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Synthesis of 3-(2-nitroalkyl) indoles by reaction of 3-(1-arylsulfonylalkyl) indoles with nitroalkanes

Alessandro Palmieri, Marino Petrini* and Elisabetta Torregiani

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

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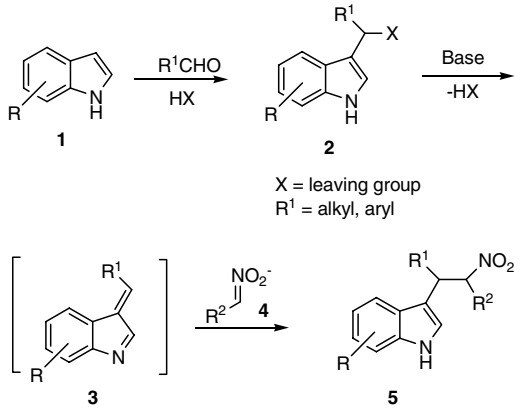
Abstract—Sulfonyl indoles act as effective precursors of vinylogous imino derivatives in the reaction with nitroalkanes under basic conditions leading to the corresponding nitro indoles in good yield. This procedure represents an effective option to the classical conjugate addition of indoles to nitroalkenes.

The introduction of functionalized alkyl frameworks in electron-rich aromatic derivatives such as indoles is usually attained by means of a Friedel–Crafts reaction that involves the utlilization of various electrophilic reagents.[1] Nitroalkenes are undoubtedly the most reactive electron-poor olefins available for this purpose because of the powerful electron-withdrawing aptitude of the nitro group.[2] The obtained 3-(2-nitroalkyl) indoles are amenable to further synthetic transformations such as reduction leading to tryptamine derivatives that are easily converted into carboline alkaloids.[3] Despite their widespread utilization, only a limited number of nitroalkenes is commercially available; furthermore many of them are rather toxic and irritant compounds so that direct manipulation of these reactive olefins is often not advisable.

A complementary approach to obtain 3-(2-nitroalkyl) indoles lies in the utilization of derivatives **2** readily obtained by reaction of indoles **1** with aldehydes in the presence of a suitable reagent HX (Scheme 1). Base assisted elimination of X^- from compounds **2** would provide vinylogous imino derivatives **3** that upon reaction with nitronate anions **4** ultimately leads to 3-(2-nitroalkyl) indoles **5**. Gramine derivatives (**2**, $X = NR_2$) obtained from Mannich reactions on indoles are the most exploited precursors of vinylogous imines **3** in the reaction with nitroalkanes under basic conditions.[4]



Scheme 1.

Elimination of the dialkyamino moiety from gramines is however, rather troublesome since it often requires high temperatures (reflux in toluene or xylene) and prolonged reaction times (10–18 h). For this reason alkylation of the tertiary amino group to a quaternary ammonium salt which is a better leaving group, frequently precedes the elimination step to the reactive intermediate **3**.[5] Furthermore, unless highly enolizable nitro compounds such as nitroacetate esters are used, substituents at C-1 (**2**, $R^1 \neq H$) are hardly tolerated using gramine derivatives.[6]

Recently, we have introduced a new class of precursors for reactive vinylogous imino derivatives **3** based on the utilization of the arysulfonyl system as a good leaving group (**2**, $X = ArSO_2$).[7,8] 3-(1-Arylsulfonylalkyl) indoles

Keywords: Conjugate addition; Imines; Indoles; Nitroalkanes; Sulfones.
* Corresponding author. Tel.: +39 0737 402253; fax: +39 0737 402297; e-mail: marino.petrini@unicam.it

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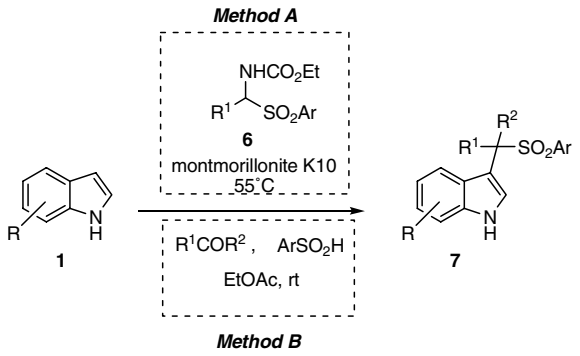


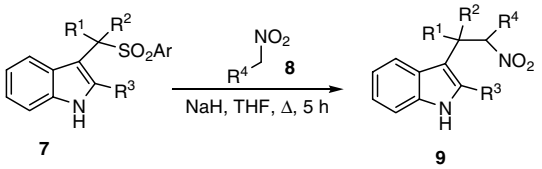
Scheme 2.

7 are readily prepared by reaction of indoles **1** with α-amidosulfones **6** in the presence of montmorillonite K-10 under solventless conditions (Scheme 2, method A)[7] or by a three-component condensation of indoles **1** with aldehydes and arenesulfinic acids (Scheme 2, method B).[8] Sulfonyl indoles **7** are able to react with Grignard as well as Reformatsky reagents leading to branched 3-alkyl indoles and 3-(3-indolyl) alkanoates under mild conditions.

We report here a further application of sulfonyl indoles **7** in the preparation of 3-(2-nitroalkyl) indoles **9** by reaction with nitroalkanes **8** under basic conditions (Scheme 3).

Among various basic promoters tested for the elimination of the arenesulfinyl group from sulfonyl indoles **7**, NaH in THF solution at reflux is the more effective in giving good yields of nitro derivatives **9** (Table 1).[9] A representative couple of nitroalkanes **8**, namely nitromethane and nitroethane have been used in the reaction with sulfonyl indoles **7** bearing different substituents at C-2 and C-1′. Phenyl substitution at C-2 does not provide any decrease in the reactivity of the corresponding sulfonyl indole **7c** allowing to efficiently prepare the corresponding nitro derivatives **9d**,**e** (Table 1, entries 4 and 5). This result is in sharp contrast to the somewhat less effective complementary process involving addition of 2-phenylindoles to nitroalkenes.[10]

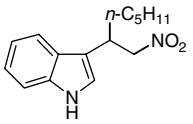
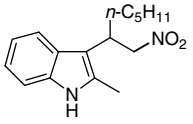
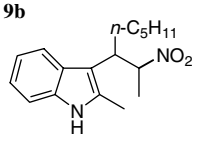
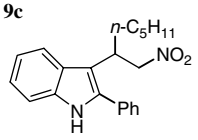
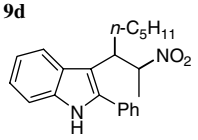
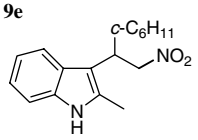
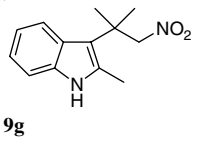
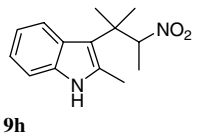
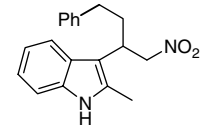
Particularly interesting is the reaction of sulfonyl indole **7e** obtained from 2-methylindole using acetone as carbonyl counterpart. This compound efficiently leads to



7a R^1= *n*-C_5H_{11}; R^2= H; R^3= H; Ar= 4-MePh
7b R^1= *n*-C_5H_{11}; R^2= H; R^3= Me; Ar= 4-MePh
7c R^1= *n*-C_5H_{11}; R^2= H; R^3= Ph; Ar= 4-MePh
7d R^1= *c*-C_6H_{11}; R^2= H; R^3= Me; Ar= Ph
7e R^1= Me; R^2= Me; R^3= Me; Ar= 4-MePh
7f R^1= $PhCH_2CH_2$; R^2= H; R^3= Me; Ar= 4-MePh

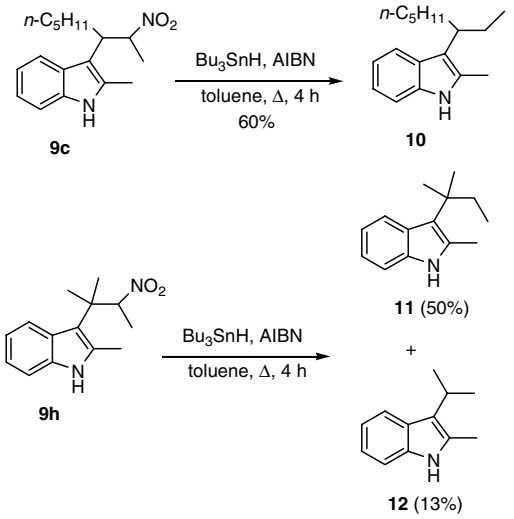
Scheme 3.

Table 1. Synthesis of 3-(1-nitroalkyl) indoles **9** by reaction of 3-(1-arylsulfonylalkyl) indoles **7** with nitroalkanes **8**[a]

Entry	Sulfone **7**	Nitroalkane **8**	Products **9**[b]	Yield[c] (%)
1	**7a**	$MeNO_2$	 **9a**	81
2	**7b**	$MeNO_2$	 **9b**	85
3	**7b**	$EtNO_2$	 **9c**	78
4	**7c**	$MeNO_2$	 **9d**	80
5	**7c**	$EtNO_2$	 **9e**	91
6	**7d**	$MeNO_2$	 **9f**	88[d]
7	**7e**	$MeNO_2$	 **9g**	84
8	**7e**	$EtNO_2$	 **9h**	90
9	**7f**	$MeNO_2$	 **9i**	82

[a] All reactions were carried out in the presence of 4 equiv NaH in THF at reflux.
[b] All products were identified on the basis of their IR and NMR spectra.
[c] Yields of pure products isolated by column chromatography.
[d] 4 equiv KH was used.

the corresponding derivatives **9g**,**h** (Table 1, entries 7 and 8), a rather unknown class of 3-(2-nitroalkyl) indoles that are difficult to prepare using conventional procedures. Reaction of sulfonyl indole **7d** bearing a cyclohexyl substituent at C-1′ which has been revealed to proceed quite sluggishly under usual conditions can be consistently accelerated using KH as basic promoter.



Scheme 4.

Although reduction of the nitro group in compounds **9** usually represents a viable entry to tryptamine derivatives, other useful synthetic manipulations of the nitro group can be envisaged.[11] The nitro group can be removed from derivatives **9** exploiting a radical substitution reaction with a hydrogen atom. This process is also referred to as a denitration reaction that is commonly carried out using Bu_3SnH as hydrogen atom donor.[12] Removal of the nitro group from secondary nitroalkanes requires higher temperatures compared to tertiary or benzylic derivatives. However, an interesting result is obtained for the reaction of nitro derivative **9c** with 2 equiv of Bu_3SnH and a catalytic amount of a radical initiator (AIBN) in toluene at reflux that after 4 h is converted into 2,3-dialkyl indole **10** in 60% yield (Scheme 4).[13]

Similarly, denitration of nitro indole **9h** gives 2,3-dialkyl indole **11** in 50% yield, but in this reaction formation of a certain amount (13%) of 2-methyl-3-isopropyl indole **12** is also observed. Formation of the latter product can be easily rationalized accounting for a reverse process that by elimination of nitroethane regenerates a vinylogous imino derivative of type **3** which is promptly reduced by Bu_3SnH.

In conclusion, sulfonyl indoles **7** are able to react under basic conditions with nitroalkanes leading to the corresponding 3-(2-nitroalkyl) indoles **9** in good yields. This procedure nicely complements the Friedel–Crafts reaction of indoles to nitroalkenes allowing the preparation of some nitro indoles such as **9g**,**h** that are not directly accessible by the conjugate addition to nitroolefins.

Acknowledgement

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.06.027.

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9. *General procedure for the preparation of 3-(2-nitroalkyl) indoles* **9**. To a stirred suspension of NaH (4.0 mmol) in dry THF (15 mL), nitroalkane **8** (1.2 mmol) and sulfonyl indole **7** (1.0 mmol) were added at room temperature. After stirring at reflux for 5 h, the reaction mixture was cooled at room temperature and quenched with 2 N HCl

(4 mL). After extraction with CH_2Cl_2 (3×10 mL), the organic phase was dried over $MgSO_4$. Removal of the solvent at reduced pressure, gave the crude nitro derivative that was purified by column chromatography (hexanes–ethyl acetate 8:2). Selected data of compounds—**9b**: Oil. IR (cm^{-1}, neat): 3644, 1650, 1555. ^1H NMR (400 MHz, $CDCl_3$): δ 0.83 (t, 3H, $J = 7.0$ Hz), 1.21–1.26 (m, 6H), 1.71–1.80 (m, 1H), 1.96–2.04 (m, 1H), 2.36 (s, 3H), 3.68–3.76 (m, 1H), 4.73–4.75 (d, 2H, $J = 7.1$ Hz), 7.06–7.15 (m, 2H), 7.26–7.28 (m, 1H), 7.52–7.54 (m, 1H), 7.83 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.0, 14.2, 22.6, 27.3, 31.7, 31.7, 36.6, 80.0, 108.8, 110.9, 118.5, 119.6, 121.3, 126.7, 132.9, 135.7. Compound **9d**: Oil. IR (cm^{-1}, neat): 3651, 1655, 1562. ^1H NMR (400 MHz, $CDCl_3$): δ 0.77 (t, 3H, $J = 7.4$ Hz), 1.02–1.19 (m, 6H), 1.65–1.78 (m, 1H), 1.97–2.09 (m, 1H), 3.85–4.01 (m, 1H), 4.47–4.48 (d, 2H, $J = 8.1$ Hz), 6.97–7.03 (m, 3H), 7.09–7.34 (m, 5H), 7.92–7.94 (m, 1H), 8.17 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.5, 27.2, 31.5, 32.1, 36.4, 80.2, 110.1, 111.5, 119.7, 120.0, 127.4, 128.6, 129.0, 129.1, 132.7, 136.3, 137.1. Compound **9h**: Oil. IR (cm^{-1}, neat): 3644, 1658, 1554. ^1H NMR (400 MHz, $CDCl_3$): δ 1.42 (d, 3H, $J = 7.0$ Hz), 1.66 (s, 3H), 1.68 (s, 3H), 2.55 (s, 3H), 5.40 (q, 1H, $J = 7.0$ Hz), 7.10–7.19 (m, 2H), 7.26–7.31 (m, 1H), 7.77–7.80 (m, 1H), 7.82 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.0, 15.9, 24.0, 27.1, 40.7, 90.0, 110.8, 119.5, 120.7, 121.3, 127.4, 131.4, 135.4.

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13. *General procedure for the denitration of 3-(2-nitroalkyl) indoles* **9c**,**h**: To a stirred solution of nitro indole **9** (1 mmol) in dry toluene (8 mL), Bu_3SnH (2.5 mmol) and AIBN (0.2 mmol) were added at room temperature. After stirring at reflux for 4 h, the reaction mixture was cooled at room temperature and the solvent was removed at reduced pressure. The residue was dissolved in ether (20 mL) and then washed with 10% aqueous KF (3×5 mL). The ethereal solution was dried over $MgSO_4$ and after removal of the solvent at reduced pressure the crude indole derivative was purified by column chromatography (hexanes–ethyl acetate 95:5). Compound **10**: Oil. IR (cm^{-1}, neat): 3390, 3049, 1379. ^1H NMR (400 MHz, $CDCl_3$): δ 0.79 (t, 3H, $J = 7.3$ Hz), 0.81–0.86 (m, 3H), 1.11–1.31 (m, 6H), 1.67–1.94 (m, 4H), 2.37 (s, 3H), 2.60–2.70 (m, 1H), 6.99–7.14 (m, 2H), 7.25–7.29 (m, 1H), 7.60–7.69 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.3, 13.0, 14.3, 22.8, 28.15, 28.7, 32.2, 35.5, 39.4, 110.4, 114.7, 118.6, 119.6, 120.5, 127.8, 131.3, 135.7.