. EI-MS (*m*/*z*, rel. int., %): 329 [(M + 2)$^+$, 8], 328 [(M + 1)$^+$, 5], 327 (M$^+$, 25), 284 (18), 270 (43), 258 (100), 235 (13), 223 (28), 121 (36) and 77 (52). Anal. calc.: C, 54.96; H, 3.07. Found: C, 55.51; H, 3.38%.

3-((1*H*-Tetrazol-5-yl)thio)-1-(4-methoxyphenyl)-1*H*-indole (3g). Light brown solid, m.p.: 165.2–166.5 °C; yield: 91%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.14 (s, 1H), 7.55 (d, J = 8.6, 2H), 7.50 (d, J = 8.3, 1H), 7.31–7.27 (m, 1H), 7.24–7.21 (m, 1H), 7.16 (d, J = 8.6, 2H) and 3.85 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 158.4, 154.9, 136.5, 135.7, 130.8, 128.9, 125.9, 123.3, 121.3, 118.5, 114.9, 111.0, 96.0 and 55.4. IR (KBr, ν): 3437, 3109, 2924, 2841, 2659, 2537, 2380, 1735, 1604, 1514, 1453, 1306, 1247, 1033, 839 and 746 cm^{-1}. EI-MS (*m*/*z*, rel. int., %): 324 [(M + 1)$^+$, 5], 323 (M$^+$, 25), 280 (25), 280 (25), 266 (32), 254 (100), 223 (19), 210 (13) and 77 (23). Anal. calc.: C, 59.43, H, 4.05. Found: C, 59.65, H, 4.39%.

3-((1*H*-Tetrazol-5-yl)thio)-1-octyl-1*H*-indole (3h). Light brown solid, m.p.: 97.6–98.3 °C (Lit.:[6a] 95.4–96.9 °C); yield: 91%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56 (d, J = 7.9, 1H), 7.36 (s, 1H), 7.29 (d, J = 8.1, 1H), 7.25–7.21 (m, 1H), 7.19–7.15 (m, 1H), 3.99 (t, J = 7.2, 2H), 1.78–1.76 (m, 2H), 1.27–1.22 (m, 10H) and 0.86 (t, J = 6.9, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.5, 136.7, 135.0, 128.8, 123.0, 121.2, 118.8, 110.4, 93.1, 46.9, 31.7, 29.8, 29.1, 29.0, 26.8, 22.5 and 14.0. IR (KBr, ν): 3443, 3106, 2953, 2923, 2853, 2714, 2556, 2486, 1702, 1614, 1492, 1457, 1370, 1299, 1165, 1020 and 739 cm^{-1}. EI-MS (*m*/*z*, rel. int., %): 329 (M$^+$, 34), 272 (58), 260 (59), 162 (100), 148 (20), 130 (29), 77 (9), 69 (23), 57 (26) and 41 (51).

3-((1*H*-Tetrazol-5-yl)tio)-1*H*-indole (3i). Brown solid, m.p.: 209.0–210.6 °C (Lit.:[6a] 210.4–211.6 °C); yield: 74% (in glycerol: 3 h, 93%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.76 (s, 1H), 7.88 (d, J = 2.8, 1H), 7.51 (d, J = 8.1, 1H), 7.45 (d, J = 7.9, 1H), 7.21 (td, J = 8.1 and 1.0, 1H), 7.12 (td, J = 7.9 and 1.0, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 155.2, 136.5, 132.9, 128.2, 122.2, 120.3, 117.8, 112.3 and 94.0. IR (KBr, ν) 3269, 2472, 2335, 1653, 1524, 1508,

1309, 1041, 746 and 603 cm^{-1}. EI-MS (*m*/*z*, rel. int., %): 218 [$(M + 1)^+$, 6], 217 (M^+, 41), 160 (30), 148 (100), 121, (14), 89 (20), 77 (20) and 45 (11).

3-((1*H*-Tetrazol-5-yl)thio)-5-bromo-1*H*-indole (3j). Light brown solid, m.p.: 209.5–210.6 °C (Lit.[6a] 209.5–211.3 °C); yield: 80% (in glycerol: 3 h, 96%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.99 (s, 1H), 7.95 (d, J = 2.8, 1H), 7.61 (d, J = 1.7, 1H), 7.48 (d, J = 8.6, 1H) and 7.33 (dd, J = 8.6 and 1.7, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 155.0, 135.3, 134.6, 130.3, 124.9, 120.1, 114.4, 113.1 and 93.9. IR (KBr, ν): 3274, 2502, 1566, 1496, 1308, 1217, 1109, 1032, 883, 870, 794, 746 and 608 cm^{-1}. EI-MS (*m*/*z*, rel. int., %): 297 [$(M + 2)^+$, 35], 296 [$(M + 1)^+$, 4], 295 (M^+, 31), 240 (65), 239 (9), 238 (59), 228 (98), 227 (23), 226 (100), 173 (41), 159 (34), 148 (38), 120 (52) and 45 (34).

3-((1*H*-Tetrazol-5-yl)thio)-5-methoxy-1*H*-indole (3k). Brown solid, m.p.: 174.5–176.0 °C; yield: 47% (in glycerol: 8 h; 63%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.64 (s, 1H), 7.81 (d, J = 2.8, 1H), 7.40 (d, J = 8.8, 1H), 6.91 (d, J = 2.3, 1H), 6.85 (dd, J = 8.8 and 2.3, 1H) and 3.73 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 155.2, 154.4, 133.4, 131.4, 129.0, 113.1, 112.4, 99.5, 93.4 and 55.3. IR (KBr, ν): 3407, 3263, 2898, 2832, 2696, 1626, 1584, 1490, 1300, 1210, 1033, 805 and 632 cm^{-1}. EI-MS (*m*/*z*, rel. int., %): 248 [$(M + 1)^+$, 5], 247 (M^+, 33), 204 (16), 190 (35), 189 (15), 180 (6), 179 (18), 178 (100), 175 (8), 163 (21), 147 (11), 135 (23), 120 (6) and 43 (21). HRMS obsd. *m*/*z*: 248.0593; $C_{10}H_{10}N_5OS$ [$(M + H)^+$] requires *m*/*z*: 248.0606.

3-((1*H*-Tetrazol-5-yl)thio)-5-(*p*-tolyl)-1*H*-indole (3l). Brown solid, m.p.: 210.3–214.0 °C (Lit.:[6a] 213.3–215.5 °C); yield: 78% (in glycerol: 8 h; 52%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.84 (s, 1H), 7.93 (s, 1H), 7.68 (s, 1H), 7.60 (d, J = 8.4, 1H), 7.52–7.49 (m, 3H), 7.23 (d, J = 7.5, 2H) and 2.32 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 155.2, 138.2, 135.9, 135.6, 133.7, 133.0, 129.3, 128.9, 126.5, 121.5, 115.4, 112.8, 94.5 and 20.4. IR (KBr, ν): 3262, 2331, 1051, 1472, 1307, 1108, 1035 and 798 cm^{-1}. EI-MS (*m*/*z*, rel. int., %): 307 (M^+, 11), 277 (19), 250 (18), 238 (44), 220 (18), 209 (23), 173 (100), 111 (22), 102 (15), 77 (9), 71 (21) and 45 (22).

3-((1*H*-Tetrazol-5-yl)thio)-2-methyl-1*H*-indole (3m). Light brown solid, m.p.: 179.5–180.3 °C (Lit.:[6a] 184.5–185.7 °C); yield: 82%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.68 (s, 1H), 7.43–7.39 (m, 2H), 7.16–7.12 (m, 1H), 7.09–7.06 (m, 1H) and 2.53 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 155.2, 143.1, 135.5, 129.2, 121.5, 120.1, 117.1, 111.3, 91.1 and 11.6. IR (KBr, ν): 3338, 3051, 2332, 1546, 1518, 1313, 1234, 1034 and 741 cm^{-1}. EI-MS (*m*/*z*, rel. int., %): 231 (M^+, 34), 174 (34), 162 (100), 130 (33), 118 (68) and 77 (27).

3-((1*H*-Tetrazol-5-yl)thio)-1*H*-indole-5-carbonitrile (3n). Beige solid, m.p.: 190.6–192.0 °C; yield: 87%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.32 (s, 1H), 8.11 (d, J = 2.7, 1H), 7.97 (s, 1H), 7.68 (d, J = 8.5, 1H) and 7.57 (dd, J = 1.5 and 8.5, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 154.8, 138.4, 135.8, 128.3, 125.1, 123.5, 120.0, 113.8, 102.7 and 95.8. IR (KBr, ν): 3277, 3103, 2227, 1617, 1505, 1468, 1422, 1340, 1038, 913, 803, 705, 636, 421. EI-MS (*m*/*z*, rel. int., %): 243 [$(M + 1)^+$, 7], 242 (M^+, 42), 214 (7), 199 (25), 173 (100), 142 (23). Anal. calc.: C, 49.58; H, 2.50. Found: C, 49.87; H, 2.80%.

5-((1-Phenyl-1*H*-pyrrol-2-yl)thio)1*H*-tetrazole (6a). Yellow solid, m.p.: 157.9–158.5 °C (Lit.:[6a] 160.1–161.4 °C); yield: 90%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.45–7.34 (m, 6H), 6.82 (dd, J = 3.6 and 1.7, 1H) and 6.40–6.39 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 155.0, 138.3, 128.7, 128.1, 127.7, 126.0, 121.6, 111.4 and 109.8. IR (KBr, ν): 3117, 2365, 1595, 1497, 1375, 1322, 1037, 765, 739 and 695 cm^{-1}. EI-MS (*m*/*z*, rel. int., %): 244 [$(M + 1)^+$, 7], 243 (M^+, 37), 186 (35), 174 (100), 130 (17), 115 (20), 77 (66), 71 (26), 51 (39) and 43 (19).

5-((1-(4-Methoxyphenyl)-1*H*-pyrrol-2-yl)thio)-1*H*-tetrazole (6b). Beige solid, m.p.: 163.3–163.8 °C; yield: 92%. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 7.29–7.24 (m, 3H), 6.96 (d, J = 8.8, 1H), 6.79 (dd, J = 3.5 and 1.6, 1H), 6.38–6.35 (m, 1H) and 3.76 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 158.7, 155.1, 131.3, 128.4, 127.5, 121.2, 113.9, 111.5, 109.6 and 55.3. IR (KBr, ν): 3117, 3011, 2360, 1605, 1517, 1249, 1038, 837, 739 and 620 cm^{-1}. EI-MS (*m*/*z*, rel. int., %): 274 [$(M + 1)^+$, 6], 273 (M^+, 38), 230 (2), 216 (20), 204 (100), 189 (46), 173 (38), 92 (15) and 77 (21). HRMS obsd. *m*/*z*: 274.0750; $C_{12}H_{12}N_5OS$ [$(M + H)^+$] requires *m*/*z*: 274.0763.

5-((1-(4-Chlorophenyl)-1*H*-pyrrol-2-yl)thio)-1*H*-tetrazole (6c). Orange solid, m.p.: 170.9–171.9 °C (Lit.:[6a] 171.2–173.1 °C); yield: 94%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.50 (d, J = 8.8, 2H), 7.40 (d, J = 8.8, 2H), 7.35 (dd, J = 3.0 and 1.8, 1H), 6.82 (dd, J = 3.7 and 1.8, 1H) and 6.40 (dd, J = 3.7 and 3.0, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 154.9, 137.2, 132.3, 128.8, 128.2, 127.9, 121.9, 111.6, 110.1. IR (KBr, ν): 3128, 3010, 2696, 2620, 2361, 1493, 1310, 1093, 1029, 837, 738 and 621 cm^{-1}. EI-MS (*m*/*z*, rel. int., %): 279 [$(M + 2)^+$, 6], 278 [$(M + 1)^+$, 3], 277 (M^+, 19), 233 (6), 219 (19), 209 (19), 173 (100), 111 (14) and 75 (20).

3,3′-Bis((1*H*-tetrazol-5-yl)thio)-1,1′-dimethyl-1*H*,1′*H*-2,2′-biindole (9a). White solid, m.p.: 265.9–268 °C; yield: 93%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.70 (d, J = 8.0, 2H), 7.58 (d, J = 7.8, 2H), 7.43–7.39 (m, 2H), 7.29–7.26 (m, 2H) and 3.67 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 154.5, 137.6, 133.9, 128.1, 123.5, 121.2, 118.6, 111.1, 99.0 and 31.2. IR (KBr, ν): 3463, 3057, 2921, 2712, 1614, 1463, 1419, 1380, 1336, 1303, 1241, 1157, 1130, 1111, 1035 and 745 cm^{-1}. EI-MS (*m*/*z*, rel. int., %): 417 (3), 374 (4), 322 (66), 307 (9), 290 (56), 258 (8) and 43 (100). HRMS obsd. *m*/*z*: 483.0890; $C_{20}H_{16}N_{10}NaS_2$ [$(M + Na)^+$] requires *m*/*z*: 483.0899.

3,3′-Bis((1*H*-tetrazol-5-yl)thio)-1*H*,1′*H*-2,2′-biindole (9b).[6f] Brown solid, m.p.: 275 °C (dec); yield: 49%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.21 (s, 2H), 7.59 (d, J = 8.1, 2H), 7.45 (d, J = 7.9, 2H), 7.33–7.29 (m, 2H) and 7.19–7.16 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 154.6, 136.7, 133.2, 128.9, 123.5, 120.9, 118.5, 112.4 and 96.1. IR (KBr, ν): 3379, 1614, 1517, 1448, 1339, 1079, 1037 and 744 cm^{-1}. HRMS obsd. *m*/*z*: 433.0753; $C_{18}H_{13}N_{10}S_2$ [$(M + H)^+$] requires *m*/*z*: 433.0766.

3,3′-Bis((1*H*-tetrazol-5-yl)thio)-1,1′-diphenyl-1*H*,1′*H*-2,2′-biindole (9c). Light brown solid, m.p.: 179.2–180.8 °C; yield: 85%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.61–7.59 (m, 2H), 7.32–7.20 (m, 12H) and 6.80 (bs, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 154.4, 137.0, 135.7, 132.6, 129.1, 128.2, 127.5, 125.7, 124.7, 122.1, 119.3, 111.0 and 103.6. IR (KBr, ν): 3451, 3058, 2920, 1704, 1595, 1498, 1450, 1379, 1333, 748 and 697 cm^{-1}. EI-MS (*m*/*z*, rel. int., %): 446 (31), 414 (41), 380 (5) and 70 (100). HRMS obsd. *m*/*z*: 607.1188; $C_{30}H_{20}N_{10}NaS_2$ [$(M + Na)^+$] requires *m*/*z*: 607.1211.

3,3′-Bis((1*H*-tetrazol-5-yl)thio)-1,1′-dibutyl-1*H*,1′*H*-2,2′-biindole (9d). White solid, m.p.: 129.2–131.5 °C; yield: 96%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.73 (d, J = 8.2, 2H), 7.54 (d, J = 7.8, 2H),

7.42–7.38 (m, 2H), 7.28–7.24 (m, 2H), 4.27–4.20 (m, 2H), 3.90–3.82 (m, 2H), 1.56–1.46 (m, 2H), 1.40–1.29 (m, 2H), 1.13–1.00 (m, 4H) and 0.61 (t, $J = 7.2$, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 154.3, 137.0, 132.9, 128.4, 123.6, 121.2, 119.2, 111.6, 99.6, 44.6, 31.2, 19.1 and 13.1. IR (KBr, ν): 3446, 3058, 2958, 2930, 2872, 1505, 1486, 1460, 1392, 1377, 1340, 1303, 1034, 1014 and 744 cm^{-1}. EI-MS (m/z, rel. int., %): 501 (2), 458 (3), 406 (100), 374 (29), 345 (98) and 44 (41). HRMS obsd. m/z: 567.1814; $C_{26}H_{28}N_{10}NaS_2$ [(M + Na)$^+$] requires m/z: 567.1832.

Bis(3-((1*H*-tetrazol-5-yl)thio)-1*H*-indol-2-yl)sulfide (9e). Brown solid, m.p.: 250 °C (dec.); yield: 80%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.10 (s, 2H), 7.44–7.40 (m, 4H), 7.25–7.22 (m, 2H) and 7.16–7.12 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 154.7, 137.1, 133.0, 128.8, 123.3, 121.0, 117.9, 112.0 and 99.7. IR (KBr, ν): 3458, 3423, 2901, 1622, 1495, 1342, 1309, 1230, 1043 and 744 cm^{-1}. HRMS obsd. m/z: 487.0288; $C_{18}H_{12}N_{10}NaS_3$ [(M + Na)$^+$] requires m/z: 487.0306.

Synthesis of 3,3′-bis((1*H*-tetrazol-5-yl)thio)-1*H*,1′*H*-2,2′-biindole (9b) employing $ZnBr_2$ in 2-PrOH : H_2O.[6f] A mixture of the di-thiocyanato **7b** (0.087 g, 0.25 mmol), $ZnBr_2$ (0.112 g, 0.5 mmol) and NaN_3 (0.081 g, 1.2 mmol) in a 1 : 1 mixture of 2-PrOH and water (5 mL) was heated to reflux for 2 h. Then, it was allowed to return to room temperature and poured over a 4 M HCl solution (5 mL); the resulting precipitate was filtered and the residue was washed with water (3 × 10 mL) and dried under vacuum to give **9b** (97 mg, 90%) as a brown solid. The spectral data were in agreement with those obtained from the reaction of **8b** with NaN_3 in PEG-400, promoted by $CeCl_3 \cdot 7H_2O$.

Acknowledgements

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

References and notes

1 (*a*) N. Sadlej-Sosnowska, *J. Org. Chem.*, 2001, **66**, 8737–8743; (*b*) P. B. Mohite and V. H. Bhaskar, *Int. J. PharmTech Res.*, 2011, **3**, 1557–1566.

2 (*a*) V. A. Ostrovskii, R. E. Trifonov and E. A. Popova, *Russ. Chem. Bull.*, 2012, **61**, 768–780; (*b*) L. V. Myznikov, A. Hrabalek and G. I. Koldobskii, *Chem. Heterocycl. Compd.*, 2007, **43**, 1–9; (*c*) T. Jin, S. Kamijo and Y. Yamamoto, *Tetrahedron Lett.*, 2004, **45**, 9435–9437; (*d*) V. V. Sureshbabu, R. Venkataramanarao, S. A. Naik and G. Chennakrishnareddy, *Tetrahedron Lett.*, 2007, **48**, 7038–7041.

3 (*a*) W. S. Marshall and J. P. Verge, *US Pat.*, 4661505, 1987; (*b*) J. W. Gillard, H. E. Morton, R. Fortin and Y. Guindon, *EP Pat.*, 0275667, 1987; (*c*) D. J. Steggles and J. P. Verge, *US Pat.*, 4675334, 1987; (*d*) H. T. Lee, P. M. O'Brian, J. A. Picard, C. F. Purchase Jr, B. D. Roth, D. R. Sliskovic and A. D. White, *EP Pat.*, 1203767, 1994; (*e*) M. J. Ogidigben, R. N. Young, K. M. Metters and D. M. Slipetz, *US Pat.*, 0204590, 2004; (*f*) J. Singh, M. E. Gurney, G. Hategan, P. Yu, D. Zembower and N. Zhou, *US Pat.*, 0079520, 2006; (*g*) A. Tamilselvi and G. Mugesh, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 3692–3697; (*h*) T. Nishimura, Y. Yoshimura, A. Miyake, M. Yamaoka, K. Takanohashi, M. Hamaguchi, S. Hirai, T. Yashiki and M. Numata, *J. Antibiot.*, 1987, **40**, 81–90; (*i*) E. Muraglia, O. D. Kinzel, R. Laufer, M. D. Miller, G. Moyer, V. Munshi, F. Orvieto, M. C. Palumbi, G. Pescatore, M. Rowley, P. D. Williams and V. Summa, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 2748–2752; (*j*) Z. A. Kaplancikli, M. D. Altintop, G. Turan-Zitouni, A. Ozdemir and O. D. Can, *J. Enzyme Inhib. Med. Chem.*, 2012, **27**, 275–280; (*k*) J. Adamec, K. Waisser, J. Kunes and J. Kaustová, *Arch. Pharm. Chem. Life. Sci.*, 2005, **338**, 385–389.

4 (*a*) F. Wincott, A. DiRenzo, C. Shaffer, S. Grimm, D. Tracz, C. Workman, D. Sweedler, C. González, S. Scaringe and N. Usman, *Nucleic Acids Res.*, 1995, **23**, 2677–2684; (*b*) R. Welz and S. Müller, *Tetrahedron Lett.*, 2002, **43**, 795–797; (*c*) E. Lieber and T. Enkoji, *J. Org. Chem.*, 1961, **26**, 4472–4479; (*d*) T. Patonay and A. Lévai, *Arch. Pharm.*, 1994, **327**, 181–186; (*e*) S. Bhattacharya and P. Kumar Vemula, *J. Org. Chem.*, 2005, **70**, 9677–9685; (*f*) M. N. Nichick, S. V. Voitekhovich, A. Shavel, A. I. Lesnikovich and O. A. Ivashkevich, *Polyhedron*, 2009, **28**, 3138–3142; (*g*) M. N. Nichick, S. V. Voitekhovich, V. Lesnyak, V. E. Matulis, R. A. Zheldakova, A. I. Lesnikovich and O. A. Ivashkevich, *J. Phys. Chem. C*, 2011, **115**, 16928–16933.

5 (*a*) Y. Slyvka, N. Pokhodylo, R. Savka, Z. Mazej, E. Goreshnik and M. Mys'kiv, *Chem. Met. Alloys*, 2010, **3**, 201–207; (*b*) V. A. Ostrovskii, G. I. Koldobskii and R. E. T. Tetrazoles, in *Comprehensive Heterocyclic Chemistry III*, ed. A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, R. J. K. Taylor and V. V. Zhdankin, Elsevier, Oxford, UK, 2008, vol. 6, pp. 257–423; (*c*) P. N. Gaponik, S. V. Voitekhovich and O. A. Ivashkevich, *Russ. Chem. Rev.*, 2006, **75**, 507–539.

6 (*a*) B. L. Kuhn, M. P. Fortes, T. S. Kaufman and C. C. Silveira, *Tetrahedron Lett.*, 2014, **55**, 1648–1652; (*b*) S. Y. Han, J. W. Lee, H. J. Kim, Y. J. Kim, S. W. Lee and Y. S. Gyoung, *Bull. Korean Chem. Soc.*, 2012, **33**, 55–59; (*c*) V. Dhayanithi, S. S. Syed, K. Kumaran, K. R. J. Sankar, R. V. Ragavan, P. S. K. Goud, N. S. Kumari and H. N. Pati, *J. Serb. Chem. Soc.*, 2011, **76**, 165–175; (*d*) B. V. LeBlanc and B. S. Jursic, *Synth. Commun.*, 1998, **28**, 3591–3599; (*e*) K. Kolo and S. M. Sajadi, *Lett. Org. Chem.*, 2013, **10**, 688–692; (*f*) V. V. Sureshbabu, B. Vasantha and H. P. Hemantha, *Synthesis*, 2011, 1447–1455.

7 (*a*) Y. Bazile, J. P. Bras, P. De Cointet, S. Nanthavong, C. Pigerol, M. Broll, P. Eymard, J. P. Werbenec and J. Fournier, *Eur. J. Med. Chem.*, 1977, **12**, 525–530; (*b*) W. G. Finnegan, R. A. Henry and R. Lofquist, *J. Am. Chem. Soc.*, 1958, **80**, 3908–3911; (*c*) P. Z. Demko and K. B. Sharpless, *J. Org. Chem.*, 2001, **66**, 7945–7950.

8 (*a*) G. Singh, R. Kumar, J. Swett and B. Zajc, *Org. Lett.*, 2013, **15**, 4086–4089; (*b*) A. K. Ghosh and B. Zajc, *J. Org. Chem.*, 2009, **74**, 8531–8540; (*c*) X. Han and J. Wu, *Org. Lett.*, 2010, **12**, 5780–5782; (*d*) E. B. Erkhitueva, A. V. Dogadina, A. V. Khramchikhin and B. I. Ionin, *Tetrahedron Lett.*, 2013, **54**, 5174–5177; (*e*) Y. Ge, A. Kazi, F. Marsilio, Y. Luo, S. Jain, W. Brooks, K. G. Daniel, W. C. Guida, S. M. Sebti and H. R. Lawrence, *J. Med. Chem.*, 2012, **55**, 1978–1998; (*f*)

N. T. Pokhodylo and N. D. Obushak, *Russ. J. Org. Chem.*, 2010, **46**, 1748–1749; (*g*) T. Kamiya, K. Tanaka and Y. Shiokawa, *US Pat.*, 4110338, 1978; (*h*) Z. P. Demko and K. B. Sharpless, *Angew. Chem.*, 2002, **114**, 2214–2217.

9 (*a*) A. Dişli and M. Salman, *Russ. J. Org. Chem.*, 2009, **45**, 151–153; (*b*) S. Kanakaraju, B. Prasanna and G. V. P. Chandramouli, *J. Chem.*, 2013, 104690; (*c*) V. Aureggi and G. Sedelmeier, *Angew. Chem., Int. Ed.*, 2007, **46**, 8440–8444; (*d*) E. Dolusic, R. Frederick, B. Masereel, L. Moineaux, L. Pochet, J. Wouters, D. Colau, P. Larrieu, L. Pilotte, V. Stroobant and B. Van Den Eynde, *J. Med. Chem.*, 2011, **54**, 5320–5334; (*e*) X. Billot, A. Chateauneuf, N. Chauret, D. Denis, G. Greig, M.-C. Mathieu, K. M. Metters, D. M. Slipetz and R. N. Young, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 1129–1132.

10 (*a*) F. Himo, Z. P. Demko, L. Noodleman and K. B. Sharpless, *J. Am. Chem. Soc.*, 2002, **124**, 12210–12216; (*b*) Z. P. Demko and K. B. Sharpless, *Org. Lett.*, 2002, **4**, 2525–2527; (*c*) P. K. Vemula and S. Bhattacharya, *J. Org. Chem.*, 2005, **70**, 9677–9685.

11 (*a*) L. Lang, B. Li, W. Liu, L. Jiang, Z. Xu and G. Yin, *Chem. Commun.*, 2010, **46**, 448–450; (*b*) M. Lakshmi Kantam, K. B. Shiva Kumar and K. Phani Raja, *J. Mol. Catal. A: Chem.*, 2006, **247**, 186–188; (*c*) M. J. Schulz, S. J. Coatz and D. J. Hlasta, *Org. Lett.*, 2004, **6**, 3265–3268; (*d*) S. Rostamizadeh, H. Ghaieni, R. Aryan and A. Amani, *Chin. Chem. Lett.*, 2009, **20**, 1311–1314.

12 (*a*) F. Himo, Z. P. Demko, L. Noodleman and K. B. Sharpless, *J. Am. Chem. Soc.*, 2003, **125**, 9983–9987; (*b*) D. Cantillo, B. Gutmann and C. O. Kappe, *J. Am. Chem. Soc.*, 2011, **133**, 4465–4475.

13 (*a*) H. Tsuruta, K. Yamaguchi and T. Imamoto, *Tetrahedron*, 2003, **59**, 10419–10438; (*b*) G. Bartoli, R. Dalpozzo, A. De Nino, L. Maiuolo, M. Nardi, A. Procopio and A. Tagarelli, *Eur. J. Org. Chem.*, 2004, 2176–2180; (*c*) C. C. Silveira, S. R. Mendes, L. Wolf and G. M. Martins, *Tetrahedron Lett.*, 2010, **51**, 2014–2016.

14 (*a*) G. A. Molander, *Chem. Rev.*, 1992, **92**, 29–68; (*b*) P. G. Steel, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2727–2751.

15 (*a*) G. Bartoli, M. C. Belluci, M. Bosco, R. Dalpozzo, A. De Nino, L. Sambri and A. Tagarelli, *Eur. J. Org. Chem.*, 2000, 99–104; (*b*) H. Liu, K. S. Shia, X. Shang and B. Y. Zhu, *Tetrahedron*, 1999, **55**, 3803–3830.

16 (*a*) G. Bartoli, E. Marcantoni, M. Marcolini and L. Sambri, *Chem. Rev.*, 2010, **110**, 6104–6143; (*b*) G. Sabitha and J. S. Yadav, in *Encyclopedia of Reagents for Organic Synthesis*, ed. L. A. Paquette, Wiley–VCH, Weinheim, Germany, 2006; (*c*) G. Bartoli, G. Di Antonio, R. Giovannini, S. Giuli, S. Lanari, M. Paoletti and E. Marcantoni, *J. Org. Chem.*, 2008, **73**, 1919–1924; (*d*) J. S. Yadav, B. V. Subba Reddy, C. Suresh Reddy and A. D. Krishna, *Tetrahedron Lett.*, 2007, **48**, 2029–2032; (*e*) N. Ahmed and J. E. Van Lier, *Tetrahedron Lett.*, 2007, **48**, 13–15; (*f*) G. Bartoli, M. Bosco, S. Giuli, A. Giuliani, L. Lucarelli, E. Marcantoni, L. Sambri and E. Torregiani, *J. Org. Chem.*, 2005, **70**, 1941–1944; (*g*) G. Bartoli, M. Bartolacci, A. Giuliani, E. Marcantoni, M. Massaccesi and E. Torregiani, *J. Org. Chem.*, 2005, **70**, 169–174; (*h*) G. Bartoli, M. Bartolacci, M. Bosco, G. Foglia, A. Giuliani, E. Marcantoni, L. Sambri and E. Torregiani, *J. Org. Chem.*, 2003, **68**, 4594–4597.

17 (*a*) C. C. Silveira, G. M. Martins and S. R. Mendes, *Tetrahedron Lett.*, 2013, **54**, 5492–5495; (*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, J. R. Soares, F. N. Victoria, D. M. Martinez and L. Savegnago, *Tetrahedron Lett.*, 2013, **54**, 4926–4929; (*d*) C. C. Silveira, S. R. Mendes and G. M. Martins, *Tetrahedron Lett.*, 2012, **53**, 1567–1570; (*e*) C. C. Silveira, S. R. Mendes, L. Wolf and G. M. Martins, *Tetrahedron Lett.*, 2010, **51**, 4560–4562.

18 C. C. Silveira, M. P. Fortes and S. R. Mendes, *Curr. Org. Chem.*, 2012, **16**, 1540–1548.

19 (*a*) C. H. C. Zhou, J. N. Beltramini, Y. X. Fana and G. Q. M. Lu, *Chem. Soc. Rev.*, 2008, **37**, 527–549; (*b*) Y. Gu and F. Jèrôme, *Green Chem.*, 2010, **12**, 1127–1138; (*c*) A. E. Díaz-Álvarez, J. Francos, B. Lastra-Barreira, P. Crochet and V. Cadierno, *Chem. Commun.*, 2011, **47**, 6208–6227.

20 (*a*) P. Singh and S. Pandey, *Green Chem.*, 2007, **9**, 254–261; (*b*) J. M. Harris, *Poly(Ethylene Glycol) Chemistry: Biotechnical and Biomedical Applications*, Plenum, New York, USA, 1992.

21 C. C. Silveira, S. R. Mendes, F. M. Líbero, E. J. Lenardão and G. Perin, *Tetrahedron Lett.*, 2009, **50**, 6060–6063.

22 K. P. Nandre, J. K. Salunke, J. P. Nandre, V. S. Patil, A. U. Borse and S. V. Bhosale, *Chin. Chem. Lett.*, 2012, **23**, 161–164.

23 (*a*) R. Kumar, P. Chaudary, S. Nimesh and R. Chandra, *Green Chem.*, 2006, **8**, 356–358; (*b*) J. Chen, S. K. Spear, J. G. Huddleston and R. D. Rogers, *Green Chem.*, 2005, **7**, 64–82; (*c*) E. Colacino, J. Martínez, F. Lamaty, L. S. Patrikeeva, L. L. Khemchyan, V. P. Ananikov and I. P. Beletskaya, *Coord. Chem. Rev.*, 2012, **256**, 2893–2920; (*d*) F. W. Wu, R. S. Hou, H. M. Wang, I. J. Kang and L. C. Chen, *Heterocycles*, 2011, **83**, 2313–2320; (*e*) Z. Li, Z. Y. Wang, W. Zhu, Y. L. Xing and Y. L. Zhao, *Synth. Commun.*, 2005, **35**, 2325–2331.

24 (*a*) M. Prieto, E. Zurita, E. Rosa, L. Muñoz, P. Lloyd-Williams and E. Giralt, *J. Org. Chem.*, 2004, **69**, 6812–6820; (*b*) C. J. Roxburgh, P. G. Sammes and A. Abdullah, *Dyes Pigm.*, 2009, **82**, 226–237; (*c*) S. A. Samsoniya, N. N. Barbakadze and I. S. Chikvaidze, *ARKIVOC*, 2012, 143–154; (*d*) S. Roy, A. Eastman and G. W. Gribble, *Tetrahedron*, 2006, **62**, 7838–7845; (*e*) X. Yang, H. Xing, Y. Zhang, Y. Lai, Y. Zhang, Y. Jiang and D. Ma, *Chin. J. Chem.*, 2012, **30**, 875–880; (*f*) H. Zhang, D. Liu, C. Chen, C. Liu and A. Lei, *Chem.–Eur. J.*, 2011, **17**, 9581–9585; (*g*) H. Zhang, Q. Cai and D. Ma, *J. Org. Chem.*, 2005, **70**, 5164–5173.

25 (*a*) T. N. Glasnov, J. D. Holbrey, C. O. Kappe, K. R. Seddon and T. Yan, *Green Chem.*, 2012, **14**, 3071–3076; (*b*) P. Diana, A. Carbone, P. Barraja, G. Kelter, H. H. Fiebig and G. Cirrincione, *Bioorg. Med. Chem.*, 2010, **18**, 4524–4529; (*c*) K. Swapna, S. N. Murthy and Y. V. D. Nageswar, *Eur. J. Org. Chem.*, 2010, 6678–6684; (*d*) H. C. Ma and X. Z. Jiang, *J. Org. Chem.*, 2007, **72**, 8943–8946; (*e*)

B. S. Lane, M. A. Brown and D. Sames, *J. Am. Chem. Soc.*, 2005, **127**, 8050–8057.

26 (*a*) G. Wu, Q. Liu, Y. Shen, W. Wu and L. Wu, *Tetrahedron Lett.*, 2005, **46**, 5831–5834; (*b*) H. R. Memarian, I. M. Baltork and K. Nikoofar, *Ultrason. Sonochem.*, 2008, **15**, 456–462.

27 (*a*) L. Cai, X. Liu, X. Tao and D. Shen, *Synth. Commun.*, 2004, **34**, 1215–1221; (*b*) J. S. Yadav, B. V. Subba Reddy and Y. Jayasudhan Reddy, *Chem. Lett.*, 2008, **37**, 652–653.

28 E. Grigat, R. Pütter and E. Mühlbauer, *Chem. Ber.*, 1965, **12**, 3777–3785.

29 J. Bergman and N. Eklund, *Tetrahedron*, 1980, **36**, 1439–1443.

30 (*a*) A. Seggio, G. Priem, F. Chevallier and F. Mongin, *Synthesis*, 2009, 3617–3632; (*b*) C. N. Johnson, G. Stemp, N. Anand, S. C. Stephen and T. Gallagher, *Synlett*, 1998, 1025–1027; (*c*) C. Koradin, W. Dohle, A. L. Rodríguez, B. Schmid and P. Knochel, *Tetrahedron*, 2003, **59**, 1571–1587; (*d*) S. Xu, X. Huang, X. Hong and B. Xu, *Org. Lett.*, 2012, **14**, 4614–4617; (*e*) E. Wincent, H. Shirani, J. Bergman, U. Rannug and T. Janosik, *Bioorg. Med. Chem.*, 2009, **17**, 1648–1653.

31 (*a*) B. Yu, A.-H. Liu, L.-N. He, B. Li, Z.-F. Diao and Y.-N. Li, *Green Chem.*, 2012, **14**, 957–962; (*b*) V. Nair, T. G. George, L. G. Nair and S. B. Panicker, *Tetrahedron Lett.*, 1999, **40**, 1195–1196.

32 G. J. Lim and S. K. Chang, Korean Patent, KR0114650, 2009.

33 (*a*) G. Bartoli, J. G. Fernández Bolaños, G. Di Antonio, G. Foglia, S. Giuli, R. Gunnella, M. Mancinelli, E. Marcantoni and M. Paoletti, *J. Org. Chem.*, 2007, **72**, 6029–6036; (*b*) G. Bartoli, R. Giovannini, A. Giuliani, E. Marcantoni, M. Massaccesi, P. Melchiorre and L. Sambri, *Eur. J. Org. Chem.*, 2006, 1476–1482; (*c*) J. Glinski, B. Keller, J. Legendziewicz and S. Samela, *J. Mol. Struct.*, 2001, **559**, 59–66.