Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 1809–1811

One-pot synthesis of polysubstituted indoles from aliphatic nitro compounds under mild conditions

Christopher A. Simoneau, Alexis M. Strohl and Bruce Ganem*

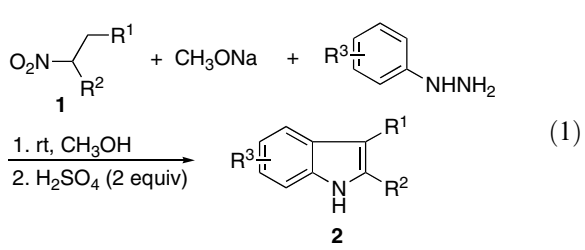
Department of Chemistry and Chemical Biology, Baker Laboratory, Cornell University, Ithaca, NY 14853-1301, United States

Received 12 December 2006; accepted 4 January 2007
Available online 10 January 2007

Abstract—Polysubstituted indoles can be prepared directly from functionalized nitroalkanes under very mildly acidic conditions in a simple, one-pot, two-stage procedure.

In the hierarchy of biologically privileged structures none surpasses those containing the indole ring system, which is prevalent in many bioactive natural products and medicinally important synthetic compounds.[1] Numerous methods have been developed for the synthesis of substituted indoles and indole-containing polycyclic ring systems,[2] which are core structural elements in such drugs as indomethacin, vincristine and manzamine, as well as in drugs for the treatment of cancer, circulatory disease, Alzheimer's, and other neurological disorders.[3]

Complex indoles are frequently synthesized by the classical Fischer method. Although historically limited to the condensations of aldehydes or ketones with arylhydrazines, the Fischer synthesis has recently been extended to the reactions of nitriles and carboxylic acids in 3-component reactions with arylhydrazines and organometallic reagents.[4] Here we describe an unexpectedly simple and effective one-pot synthesis of substituted indoles **2** from aliphatic nitro compounds **1**, Eq. 1, that avoids the strongly acidic conditions usually associated with the Nef reaction.

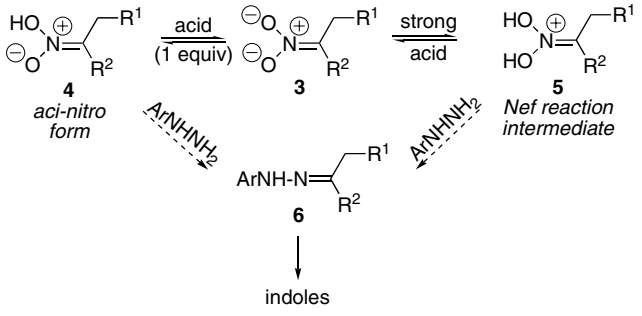


(1)

Our findings extend the range of the Fischer indole synthesis to functionalized aliphatic nitro compounds, which can be convergently assembled from readily available building blocks by alkylation or conjugate addition reactions involving nitro-stabilized carbanions.[5]

Initially, we envisioned transforming nitroalkanes via their nitronate anions **3** (Scheme 1) either to the derived *aci*-nitro species **4** or the di-protonated species **5**, which might subsequently undergo nucleophilic addition and N/N interchange to produce arylhydrazones **6**. While the classical Nef reaction of **3** can lead to **6** in two steps via carbonyl intermediates, it requires concentrated acid conditions and results in numerous byproducts.[6]

In searching for examples of nucleophilic additions to species like **4** or **5** we discovered several reports of successful condensations of primary nitroalkanes **7** with



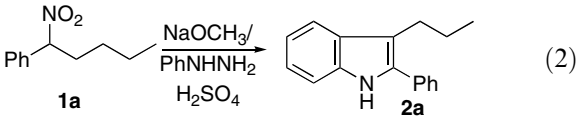
Scheme 1. Pathways for nitronate-to-imine interchange.

* Corresponding author. Tel.: +1 607 255 7360; fax: +1 607 255 6318; e-mail: bg18@cornell.edu

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.01.031

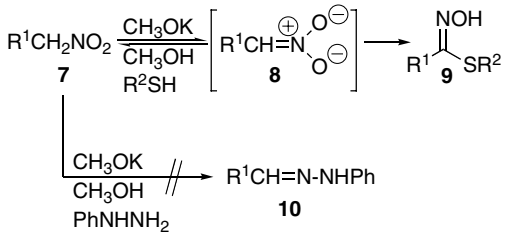
thiols (1–3 equiv) in the presence of $KOCH_3/CH_3OH$ to form thiolhydroxamate esters **9** (Scheme 2).[7] Nitronate **8** formed under such basic conditions might, in principle, react with arylhydrazines to afford the corresponding arylhydrazones **10**. However, we were unable to obtain **10** by replacing the thiol component with phenylhydrazine.

By contrast, when 1-nitro-1-phenylpentane **1a** ($R^1 = n$-propyl, $R^2 = Ph$) was combined with a solution of phenylhydrazine **7** and $NaOCH_3$ (1.1 equiv each, 1 h, rt), in CH_3OH, then acidified with sulfuric acid (2 equiv) and heated (90 °C, 24 h), indole **2a** was obtained in 68% yield, Eq. 2.[4]



(2)

Under these mildly acidic conditions, protonation of the nitronate of **1a** most likely formed the corresponding *aci*-nitro tautomer (e.g., **4**) and not the iminium species (e.g., **5**). Both valerophenone and the corresponding oxime were detected by TLC prior to capture by phenylhydrazine and conversion to indole **2a** by Fischer cyclization. A control experiment omitting phenylhydrazine was conducted in which **1a** was treated with $NaOCH_3$ (1.1 equiv) in CH_3OH, then with H_2SO_4 (2 equiv). Both valerophenone (40%) and the corresponding oxime (30%) were obtained, as well as other unidentified impurities. Such a product distribution is common in Nef reactions that are conducted under insufficiently acidic conditions. The standard Nef reaction procedure involves pouring nitronate anion **3** directly into concentrated aqueous acid, which suppresses oxime formation via hydrolysis of **5** instead of **4**.



Scheme 2. Thiohydroxamate esters from nitroalkanes.

Another control experiment showed that when a CH_3OH solution of valerophenone oxime was heated with phenylhydrazine (1.1 equiv) and H_2SO_4 (2 equiv), indole **2a** was produced in an 82% yield. Thus, our data indicate that nitroalkanes may be converted to indoles via the corresponding nitronates in one pot using just mild H_2SO_4 treatment (2 equiv).[8] Under those conditions, *aci*-nitro, ketone and oxime intermediates are all convergently transformed into the requisite phenylhydrazone, which then undergoes Fischer indole cyclization under the same gentle conditions. The results summarized in Table 1 with a variety of nitroalkanes and substituted arylhydrazines demonstrate the scope and generality of the method.

The examples in Table 1 indicate that both primary and secondary nitroalkanes are readily transformed into polysubstituted indoles. The process is also successful using *ortho*, *meta* and *para*-substituted arylhydrazines. As expected, the reaction of nitrocyclohexane **1b** with *m*-chlorophenylhydrazine formed regioisomeric indoles **2d** and **2e** in roughly equal amounts.

Nitroalkane **1d**, which has methylene groups in the β and β′-positions, formed two isomeric indoles **2h** and **2i**, with the major product **2i** arising from the conjugated enehydrazine intermediate. Likewise, the reaction of **1e** with *p*-methoxyphenylhydrazine furnished isomeric indoles **2k** and **2l** in roughly equal amounts. However, $PhNHNH_2$ reacted with **1e** to furnish a single indole product **2j**. This variation in product outcomes with **1e** using different arylhydrazines, although surprising, may reflect subtle electronic effects of the *p*-methoxy substituent on the hydrazone–enehydrazine equilibrium required for Fischer cyclization.

In conclusion, a one-pot transformation of alphatic nitroalkanes into polysubstituted indoles has been developed. The process capitalizes on the versatile behavior of nitronate anions, which are efficiently protonated and scavenged by arylhydrazines with multiplex chan-

Table 1. One-pot synthesis of substituted indoles **2** from nitroalkanes **1**

Nitroalkane	$ArNHNH_2$	Indole[9] (yield %)
1a 1-Nitro-1-phenylpentane	$PhNHNH_2$ **7**	2-Phenyl-3-propylindole **2a** (68)
1b Nitrocyclohexane	**7**	Tetrahydrocarbazole **2b** (72)[10]
1b	*o*-Cl-**7**	8-Chlorotetrahydrocarbazole **2c** (66)[11]
1b	*m*-Cl-**7**	7-Chlorotetrahydrocarbazole **2d** (32)[11]
		5-Chlorotetrahydrocarbazole **2e** (26)[11]
1b	*p*-OCH_3-**7**	6-Methoxytetrahydrocarbazole **2f** (66)[12]
1c 1-Nitropropane	**7**	3-Methylindole **2g** (50)
1d 2-Nitro-1-phenylbutane	**7**	2-Benzyl-3-methylindole **2h** (18)[13]
		2-Ethyl-3-phenylindole **2i** (56)[14]
1e Methyl 4-nitrohexanoate	**7**	3-Methylindole-2-propionic acid methyl ester **2j** (70)
1e	*p*-OCH_3-**7**	5-Methoxy-3-methylindole-2-propionic acid methyl ester **2k** (36)
		2-Ethyl-5-methoxyindole-3-acetic acid methyl ester **2l** (30)[15]
1f 5-Nitro-1-pentene	**7**	3-Allylindole **2m** (42)[16]

neling of products into the Fischer indole reaction pathway. It can be expected that this convergence of Nef and Fischer methodology will further extend the utility of aliphatic nitro compounds beyond the standard Henry, Michael, and Knoevenagel reactions and will serve as a practical and useful approach to the important families of medicinally active compounds.

Acknowledgements

This research was supported in part by the US National Institutes of Health (T32 GM 08500). Support of the Cornell NMR Facility has been provided by NSF (CHE 7904825; PGM 8018643) and NIH (RR02002).

Supplementary data

Representative experimental procedures for the synthesis of indoles described in the table, as well as supporting spectroscopic data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.031.

References and notes

1. Reviews: (a) Katritzky, A. R.; Pozharskii, A. F. In *Handbook of Heterocyclic Chemistry*; Pergamon: Oxford, 2000; (b) Hibino, S.; Choshi, T. *Nat. Prod. Rep.* **2001**, *18*, 66.
2. Gribble, G. W. *J. Chem. Soc. Perkin Trans. 1* **2000**, 1045.
3. See, for example: (a) Wilkinson, S. L. *Chem. Eng. News* **2002**, *80*, 45; (b) Heinrich, T.; Bottcher, H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2681.
4. Simoneau, C. A.; Ganem, B. *Tetrahedron* **2005**, *61*, 11374.
5. (a) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933; (b) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877.
6. (a) Pinnick, H. W. *Org. React.* **1990**, *38*, 655; (b) Ballini, R.; Petrini, M. *Tetrahedron* **2004**, *60*, 1017.
7. (a) Keller, T. H.; Yelland, L. J.; Benn, M. H. *Can. J. Chem.* **1984**, *62*, 437; (b) Buchanan, J. B. U.S. Patent 3,787,470, 1974; *Chem Abstr.* **1974**, *80*, 82059; (c) Copenhaver, J. W. U.S. Patent 2,786,865, 1957; *Chem Abstr.* **1957**, *51*, 77105.
8. *Representative experimental procedure*: Synthesis of tetrahydrocarbazole **2b**: Sodium methoxide (1.0 M in CH_3OH, 0.32 mL, 0.32 mmol) was added to a solution of phenylhydrazine (0.32 mmol) in methanol (0.90 mL) under argon at rt. Nitrocyclohexane (0.29 mmol) was added and the reaction mixture stirred at rt for 2 h under argon. The reaction mixture was cooled to 0 °C, acidified with sulfuric acid (0.59 mmol), then heated in an oil bath at 90 °C for 3 h. After cooling the reaction to 0 °C, the bulk of methanol was removed in vacuo and the resulting oil was partitioned between ether (6 mL) and water (3 mL). After separating the layers, the aqueous phase was extracted twice more and the combined ether layers were washed with saturated NaCl (1 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (8:1 hexanes–ethyl acetate, $R_f = 0.3$), to afford the known tetrahydrocarbazole **2b** as a white solid (36 mg, 72%).
9. All indoles were prepared following the procedure for **2a** except heating only 1–3 h at 90 °C.
10. Ribeiro, G. L.; Khadilkar, B. M. *Synthesis* **2001**, 370.
11. Dodsworth, D. J.; Quesada, P. A.; DeRosa, M. K. *J. Heterocycl. Chem.* **1988**, *25*, 167.
12. Caubere, C.; Caubere, P.; Ianelli, S.; Nardelli, M.; Jamart-Grégoire, B. *Tetrahedron* **1994**, *50*, 11903.
13. Wiedenau, P.; White, A. W. *Tetrahedron* **1983**, *39*, 3767.
14. Baccolini, G.; Bartoli, G.; Marotta, E.; Todesco, P. E. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2695.
15. Dillard, R. D.; Bach, N. J.; Draheim, S. E.; Berry, D. R.; Carlson, D. G.; Chirgadze, N. Y.; Clawson, D. K.; Hartley, L. W.; Johnson, L. M.; Jones, N. D.; McKinney, E. R.; Mihelich, E. D.; Olkowski, J. L.; Schevitz, R. W.; Smith, A. C.; Snyder, D. W.; Sommers, C. D.; Wery, J.-P. *J. Med. Chem.* **1996**, *39*, 5119.
16. Cardillo, B.; Casnati, G.; Pochini, A.; Ricca, A. *Tetrahedron* **1967**, *23*, 3771.