Electrophilic Aromatic Substitution by Use of *N*-Tosyliminium Ions; Elaboration of 3-Aryl Tetrahydroisoquinolines

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Dedicated to Prof. Edmundo A. Rúveda on occasion of his 65th birthday

Abstract: The elaboration of 3-aryltetrahydroisoquinoline derivatives by electrophilic aromatic substitution of polysubstituted phenols and phenyl ethers with Lewis acid-generated tosyliminium ions is reported.

Key words: *N*-tosyliminium ions, phenyl ethers, Schefferine, 3-aryltetrahydroisoquinolines, electrophilic aromatic susbstitution

The 3-aryltetrahydroisoquinolines constitute a relevant class of compounds among the isoquinoline alkaloids, being important synthetic intermediates for the elaboration of protoberberines, pavines, isopavines and benzo[*c*]phenanthridines.[1] They also enjoy considerable attention as potential therapeutic agents.[2]

Many strategies, developed and employed for the synthesis of these compounds, proved not to be very satisfactory. Among them, the Bischler-Napieralski cyclization has been regarded as one of the most successful; however, reports of poor yields or inability to access the desired synthetic targets using this route are widely found in the literature[3] and considerable efforts have been made to overcome these situations.[4]

Alternative strategies aimed towards these compounds include a modified version of the Pictet-Spengler reaction by which 1,2-diarylethylamines are treated with formaldehyde[5] and the cyclization of aminonitriles;[6] 3-aryltetrahydroisoquinolines have also been obtained by degradation of more complex structures.[7]

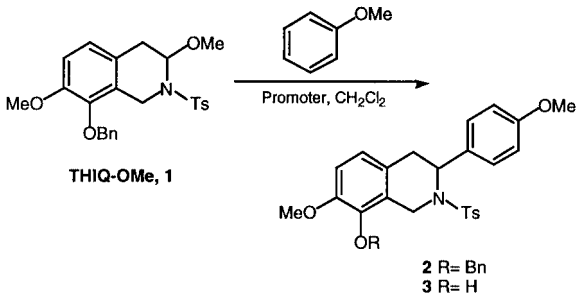
Recently, this laboratory disclosed the synthesis of 3-substituted tetrahydroisoquinolines by reaction of model silicon-based carbon nucleophiles with *N*-tosyliminium ions, generated in situ from suitable tetrahydroisoquinoline precursors under Lewis acid promotion.[8] We also described the use of this transformation as a key step in the total synthesis of a natural product.[9]

Herein, we wish to report that polysubstituted phenols and their ethers can be successfully employed as carbon nucleophiles in this process, a variation of the known Friedel-Crafts alkylation. This represents a novel and useful extension of the scope of this reaction and a new entry to 3-aryltetrahydroisoquinolines.

Compared with the intermolecular alkylation of aromatics with *N*-sulfonyliminium ions, the intramolecular version of this transformation has long been known[10] and has been extensively employed in modified Pictet-Spengler type cyclization reactions leading to tetrahydroisoquinolines, the sulfonyl group being responsible for the increased electrophilicity of the iminium and sometimes crucial for the success of the transformation.[10a-c] Certain sulfur-[10d,e] and selenium-based reagents[10f] have been reported to react with sulfonamides generating an electrophilic species under Lewis acid promotion. The same synthetic scheme was also recently used for the elaboration of chiral 1-substituted tetrahydroisoquinolines.[10f,g]

To develop our strategy, assays of feasibility of the proposed transformation, reaction outcome, as well as a search for suitable promoters and reaction conditions were carried out systematically with tosylamidal **1**, our previously reported *N*-tosyliminium ion precursor model,[8] and anisole as test carbon nucleophile. The results, summarized in Table 1, revealed that BF_3•Et_2O and ZnI_2

Table 1 Reaction of Tosylamidal **1** with Anisole, Employing Various Lewis Acids as Promoters



Entry	Promoter	Reaction Conditions (Product)[a]	Yield[b]
1	$SnCl_4$	-78 °C, 30 min, -60 °C, 1h (**2**)	77
2	$SnCl_4$	-78 °C, 30 min, -30 °C, 30 min (**3**)	75
3	$TiCl_4$	-78 °C, 30 min, -30 °C, 20 min (**3**)	78
4	$BF_3.Et_2O$	-78 °C, 30 min, -30 °C, 20 min (**2**)	88
5	ZnI_2	22 °C, 4h,))))[c,d] (**2**)	88
6	$FeCl_3$	22 °C, 4h,))))[c] (**2**)	84
7	$SnCl_2$	-78 °C, 30 min, -20 °C, 3h[e] (**2**)	<5
8	$MgBr_2.Et_2O$	-78 °C, 25 min, -20 °C, 2.5h[e] (**2**)	0
9	Et_2AlCl	-78 °C, 25 min, -20 °C, 2.5h (**2**)	46
10	TMSOTf	-78 °C, 30 min, -60 °C, 3.5h (**2**)	83

[a]Purified by flash-chromatography; *ortho* isomer not detected; [b]Isolated yield (%); [c]Inverse addition; [d]No product was detected after 2 h at -20 °C; [e]No significant yield changes after 2 h at room temperature

(entries 4 and 5) gave the highest yields of the expected product **2**, the latter requiring "inverse" addition of **1** to the Lewis acid, longer reaction time, comparatively higher (ambient) temperature and sonication (as did $FeCl_3$ because of its poor solubility). On the other hand, Et_2AlCl behaved as a poor promoter and the weaker Lewis acids $SnCl_2$ and $MgBr_2 \bullet Et_2O$ (entries 7-9) were ineffective. Therefore, $BF_3 \bullet Et_2O$ was selected as promoter for further testing the scope and limitations of this transformation.

Most of the reactions were rather slow at –78 ºC; therefore, conditions between –60 ºC and room temperature were used according to the reactivity of the promoter. Not surprisingly, it was found that $SnCl_4$ and $TiCl_4$ were highly effective at –30 ºC providing **3**, a consequence of concomitant debenzylation of the product. In the case of $SnCl_4$, however, this side reaction was avoided by running the alkylation at –60 ºC (entries 1 and 2).

When polysubstituted phenyl ethers were employed as the nucleophilic components (Table 2), good to excellent yields of products were obtained, showing that this reaction is tolerant to alkyl, allyl and halogen groups. Selectivity was also very good, probably aided by the bulk of the electrophile; products expected from a conventional Friedel-Crafts type alkylation were isolated.

Only traces of regioisomers were detected and compounds arising from self-alkylation of the starting tetrahydroisoquinoline were not isolated, presumably because of its comparatively poor ability to compete with the more concentrated, less hindered and more reactive phenols and phenyl ethers present in the reaction mixture. However, in the absence of added nucleophile, reaction of **1** with $BF_3 \bullet Et_2O$ at –60 ºC slowly lead to a complex and unseparable mixture of products.

The structures of all of the resulting 3-aryltetrahydroisoquinolines were unequivocally assigned by exhaustive analysis of their NMR spectra, including extensive NOE experiments in which enhancement of the signal of H-3 in the heterocyclic moiety by irradiation of selected protons of the 3-aryl substituent and vice versa were used as the key diagnostic tools.

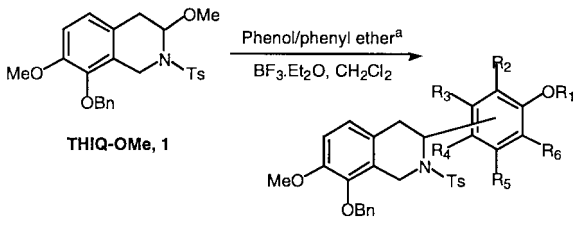
In a typical experiment, a CH_2Cl_2 solution of $BF_3 \bullet Et_2O$ as Lewis acid promoter (0.51 mL, 0.29 mmol) was added to a mixture of tetrahydroisoquinoline **1** (110 mg, 0.243 mmol) and 4-allyl-1,2-dimethoxybenzene (0.49 mmol), dissolved in dry CH_2Cl_2 (3 mL) and stirred under argon at –78 ºC. The reaction mixture was stirred for 15 min at –78 ºC and then the temperature was left to slowly rise to –30 ºC until the reaction was completed (30 min), when brine (10 mL) was added and the reaction product was extracted with EtOAc (4 × 25 mL). The organic extracts were combined, washed with brine (10 mL), dried (Na_2SO_4), concentrated in vacuum and flash-chromatographed, providing **4** (128 mg, 88%), as an oil which crystallized on standing.[11]

The same protocol was successfully applied to polyfunctionalized phenols; however, this furnished sometimes regioisomeric mixtures of products (entries 9, 11 and 14), as a result of similar degrees of activation of non-equivalent positions. The entire range of reactions were performed with $BF_3 \bullet Et_2O$ as promoter. $FeCl_3$ gave surprisingly high yields of products; for example 90% with phenol. $SnCl_4$ provided modest yields of the corresponding debenzylated 3-aryltetrahydroisoquinoline derivatives in the cases of phenol and guaiacol (43% and 48% respectively).

Selectivity changes associated with the protection of the phenolic OH were observed. As expected, exclusive alkylation *para* to the phenol moiety took place in 2-methyl-6-methoxyphenol (entry 13), while the related phenyl ether (entry 5) gave a contiguously substituted product, resulting from alkylation *ortho* to one of the methoxy groups.

The groups of Suzuki and Toshima recently demonstrated that in the presence of Lewis acids, glycosides serve as efficient glycosyl donors to phenols. *C*-aryl glycosides are obtained as a result of an *O*→*C* glycoside rearrangement of the intermediate *O*−phenyl glycosides formed under Lewis acid assistance.[12a,b] The overall transformation resembles a Fries rearrangement and results in an *ortho*-substituted phenol derivative. With thioglycosides, however, the same approach lead to the *C*-(4-hydroxyphenyl) analogs.[12c]

Table 2 Synthesis of 3-Aryltetrahydroisoquinolines by Reaction of Tosylamidal **1** with Polysubstituted Phenols and Phenyl Ethers Under $BF_3 \bullet Et_2O$ Promotion



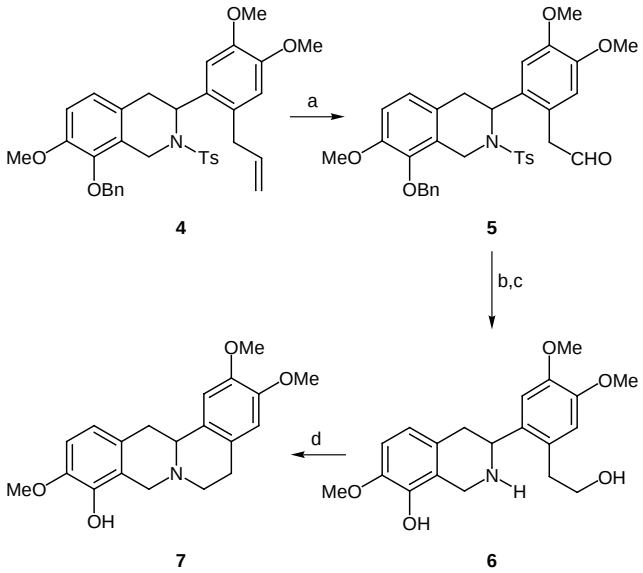
	3-Aryltetrahydroisoquinolines[c]						
Entry[b]	R_1	R_2	R_3	R_4	R_5	R_6	Yield[d]
1	Me	H	H	THIQ	H	H	88
2	Me	OMe	H	THIQ	H	H	85
3	Me	OMe	H	THIQ	Allyl	H	88
4	Me	Br	H	THIQ	H	H	85
5	Me	OMe	Me	THIQ	H	H	89
6	—CH_2—O		H	THIQ	H	H	95
7	H	H	H	THIQ	H	H	85
8	H	OMe	H	THIQ	H	H	98
9	H	THIQ	H	H	OMe	H	33
	H	H	OMe	THIQ	H	H	32
10	H	Me	H	THIQ	H	H	77
11	H	OMe	OMe	THIQ	H	H	16
	H	OMe	OMe	H	H	THIQ	64
12	H	Br	H	THIQ	H	Me	98
13	H	OMe	H	THIQ	H	Me	98
14	H	THIQ	H	OMe	H	H	63
	H	H	THIQ	OMe	H	H	20

[a]2 equivalents were employed; [b]For Starting phenol/phenyl ether: H instead of THIQ; [c]THIQ: 3-tetrahydroisoquinolyl residue; [d]Isolated yield after flash chromatography

Due to similarities in the chemistry of oxonium and iminium ions[13] and speculating that the same kind of rearrangement could take place in the case of tosylamidals, tetrahydroisoquinoline **1** was submitted to reaction with phenol and various Lewis acids under varying conditions of temperature and time. Unfortunately, however, the *para* substituted phenol shown in entry 7 of Table 2 was always obtained and neither significant amounts of the *ortho* isomer nor the 3-phenoxy tetrahydroisoquinoline could be isolated.

Interestingly, application of this novel and general approach to 3-aryltetrahydroisoquinolines provided a new and original total synthesis of Schefferine (**7**), a phenolic tetrahydroprotoberberine alkaloid isolated by Gellert and Rudzats[14] from *Schefferomitra subaequalis* Diels, an anonaceous liana widely found in New Guinea.

To that end, 3-aryltetrahydroisoquinoline derivative **4** synthesized as shown in entry 3 of Table 2, was submitted to an osmium tetraoxide-catalyzed oxidative fission of its terminal olefin moiety; employing sodium periodate as co-oxidant[15] aldehyde **5** was obtained, as depicted in the Scheme. This, in turn, was reduced with sodium borohydride and the resulting primary alcohol was then simultaneously reductively detosylated and debenzylated with sodium in refluxing liquid ammonia, furnishing the phenolic aminoalcohol **6** in good yield.



Reagents and conditions: a) OsO_4 (cat.), $NaIO_4$, THF-H_2O, 77%; b) $NaBH_4$, MeOH-Et_2O (4:1), 92%; c) 1. Na, NH_3, –33 °C; 2. NH_4Cl, –33 °C to RT, 83%; d) PPh_3, DEAD, HBF_4, THF, reflux, 82%.

Scheme

Intramolecular Mitsunobu-type amination with the classical DEAD-PPh_3 couple employing HBF_4 as additive[16] completed the synthesis, finally providing the tetracyclic compound **7** which was found to be spectroscopically identical with the natural product.

In conclusion, it was demonstrated that polysubstituted phenols and phenyl ethers can be conveniently functionalized employing a tosyliminium ion as the electrophile. The use of *N*-tosyliminium ions as 3-tetrahydroisoquinolyl donors resulted in a new entry to valuable 3-aryl tetrahydroisoquinolines. Taking advantage of this new carbon-carbon bond forming reaction, a novel and original total synthesis of the tetrahydroprotoberberine alkaloid Schefferine was achieved. Further applications of this strategy are being studied.

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(11) All new compounds were satisfactorily characterized by spectroscopic and analytical means. Data of **4**: mp 120-121.5 ºC (hexane-EtOAc); ^{1}H NMR δ: 2.41 (s, 3H), 2.79 (dd, *J* = 9.0, 11.8 Hz, 1H), 3.36 (brd, 2H), 3.60 (s, 3H), 3.68 (dd, *J* = 5.4, 11.8 Hz, 1H), 3.85 (s, 3H), 3.87 (s, 3H), 3.89 (d, *J* = 15.9 Hz, 1H), 4.38 (dd, *J* = 5.4, 9.0 Hz, 1H), 4.55 (d, *J* = 15.9 Hz, 1H), 4.93-5.10 (m, 2H), 5.03 (d, *J* = 11.1 Hz, 1H), 5.12 (d, *J* = 11.1 Hz, 1H), 5.85-6.06 (m, 1H), 6.23 (s, 1H), 6.48 (d, *J* = 8.7 Hz, 1H), 6.68 (s, 1H), 6.71 (d, *J* = 8.7 Hz, 1H), 7.25 (d, *J* = 8.2 Hz, 2H), 7.30-7.50 (m, 5H) and 7.57 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR δ: 21.37, 36.91, 39.77, 44.31, 49.89, 55.69,* 55.81, 74.22, 111.20, 112.42, 112.71, 115.79, 124.39, 126.77, 127.49,* 127.97,# 128.25,* 129.47,* 130.11, 130.22, 132.34, 133.57, 137.32, 137.42, 143.28,* 147.24, 147.62 and 150.25 (asterisk: the signal is produced by two carbon atoms; "#": the resonance is attributable to 3 carbons); HREIMS, calcd. for $C_{35}H_{37}NO_6S$: 599.2342; found: 599.2347.

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