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Efficient Method for the Synthesis of 2,3-Unsubstituted Nitro Containing Indoles from *o*-Fluoronitrobenzenes

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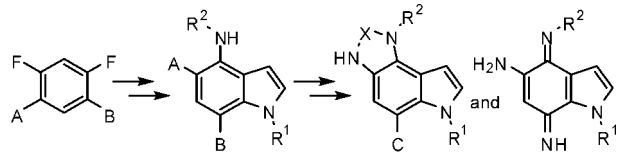
ABSTRACT



A, B = NO_2 or H, C = NH_2 or H
R^1, R^2 = H or alkyl or aryl

A methodology was developed for the efficient synthesis of 2,3-unsubstituted nitro containing indoles via acid catalyzed intramolecular electrophilic cyclization. Subsequent reduction of nitro groups allows the construction of some indole fused heterocycles and indole quinone diimines. This strategy provides an efficient method for the preparation of biologically and medicinally interesting molecules.

The construction of privileged structures is an important strategy in medicinal chemistry. The indole ring system is one of the most prevalent structural motifs found in biologically active compounds of both natural and synthetic origin. For well over 100 years, the synthesis and functionalization of indoles has been a major area of focus for synthetic organic chemists, and numerous methods for the preparation of indoles have been developed.[1] Acid catalyzed intramolecular electrophilic cyclization-elimination of 2-anilino acetals was one of the early concepts for indole construction. But the first reports of success by this method were found to be unreproducible even by succeeding authors. A thorough reinvestigation by Chastrette in 1962 confirmed the general failure under Brønsted acid conditions, although some 2-substituted indoles could be obtained in fair yields by using BF_3 as catalyst in benzene solution.[2,4] Forbes and coworkers[3a] subsequently achieved production of some *N*-alkyl- (but not *N*-unsubstituted) indoles from the corresponding anilino acetals by treatment with BF_3−HOAc in trifluoroacetic anhydride. Nordlander[4a] and Sundberg[4b] and coworkers modified and realized this method in many cases by cyclization following initial acylation of the amino function in 1980s and concluded some experiences of this method. The protonation of the anilino nitrogen will greatly deactivate the aromatic ring for the electrophilic cyclization. The success of their method could be attributed in part to effectively reducing the aniline nitrogen basicity through acylation without severe deactivation of the aromatic ring or acetal function. Substituents deactivating relative to

(1) (a) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875–2911. (b) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2491–2515. (c) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045–1075. (d) Zhang, Y.; Donahue, J. P.; Li, C. J. *Org. Lett.* **2007**, *9*, 627–630. (e) Opatz, T.; Ferenc, D. *Org. Lett.* **2006**, *8*, 4473–4475. (f) Du, Y.; Liu, R.; Linn, G.; Zhao, K. *Org. Lett.* **2006**, *8*, 5919–5922.

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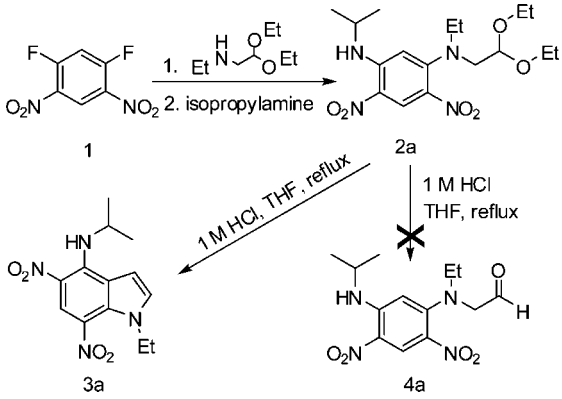
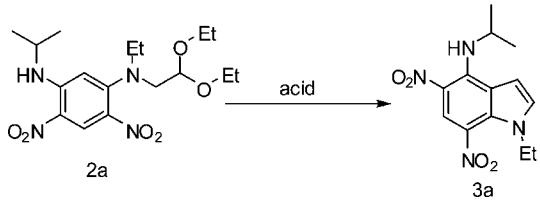
Scheme 1



hydrogen would thwart the cyclization. The method is also adversely affected by substituents in the prospective 7-position (ortho to amino).[4]

Table 1. Optimization of Cyclization Conditions



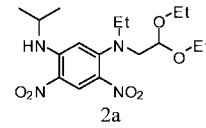
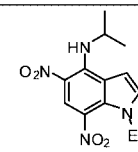
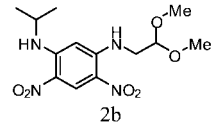
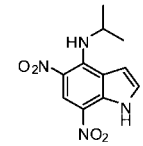
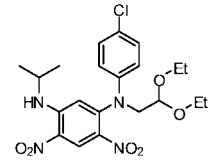
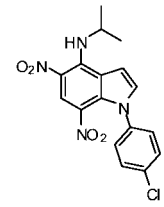
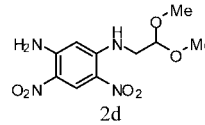
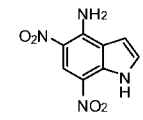
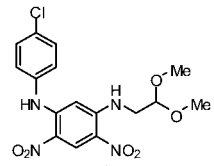
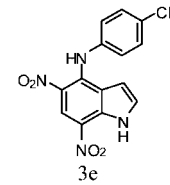
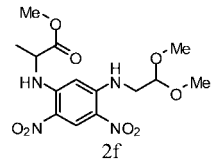
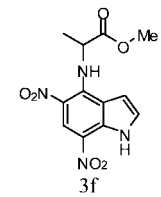
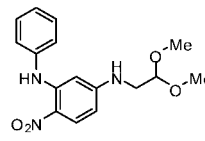
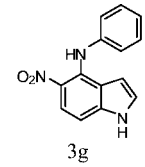
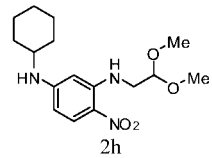
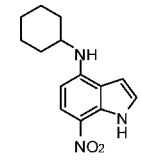
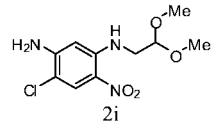
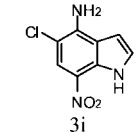
entry	solvent (mL)	acid (equiv)	time	yield (%)
1[a]	THF (2)	1 M HCl (1.0)	8 h	64
2[a]	THF (2)	MsOH (0.3)	23 h	71
3[a]	THF (2)	TFA (10.0)	8 h	81
4[a]	THF (2)	$TiCl_4$ (1.0)	30 min	51
5[b]	CH_2Cl_2 (5)	TFA (5.0)	3 h	66
6[b]	CH_2Cl_2 (5)	TFA (1.3)	20 h	92

[a] Reaction was carried out at reflux. [b] Reaction was carried out at rt.

Herein, we report an efficient method for the synthesis of some 2,3-unsubstituted nitro containing indoles from 2,4-difluoro-1,5-dinitrobenzene or 2,4-difluoronitro-benzene and aminoacetaldehyde dialkylacetals via acid catalyzed intramolecular electrophilic cyclization. This synthesis was inspired by an unexpected observation as shown in Scheme 1. When compound **2a** was treated with 1 M HCl in THF to hydrolyze the acetal group, dinitroindole **3a** was obtained in 64% yield instead of the expected aldehyde. This obviously violated the conclusion of Nordlander and Sundberg because there are two deactivating nitro groups on the phenyl ring. After carefully checking of the ^{1}H NMR of compound **2a**, it was found the chemical shift of the proton between two amino groups sit at 6.17 ppm, whereas that of unsubstituted benzene is 7.26 ppm.[5] This means that the electron density of the

(5) Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512–7515.

Table 2. Examples of Indoles Prepared

entry	substrate	product	time yield (%)
1[a]	 2a	 3a	20 h (92)
2[b]	 2b	 3b	30 h (93)
3[b]	 2c	 3c	5 h (64)
4[b]	 2d	 3d	14 h (75)
5[b]	 2c	 3e	reflux 28 h (25)
6[b]	 2f	 3f	30 h (71)
7[b]	 2g	 3g	20 h (50)
8[b]	 2h	 3h	24 h (94)
9[b]	 2i	 3i	20 h (53)

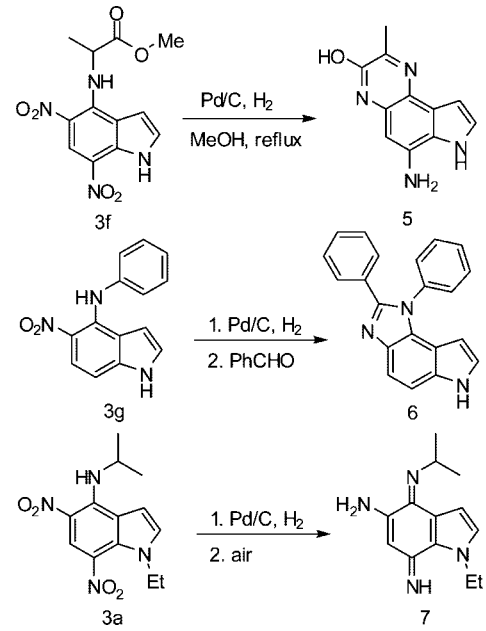
All yields are of isolated product. [a] Use 1.3 equiv of TFA. [b] Use 5.0 equiv of TFA. Reactions were carried out at rt except entry 5.

corresponding position is unexpectedly high and promoted this cyclization.

This direct acid catalyzed cyclization provided a fast and efficient way for the preparation of multisubstituted indoles which may have the potential to be transformed to many privileged structures. Considering this, the conditions and scale of this reaction were further investigated. Compound **2a** was first used as the model substrate to optimize the reaction conditions as shown in Table 1. Strong inorganic and organic acids were used as catalysts and it was found TFA in THF gave higher yield. When the solvent was changed from THF to CH_2Cl_2, the reaction could finish at room temperature and the yield could reach 92%. The reaction finished very fast with 5.0 equiv of TFA (entry 5), but the yield was low due to the formation of some unidentified byproducts. Then TFA load was lowered to 1.3 equiv and excellent yield was obtained (entry 6). After determining the optimized condition—TFA (1.3 equiv), CH_2Cl_2 (0.1 M solution for substrate) at room temperature—we tried to examine the substrate scope of the reaction. The substrates for the cyclization were prepared by reaction of 2,4-difluoro-1,5-dinitrobenzene or 2,4-difluoronitrobenzene with amines in a separated substitute procedure or a one pot method according to the literature.[6] With all the other substrates, however, the reaction did not go to completion, even with prolonged reaction time under the above optimized condition. When more TFA was loaded (5.0 equiv), a better result could be obtained. Substrates with different substitutions on amino group were tried for cyclization as shown in Table 2. Good to excellent yields for the isolated products were achieved. We also tried to use ethoxy and ethylthio to replace one of the amino groups to see if the molecules can also undergo this cyclization, but unfortunately, no corresponding product was found.

Encouraged by the above results, we initiated further investigation to explore the possibility of preparing other privileged structures derived from indoles prepared from the above cyclizations. *o*-Nitroanilines are versatile substrates for the construction of benzofused heterocycles.[7] It will be a useful method for the preparation of many indole fused heterocycles with bioactive interests. Reduction of the nitro groups of compounds **3f** and **3g** followed by cyclization, compounds **5** and **6** were successfully obtained in yields of 79 and 43%, respectively (Scheme 2). Indole-4,7-quinones were reported to have various bioactivities.[8] Indole quinone diimine is an isostere of indole quinone, it may also have various activities and expands the diversity of the scaffold, but no synthetic route to it has been reported. Reduction of the nitro groups of compound **3a**, and left the reaction mixture exposed to the air, indole quinone diimine **7** was successfully obtained in 49% yield.

Scheme 2. Indole Derived Structures



In conclusion, we have developed a method for the preparation of 2,3-unsubstituted nitro containing indoles from commercially available 2,4-difluoro-1,5-dinitrobenzene or 2,4-difluoronitrobenzene and 2-aminoacetaldehyde dimethylacetal (or its *N*-substituted derivatives) under mild conditions. The nitro groups of resulting indoles can be reduced and then further transformed to other indole fused structures or indole quinone diimines, that are useful for the construction of biologically interesting molecules.

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Supporting Information Available: Detailed synthetic procedures, characterization data, and ^{1}H NMR, ^{13}C NMR of synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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