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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

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. Though historically limited to condensations of aldehydes or ketones with arylhydrazines, the Fischer synthesis has recently been extended to 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** (Eqn 1) that avoids the strongly acidic conditions usually associated with the Nef reaction.

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

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

Supplementary Data

Representative experimental procedures for the synthesis of indoles described in the Table, as well as supporting spectroscopic data.

Supplementary data can be found online at ScienceDirect.

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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 thiols (1–3 equiv) in the presence of KOCH₃/CH₃OH 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** (R¹ = *n*-propyl, R² = Ph) was combined with a solution of phenylhydrazine **7** and NaOCH₃ (1.1 equiv each, 1 h, rt), in CH₃OH, then acidified with sulfuric acid (2 equiv) and heated (90 °C, 24 h), indole **2a** was obtained in 68% yield (Eqn 2).⁴

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 NaOCH₃ (1.1 equiv) in CH₃OH, then with H₂SO₄ (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 the nitronate anion **3** directly into concentrated aqueous acid, which suppresses oxime formation via hydrolysis of **5** instead of **4**.

Another control experiment showed that when a CH₃OH solution of valerophenone oxime was heated with phenylhydrazine (1.1 equiv) and H₂SO₄ (2 equiv), indole **2a** was produced in 82% yield. Thus, our data indicate that nitroalkanes may be converted to indoles via the corresponding nitronates in one pot using just mild H₂SO₄ 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 the Table with a variety of nitroalkanes and substituted arylhydrazines demonstrate the scope and generality of the method.

The examples in the Table 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, 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, reaction of **1e** with *p*-methoxyphenylhydrazine furnished isomeric indoles **2k** and **2l** in roughly equal amounts. However, PhNHNH₂ 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 aliphatic 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 channeling 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 important families of medicinally active compounds.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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8. Representative experimental procedure: Synthesis of tetrahydrocarbazole **2b**: Sodium methoxide (1.0 M in CH₃OH, 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 MgSO₄, 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%).

Scheme 1.
Pathways for nitronate-to-imine interchange

Scheme 2.
Thiohydroxamate esters from nitroalkanes

Table
One-Pot Synthesis of Substituted Indoles **2** from Nitroalkanes **1**

nitroalkane	ArNHNH ₂	Indole (% yield) ^a
1a 1-nitro-1- phenylpentane	PhNHNH ₂	2-phenyl-3-propylindole 2a (68)
1b nitrocyclo- hexane	7	tetrahydrocarbazole 2b (72) ^b
1b	<i>o</i> -Cl- 7	8-chlorotetrahydrocarbazole 2c (66) ^c
1b	<i>m</i> -Cl- 7	7-chlorotetrahydrocarbazole 2d (32) ^c
		5-chlorotetrahydrocarbazole 2e (26) ^c
1b	<i>p</i> -OCH ₃ - 7	6-methoxytetrahydrocarbazole 2f (66) ^d
1c 1- nitropropane	7	3-methylindole 2g (50)
1d 2-nitro-1- phenylbutane	7	2-benzyl-3-methylindole 2h (18) ^e
		2-ethyl-3-phenylindole 2i (56) ^f
1e methyl 4- nitrohexanoate	7	3-methylindole-2-propionic acid methyl ester 2j (70)
1e	<i>p</i> -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) ^g
1f 5-nitro-1- pentene	7	3-allylindole 2m (42) ^h

^a All indoles were prepared following the procedure for **2a** except heating only 1–3 h at 90 °C;

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