Solventless Clay-Promoted Friedel−Crafts Reaction of Indoles with α-Amido Sulfones: Unexpected Synthesis of 3-(1-Arylsulfonylalkyl) Indoles
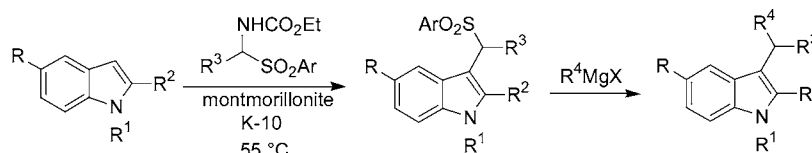
Roberto Ballini, Alessandro Palmieri, Marino Petrini,* and Elisabetta Torregiani

Dipartimento di Scienze Chimiche, Università di Camerino, via S. Agostino, 1 I-62032 Camerino, Italy

marino.petrini@unicam.it

ABSTRACT

Friedel−Crafts reaction of indoles with α-amido sulfones in the presence of montmorillonite K-10 leads unexpectedly to 3-(1-arylsulfonylalkyl) indoles in good yield. The obtained products can be further desulfonylated under reductive or alkylative conditions giving linear and branched 3-substituted indoles.

The introduction of functionalized alkyl frameworks at the 3-position in indole systems is a common practice directed to the synthesis of biologically active compounds.[1] Apart from few notable exceptions,[2] the vast majority of the available methods to attain this result use a Friedel−Crafts (F−C) reaction exploiting the electron-rich nature of the indole nucleus.[3]

A common feature of all these procedures resides in the utilization of highly electrophilic reagents generated under Lewis or Brønsted acidic conditions.[4] Activation by acid promoters is particularly needed when poor electrophiles, such as imines **2**, are used for this purpose (Scheme 1).

Conversion of these nitrogen derivatives into iminium ions ensures a rapid reaction with various indoles **1** to give 3-indolyl methanamines **3** that are pivotal intermediates in alkaloid syntheses.

The efficiency of this process is affected by the reaction conditions since the amino group in the benzylic position can eliminate to give bisindoles as byproducts.[5] This apparent drawback represents a useful synthetic opportunity since

(1) (a) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, 1−48. (b) Saxton, J. E. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998. (c) Sundberg, R. J. *Indoles*; Academic Press: New York, 1997. (d) Saxton, J. E. *Nat. Prod. Rep.* **1997**, 559−590.

(2) (a) Ballini, R.; Rabanedo Clemente, R.; Palmieri, A.; Petrini, M. *Adv. Synth. Catal.* **2006**, *348*, 191−196. (b) Wynne, J. H.; Stalick, W. M. *J. Org. Chem.* **2002**, *67*, 5850−5853. (c) Mahboobi, S.; Wiegrebe, W.; Popp, A. *J. Nat. Prod.* **1999**, *62*, 577−579. (d) Koike, T.; Takeuchi, N.; Hagiwara, M.; Yamazaki, K.; Tobinaga, S. *Heterocycles* **1999**, *51*, 2687−2695. (e) Koike, T.; Hagiwara, M.; Takeuchi, N.; Tobinaga, S. *Heterocycles* **1997**, *45*, 1271−1280.

(3) Review: (a) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Synlett* **2005**, 1199−1222. For some very recent examples see: (b) Jia, Y.-X.; Zhu, S. F.; Yang, Y.; Zhou, Q.-L. *J. Org. Chem.* **2006**, *71*, 75−80. (c) Yamazaki, S.; Iwata, Y. *J. Org. Chem.* **2006**, *71*, 739−743. (d) Lu, S.-F.; Du, D.-M.; Xu, J. *Org. Lett.* **2006**, *8*, 2115−2118. (e) Li, D.-P.; Guo, Y.-C.; Ding, Y.; Xiao, W.-J. *Chem. Commun.* **2006**, 799−801. (f) Evans, D. A.; Fandrick, K. R.; Song, H.-J. *J. Am. Chem. Soc.* **2005**, *127*, 8942−8943. (g) Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6576−6579. (h) Palomo, C.; Oiarbide, M.; Kardak, B. G.; Garcia, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154−4155.

(4) Acid catalysis can be sometimes avoided when particularly reactive electrophiles are used in the reaction with indoles: (a) Jiang, B.; Huang, Z.-G. *Synthesis* **2005**, 2198−2204. (b) Dessole, G.; Herrera, R. P.; Ricci, A. *Synlett* **2004**, 2374−2378.

(5) (a) Mi, X.; Luo, S.; He, J.; Cheng, J.-P. *Tetrahedron Lett.* **2004**, *45*, 4567−4570. (b) Xie, W.; Bloomfield, K. M.; Jin, Y.; Dolney, N.; Wang, P. G. *Synlett* **1999**, 498−500.

Scheme 1
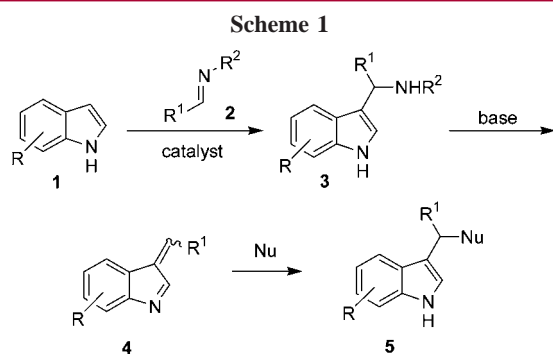
elimination of the amino framework from **3** leads to reactive vinylogous imino derivatives **4** that may add nucleophilic species giving branched 3-substituted indoles **5**.[6]

Compared with *N*-alkylimines, *N*-acylimines and their corresponding iminium ions[7] are considerably more reactive toward nucleophiles and can be profitably used in a number of synthetic applications, including catalytic enantioselective processes.[8] The poor stability of *N*-acylimino derivatives makes preferable their in situ formation from suitable α-substituted amido precursors that, by acid-promoted elimination of a good leaving group, furnish the azomethine electrophile ready to react with the appropriate indole.[9]

Concerning the nature of the acid promoter for the F–C reaction, Lewis acids formerly used for this purpose can be replaced by less hazardous and eco-friendly solid acid compounds.[10] Working under heterogeneous conditions, solid acids can be often used without any added solvent and allow easy workup of the corresponding reaction mixture. Recently, we have demonstrated that α-amido sulfones **6** are useful precursors of *N*-acyliminium ions **7** that, once they formed, can react with several nucleophiles, such as allylsilanes, silyl ketene acetals, and electron-rich aromatics, leading to the corresponding adducts **8** (Scheme 2).[11]

With the aim of searching for a new route to 3-substituted indoles, we reacted indole **1b** with α-amido sulfone **6a** in

(6) (a) Semenov, B. B.; Novikov, K. A.; Lysenko, K. A.; Kachala, V. V. *Tetrahedron Lett.* **2006**, *47*, 3479−3483. (b) Freed, J. D.; Hart, D. J.; Magomedov, N. A. *J. Org. Chem.* **2001**, *66*, 839−852. (c) Dubois, L.; Dorey, G.; Potier, P.; Dodd, R. H. *Tetrahedron: Asymmetry* **1995**, *6*, 455−462.

(7) (a) Fišera, L. *Science of Synthesis*; Padwa, A., Ed.; Thieme: Stuttgart, 2004; Vol. 27, p 349. (b) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431−1628. (c) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817−3856.

(8) (a) Wang, Y.-Q.; Song, W. J.; Hong, R.; Li, H.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156−8157. (b) Jia, Y.-X.; Xie, J.-H.; Duan, H.-F.; Wang, L.-X.; Zhou, Q.-L. *Org. Lett.* **2006**, *8*, 1621−1624. (c) Johannsen, M. *Chem. Commun.* **1999**, 2233−2234.

(9) DeNinno, M. P.; Eller, C.; Etienne, J. B. *J. Org. Chem.* **2001**, *66*, 6988−6993.

(10) (a) Singh, D. U.; Singh, P. R.; Samant, S. D. *Synth. Commun.* **2006**, *36*, 1265−1271. (b) Bartoli, G.; Bosco, M.; Giuli, S.; Giuliani, A.; Lucarelli, L.; Marcantoni, E.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2005**, *70*, 1941−1944. (c) Bandini, M.; Fagioli, M.; Umani-Ronchi, A. *Adv. Synth. Catal.* **2004**, *346*, 545−548. (d) Bartoli, G.; Bartolacci, M.; Bosco, M.; Foglia, G.; Giuliani, A.; Marcantoni, E.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2003**, *68*, 4594−4597. (e) Chakrabarty, M.; Basak, R.; Ghosh, N. *Tetrahedron Lett.* **2001**, *42*, 3913−3915.

(11) (a) Petrini, M. *Chem. Rev.* **2005**, *105*, 3949−3977. (b) Petrini, M.; Torregiani, E. *Tetrahedron Lett.* **2005**, *46*, 5999−6003.

Scheme 2
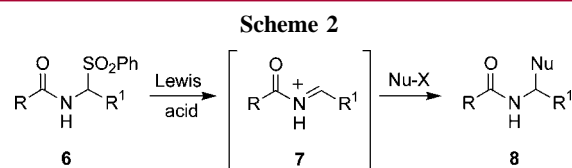
the presence of $TiCl_4$ at low temperature following our usual procedure.[11b] Unexpectedly, the major product obtained in this reaction was 3-substituted indole **9f** bearing a tolylsulfonyl group instead of the carbamoyl moiety (Table 1, entry 1).

Table 1. Reaction of Indole **1b** with α-Amido Sulfone **6a**
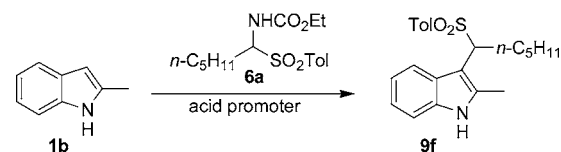
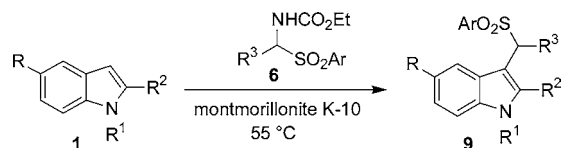| entry	acid promoter (g/mmol **1b**)	solvent	T (°C)	time (h)	yield **9f** (%)[d]
1	$TiCl_4$ (2 equiv)	CH_2Cl_2	−78[c]	6	55
2	none	CH_2Cl_2	40	18	traces
3[a]	HSZ-360 (1.7)	CH_2Cl_2	40	4	51
4[b]	K-10 (1.7)	CH_2Cl_2	40	3	95
5[b]	K-10 (1.7)	none	20	9	traces
6[b]	K-10 (1.7)	none	55	3	94
7[b]	K-10 (0.9)	none	55	3	88
8	SiO_2 (1.2)	none	55	3	73

[a] Zeolite. [b] Montmorillonite. [c] For 0.5 h at −78 °C then 5.5 h at rt. [d] Isolated yields. All reactions were carried out on 1 mmol scale.

The absence of the acidic promoter does not produce any appreciable result (Table 1, entry 2), but interestingly, solid acid compounds are effective in promoting the same process under various conditions. Zeolite HSZ-360 gives modest results, but less expensive montmorillonite K-10 leads to the formation of sulfone **9f** in good yield using the same conditions (Table 1, entries 3 and 4). At room temperature, in the absence of any solvent, the conversion becomes ineffective, while increasing the temperature up to 55 °C produces substituted indole **9f** in good yield (Table 1, entries 5 and 6). The amount of the acid promoter clearly affects the efficiency of the process; although montmorillonite K-10 is a quite inexpensive support, its loading can be reduced to 0.9 g/mmol of substrate with only a modest lowering of the indole chemical yield (Table 1, entry 7). Finally, silica gel is also active as acid support for this process, but it is more expensive and gives lower yield of product **9f** than montmorillonite K-10 (Table 1, entry 8).

This unprecedented synthetic process represents a valuable and general method to prepare several 3-(1-arylsulfonylalkyl) indoles **9** starting from indoles **1** and various α-amido sulfones **6** as displayed in Table 2.

The yields of the obtained sulfonyl indole derivatives **9** are usually satisfactory, and there is no clear relationship

Table 2. Synthesis of 3-Substituted Indoles **9** by Reaction of Indoles **1** with Sulfones **6** Promoted by Montmorillonite K-10[a]

1a R = R[1]= R[2]= H   **6a** R[3]= n-C$_5$H$_{11}$ Ar = 4-MePh
1b R = R[1]= H, R[2]= Me   **6b** R[3]= PhCH$_2$CH$_2$, Ar = 4-MePh
1c R = R[1]= H, R[2]= Ph   **6c** R[3]= c-C$_6$H$_{11}$ Ar = Ph
1d R = R[2]= H, R[1]= Me   **6d** R[3]= Ph, Ar = 4-MePh
1e R = MeO, R[1]= R[2]= H   **6e** R[3]= 4-NO$_2$Ph, Ar = 4-MePh
1f R = CN, R[1]= R[2]= H

entry	indole **1**	α-amido sulfone **6**	product **9**	time (h)	yield (%)[b]
1	**1a**	**6a**	**9a**	6	71
2	**1a**	**6b**	**9b**	7	70
3	**1a**	**6c**	**9c**	7	72
4	**1a**	**6d**	**9d**	7	80
5	**1a**	**6e**	**9e**	15	71
6	**1b**	**6a**	**9f**	3	88
7	**1b**	**6b**	**9g**	6	90
8	**1b**	**6c**	**9h**	6	79
9	**1b**	**6d**	**9i**	7	69
10	**1b**	**6e**	**9j**	9	70
11	**1c**	**6a**	**9k**	6	46
12	**1d**	**6a**	**9l**	6	62
13	**1e**	**6a**	**9m**	5	76
14	**1f**	**6b**	**9n**	6	70
15	**1f**	**6a**	**9o**	5	80

[a] Reaction conditions: sulfone **6** (3 mmol), indole **1** (3.2 mmol), and montmorillonite K-10 (2.7 g) heated at 55 °C. [b] Isolated yields

between the nature of the reagent substituents and the efficiency of the process, except in the case of 2-phenyl indole **1c** that gives a poor conversion into indole **9k** probably because of the steric hindrance exerted by the phenyl group with respect to the hydrogen or methyl group (Table 2, entry 11). The nature of the alkoxy group in the carbamoyl moiety in α-amido sulfones is also important since early attempts to use benzyloxy and *tert*-butyloxycarbamoyl sulfones gave unreliable results.[12]
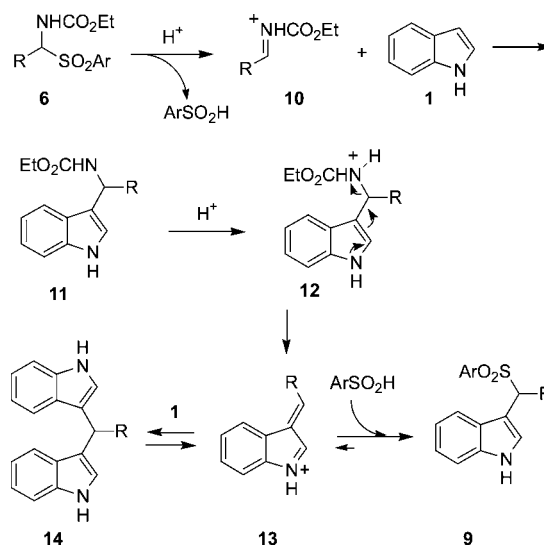
A plausible mechanism that explains the formation of compounds **9** starts from the *N*-acyliminium ion **10** that is formed by elimination of arenesulfinic acid from the α-amido sulfone **6** under acid conditions (Scheme 3).

Reaction of the strong electrophile **10** with indole **1** gives the F−C product **11** that is protonated and suffers elimination of ethyl carbamate, leading to vinylogous iminium ion **13**.[13] At this point, the iminium ion **13** can react with indole **1** in a second F−C reaction giving bisindole **14** or adds ArSO$_2$H to afford product **9**. Formation of compound **9** is favored because the F−C reaction leading to bisindole **14** is probably

Scheme 3

a fast and reversible process; in addition, product **9** is probably thermodynamically more stable than bisindole **14**. As a matter of fact, bisindole **14** can be observed during the course of the reaction by TLC analysis, and its complete disappearance usually announces the end of the process. Furthermore, variable amounts of bisindole **14** can be isolated from the reaction mixture after 0.5 h at 55 °C.[14]

The ready availability of sulfonyl indoles **9** opens new synthetic opportunities for a suitable functionalization of indoles at the 3 position, exploiting the well-known aptitude of the arenesulfonyl moiety to act as a good leaving group.[15] Substitution of the arenesulfonyl group with a hydrogen atom would lead to the 3-alkyl indole derivative formally arising from an alkylation reaction of the indole ring. Removal of the arenesulfonyl group in benzylic and allylic positions is usually best effected under radical conditions, taking advantage of the stability of the corresponding radical intermediate.[16]

Therefore, reduction of sulfones **9** using Bu$_3$SnH in toluene at reflux gives the corresponding indole derivatives **16** in satisfactory yield (Table 3, method A, entries 1, 3, 4, and 7). A comparison of this procedure with the classical desulfonylation using 6% Na−Hg amalgam (Table 3, method B) shows that the former reaction is more efficient in

(12) Extensive decomposition of the α-amido sulfone has been observed in this process, especially for *tert*-butyloxycarbamoyl sulfones.

(13) Ke, B.; Qin, Y.; He, Q.; Huang, Z.; Wang, F. *Tetrahedron Lett.* **2005**, *46*, 1751−1753.

(14) Under certain circumstances, the bisindole is stable enough with respect to the sulfonyl indole that it may become the main product as in the reaction of indole **1b** with imino ester precursor **6f** that gives predominantly bisindole **15**.
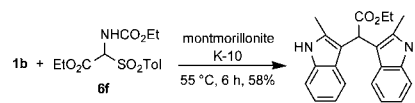
(15) (a) Nájera, C.; Yus, M. *Tetrahedron* **1999**, *55*, 10547−10658. (b) Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon Press: Oxford, 1993.

(16) (a) Padwa, A.; Muller, C. L.; Rodriguez, A.; Watterson, S. H. *Tetrahedron* **1998**, *55*, 9651−9666. (b) Morimoto, Y.; Mikami, A.; Kuwabe, S.; Shirahama, H. *Tetrahedron: Asymmetry* **1996**, *7*, 3371−3390. (c) Giovannini, R.; Petrini, M. *Synlett* **1995**, 973−974. (d) Smith, A. B., III; Hale, K. J.; McCauley, J. P., Jr. *Tetrahedron Lett.* **1989**, *30*, 5579−5582.

**Table 3.** Reductive Desulfonylation of Indoles **9** under Various Conditions[a]

Method A: Bu$_3$SnH, AIBN, PhMe
Method B: Na-Hg, EtOH
Method C: LiAlH$_4$, THF

9 → **16**
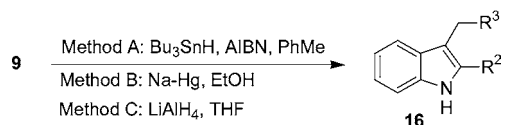
entry	indole **9**	product **16**	method[a]	time (h)	yield (%)[b]
1	**9d**	**16a**	A	4	86
2	**9d**	**16a**	B	2	61
3	**9f**	**16b**	A	3	85
4	**9g**	**16c**	A	8	77
5	**9g**	**16c**	C	2	85
6	**9i**	**16d**	B	4	62
7	**9j**	**16e**	A	8	56

[a] Reaction conditions. Method A: sulfonyl indole **9** (1 mmol), Bu$_3$SnH (2 mmol), and AIBN (0.3 mmol) in toluene (12 mL) at reflux. Method B: **9** (1 mmol), 6% Na−Hg amalgam (1.5 g), and Na$_2$HPO$_4$ (4 mmol) in EtOH (10 mL) at rt. Method C: **9** (1 mmol) and LiAlH$_4$ (3 mmol) in THF (12 mL) at rt. [b] Isolated yields.

providing indole **16a** (Table 3, entries 1 and 2).[17] Complex hydride LiAlH$_4$ is seldom used for this purpose, but the basic character of this reagent makes possible a mechanism already outlined in Scheme 1 that involves elimination to the imino-like derivative **4** followed by its reduction to compound **5** (Nu = H). Thus reduction of sulfone **9g** using LiAlH$_4$ in THF affords the corresponding indole derivative **16d** with a considerable degree of efficiency (Table 3, method C, entry 5).

The success of the reductive cleavage of the ArSO$_2$ group by LiAlH$_4$ clearly suggests the possibility of using Grignard reagents in a strictly related fashion to obtain alkylation of the indole side chain. Some preliminary results concerning the reaction of simple Grignard reagents **17** with sulfones **9** at −35 °C show that this process is possible and leads to the corresponding substituted indoles **18** in good yield (Table 4).

(17) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1345−1353.

Table 4. Reaction of Indoles **9** with Grignard Reagents **17**[a]

R^{4}MgX **17**, THF, -35 °C, 1.5h

9 → **18**
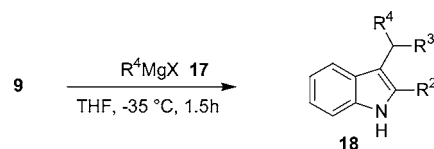
		Grignard reagent **17**			
entry	indole **9**	R^4		product **18**	yield (%)[b]
1	**9d**	Me	**17a**	**18a**	75
2	**9f**	*n*-Bu	**17b**	**18b**	94
3	**9f**	CH=CH$_2$	**17c**	**18c**	77
4	**9g**	Me	**17a**	**18d**	85
5	**9g**	*n*-Bu	**17b**	**18e**	91

[a] Reaction conditions: sulfonyl indole **9** (1 mmol) in THF (12 mL), Grignard reagent (3 mmol) added dropwise at −35 °C. [b] Isolated yields.

In summary, we have devised an unprecedented procedure for the synthesis of 3-(1-arylsulfonylalkyl) indoles by Friedel−Crafts reaction of α-amido sulfones with indoles in the presence of montmorillonite K-10 under solventless conditions. These rather unknown sulfonyl indole derivatives[18] can be desulfonylated under reductive conditions giving 3-alkyl indoles or alkylated upon reaction with Grignard reagents giving branched 3-alkyl indoles. Further studies of reactions of 3-(1-arylsulfonylalkyl) indoles with other nucleophilic systems are currently underway in our laboratory.

Supporting Information Available: General experimental procedures, spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061604W

(18) (a) Krasovsky, A. L.; Druzhinin, S. V.; Nenajdenko, V. G.; Balenkova, E. S. *Tetrahedron Lett.* **2004**, *45*, 1129−1132. (b) Licari, J. J.; Dougherty, G. *J. Am. Chem. Soc.* **1954**, *76*, 4039−4040.