Tetrahedron Letters 50 (2009) 4423–4426

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Straightforward selective preparation of nitro- or amino-indoles from 2-halonitroanilines and alkynes. First synthesis of 7-amino-5-nitroindoles

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ARTICLE INFO

Article history:
Received 2 April 2009
Revised 5 May 2009
Accepted 13 May 2009
Available online 18 May 2009

Keywords:
Nitroindoles
Aminoindoles
Reduction
Coupling
Cyclization

ABSTRACT

A one-pot selective synthesis of 2-substituted C5-, C6-, and C7-nitro- or amino-indoles has been developed from 2-halonitroanilines. These two types of nitrogen-substituted indoles have been selectively obtained by only varying the solvent used in the tandem Sonogashira coupling/heteroannulation reaction. Moreover, from commercially available 2-bromo-4,6-dinitroaniline an unprecedented in situ selective reduction of one of the nitro groups has allowed the synthesis of new 7-amino-5-nitro-2-substituted indoles.

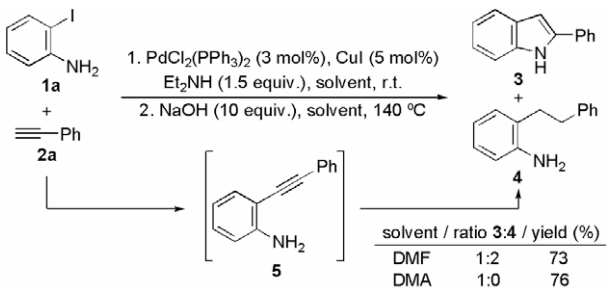
Indoles bearing nitrogen substituents on the benzenoid moiety are often found to exhibit biological activity,[1] and so the development of synthetic methodologies that allow the easy access to this type of compounds is of current interest. Among them, nitroindoles[2] are useful starting materials to a wide range of nitrogen-substituted indole derivatives such as aminoindoles and azidoindoles.[3] Considering the many methods available for the indole-ring synthesis, the cyclization under basic conditions of *o*-alkynylanilines, usually prepared from *o*-haloanilines via the Sonogashira reaction, is a valuable methodology.[4] In this context, the synthesis of different 2-substituted-nitroindoles derivatives has been reported from commercially available 2-haloanilines,[4b–d] or 2-amino-nitrophenols by this cross-coupling–heteroannulation approach.[5] Following our interest in the development of new methods for the synthesis of regioselectively functionalized indoles,[6] we have recently developed an efficient route to 2-substituted indoles from 2-iodoanilines and terminal alkynes, using a NaOH-mediated 5-*endo*-*dig* cyclization as the key step.[7] Herein, we wish to report a novel one-pot procedure for the synthesis of 2-substituted indoles possessing selectively a nitro or an amino substituent at the C5, C6, or C7 positions.

When we attempted the synthesis of 2-phenylindole from 2-iodoaniline **1a** and phenylacetylene **2a** under our previously reported conditions,[7] we observed the formation of 2-(2-phenylethyl)aniline **4** (48% yield) along with the expected 2-phenylindole **3** (25% yield) (Scheme 1).

We thought that the formation of **4** could be due to competitive hydrogenation of intermediate 2-alkynylaniline **5** under the reaction conditions. Surprisingly, we observed that a simple solvent change from DMF to *N*,*N*-dimethylacetamide (DMA) completely avoided the formation of the side product **4** allowing the isolation of 2-phenylindole **3** in 76% yield (Scheme 1).

This result suggests that when the reaction is performed in DMF an ammonium formate derivative, which is known to act as a source of hydrogen,[8] is generated under the basic reaction conditions.

Having in mind that a simultaneous reduction of nitro- to amino-group has been observed in a Pd-catalyzed Suzuki cross-coupling reaction,[9] and taking advantage from the finding that a hydrogen source must be generated under our reaction conditions in DMF as solvent, we reasoned that nitroindoles or aminoindoles



Scheme 1. One-pot Sonogashira coupling/NaOH-mediated reactions of 2-iodoaniline **1a** with phenylacetylene **2a**.

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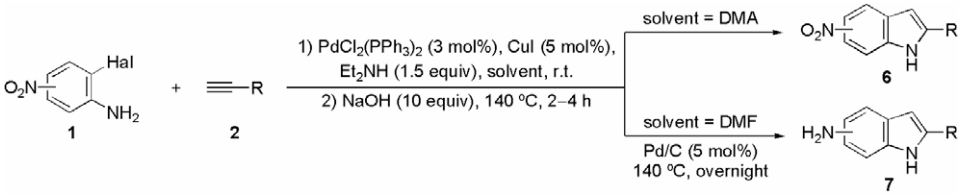
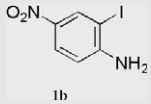
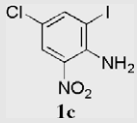
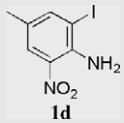
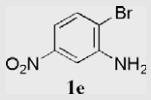
doi:10.1016/j.tetlet.2009.05.027

Table 1
Synthesis of nitroindoles **6** and aminoindoles **7** from 2-halonitroanilines **1** and terminal alkynes **2**

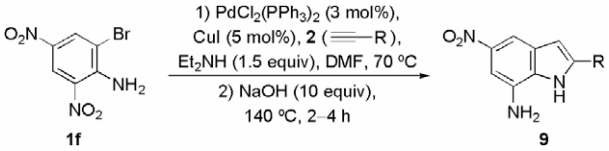


Entry	Starting aniline	Alkyne	R	Solvent	Product	Yield[a] (%)
1		**2a**	Ph	DMA	**6ba**: R = Ph	84
2		**2b**	*c*-C_6H_9[b]	DMA	**6bb**: R = *c*-C_6H_9	76
3		**2c**	*n*-Bu	DMA	**6bc**: R = *n*-Bu	89[c]
4		**2d**	*n*-C_5H_{11}	DMA	**6bd**: R = *n*-C_5H_{11}	81
5		**2a**	Ph	DMF	**7ba**: R = Ph	55
6		**2b**	*c*-C_6H_9[b]	DMF	**7bb**: R = *c*-C_6H_9	48
7		**2c**	*n*-Bu	DMF	**7bc**: R = *n*-Bu	65
8		**2d**	*n*-C_5H_{11}	DMF	**7bd**: R = *n*-C_5H_{11}	66
9		**2e**	4-F-3-MeC_6H_3	DMF	**7be**: R = 4-F-3-MeC_6H_3	44[c]
10		**2c**	*n*-Bu	DMA	**6cc**: R = *n*-Bu	55[c]
11		**2f**	3-ClC_6H_4	DMA	**6cf**: R = 3-ClC_6H_4	76[c]
12		**2b**	*c*-C_6H_9[b]	DMF	**7cb**: R = c-C_6H_9	40
13		**2c**	*n*-Bu	DMF	**7cc**: R = *n*-Bu	46
14		**2d**	*n*-C_5H_{11}	DMF	**7cd**: R = *n*-C_5H_{11}	45[c]
15		**2a**	Ph	DMA	**6da**: R = Ph	69
16		**2d**	*n*-C_5H_{11}	DMA	**6dd**: R = *n*-C_5H_{11}	52[c]
17		**2b**	*c*-C_6H_9[b]	DMF	**7db**: R = *c*-C_6H_9	30
18		**2a**	Ph	DMA	**6ea**: R = Ph	60
19		**2d**	*n*-C_5H_{11}	DMA	**6ed**: R = *n*-C_5H_{11}	47
20		**2a**	Ph	DMF	**7ea**: R = Ph	45
21		**2d**	*n*-C_5H_{11}	DMF	**7ed**: R = *n*-C_5H_{11}	32
22		**2g**	4-MeC_6H_4	DMF	**7eg**: R = 4-MeC_6H_4	43

[a] Isolated yield after column chromatography.
[b] 1-Cyclohexenyl.
[c] Carried out under microwave irradiation (140 °C, maximum wattage supplied 80 W): 20 min for the cyclization step and 30 min for the reduction.

could be selectively synthesized from the same starting 2-halonitroanilines **1** by a simple selection of the reaction solvent. To our delight, we found that whereas the use of DMA as solvent allowed the preparation of expected nitroindoles **6** in good yields, when DMF was employed a simultaneous reduction of the nitro- to the corresponding amino-group took place allowing the preparation of aminoindoles **7** in moderate yields[10] (Table 1). In some cases, when DMF was used, the reduction of the intermediate nitroindoles **6** takes place slowly. However, we found that the addition of Pd/C (5 mol %) to the reaction mixture allowed the complete reduction in reasonable times. Aryl-, alkyl-, and alkenyl-groups could be placed at the C-2 of the final indoles **6** and **7** starting from different alkynes **2a–g** (Table 1). Regarding the starting 2-halonitroaniline, the use of commercially available **1b** allows the synthesis of 4-nitroindoles **6ba–d** in high yields (entries 1–4) and 4-aminoindoles **7ba–e** in moderate to good yields (entries 5–9). On the other hand, C7-nitroindoles **6cc**, **f** and **6da**, **d** (entries 10–11, 15–16) as well as C7-aminoindoles **7cb–d** and **7db** (entries 12–14, 17) were obtained from 2-iodoanilines **1c** and **1d**[11] in moderate yields. Finally, C6-nitrogen-substituted indoles **6ea, d** and **7ea–g** (entries 18–22) were also synthesized from commercially available 2-bromoaniline **1e** in moderate yields. We have also found that the reaction times for the NaOH-mediated cyclization and the simultaneous reduction of the nitro groups could be dramatically reduced by carrying out the process under microwave irradiation.[12]

Table 2
Synthesis of 7-amino-5-nitro-2-substituted indoles **9** from 2-bromo-4,6-dinitroaniline **1f** and terminal alkynes **2**[14]



Entry	Alkyne	R	Product	Yield[a] (%)
1	**2a**	Ph	**9a**	46
2	**2b**	*c*-C_6H_9[b]	**9b**	36
3	**2c**	*n*-Bu	**9c**	40
4	**2d**	*n*-C_5H_{11}	**9d**	50
5	**2f**	3-ClC_6H_4	**9e**	44
6	**2g**	4-MeC_6H_4	**9f**	43

[a] Isolated yield after column chromatography.
[b] 1-Cyclohexenyl.

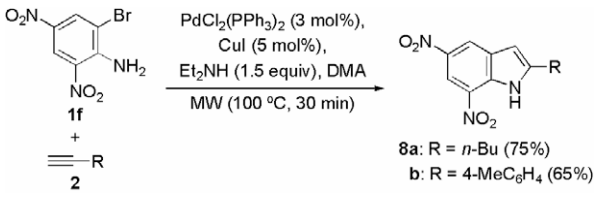
In order to further evaluate the scope of the process, we decided to use commercially available 2-bromo-4,6-dinitroaniline **1f** as starting 2-halonitroaniline. Due to the strong electron-withdrawing effect of the two nitro groups, the cyclization of intermediate *o*-alkynylanilines to the corresponding 2-substituted 5,7-dinitroindoles **8** took place without the addition of base (Scheme 2). This process could also be carried out under microwave irradiation affording compounds **8** in good yields and in short reaction times (Scheme 2).

Surprisingly, when we carried out the same reaction between **1f** and terminal alkynes **2** under the reaction conditions described above for the synthesis of aminoindoles **7**, (i.e., by using DMF as solvent instead of DMA and with the addition of NaOH after the Sonogashira coupling), we obtained the indole derivatives **9** where only one of the two nitro groups had been reduced to the corresponding amino group. In this case the reaction does not require the additional treatment with Pd/C catalyst.[13] Although at the moment we have no explanation for this selective reduction and the yields of the isolated compounds **9** are moderate, this result is very interesting because to the best of our knowledge there is no method described in the literature for the synthesis of 7-amino-5-nitroindoles.

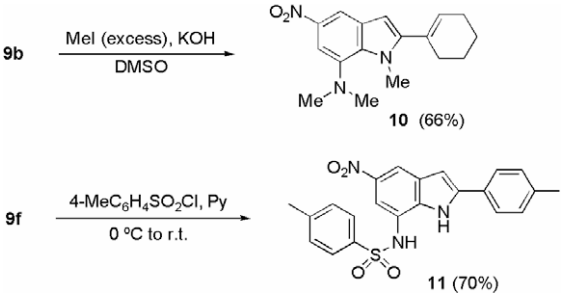
We have also prepared some derivatives of these interesting indoles **9**. A complete methylation reaction was observed upon treatment of aminonitroindole **9b** with excess of methyl iodide that allowed the isolation of trimethyl derivative **10** (Scheme 3). Gratifyingly, the indole derivative **11**, obtained from **9f** by sulfonamide formation, could be crystallized and its structure confirmed by single-crystal X-ray diffraction analysis (Scheme 3 and Fig. 1).[15]

The relevance of this new synthesis of 7-amino-5-nitroindoles **9** is supported by the fact that reduction of 5,7-dinitroindole **8a** under conventional conditions (H_2 with Pd/C in EtOH) gave rise to the corresponding 5,7-diaminoindole derivative in 80% yield.[16]

To sum up, we have described a useful new approach to the synthesis of 2-substituted indoles bearing an amino or a nitro group at the benzenoid moiety based on a simultaneous reduction of nitro-



Scheme 2. Synthesis of 5,7-dinitroindoles **8**.



Scheme 3. Preparation of 7-amino-5-nitroindole derivatives **10** and **11**.

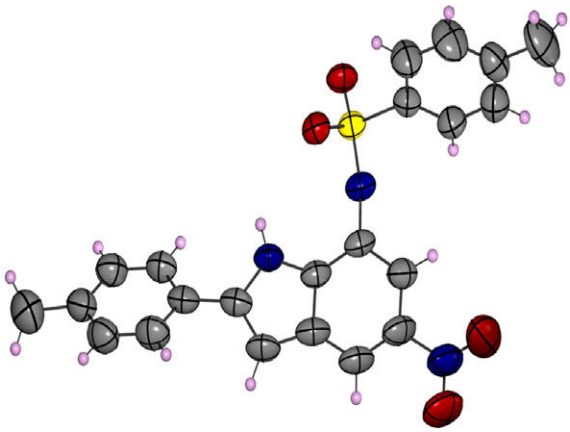


Figure 1. Crystal structure of compound **11** (a molecule of Et_2NH has been omitted for clarity).

to amino-group when DMF was used as solvent. Although in some cases the yields are moderate, this methodology easily allows the synthesis of regioselectively nitrogen-functionalized indoles in a one-pot procedure from commercially or easily available starting materials. An unprecedented selective synthesis of new 7-amino-5-nitroindoles from 2-bromo-4,6-dinitroaniline has also been developed.

Acknowledgments

We gratefully thank Ministerio de Educación y Ciencia (MEC) and FEDER (CTQ2007-61436/BQU) and Junta de Castilla y León (BU021A09) for financial support. V.G. thanks MEC for a FPU predoctoral fellowship. Many thanks are due to Dr. F. Rodríguez (Universidad de Oviedo) for helpful comments.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.027.

References and notes

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10. The moderate yields obtained could be due to the prolonged reaction times under basic conditions. Also, in some cases we observed small amounts of by-products derived from partial or total reduction of the triple bond in *o*-alkynylanilines intermediates such as **5**. However, aniline derivatives from reduction of the corresponding halides were never detected, see: Zawisza, A. M.; Muzart, J. *Tetrahedron Lett.* **2007**, *48*, 6738–6742.
11. These *o*-iodoanilines were obtained from commercially available 4-chloro-2-nitroaniline and 4-methyl-2-nitroaniline, respectively, by iodination with ICl in AcOH.
12. The mixture was charged under air in a 35-mL thick-walled glass sealed tube and irradiated, under stirring, at 70 °C in the microwave cavity for 10 min (Sonogashira coupling). After cooling, freshly powdered NaOH (10 equiv) was added to the reaction mixture and it was heated at 140 °C in the microwave cavity for 20 min (cyclization). After cooling, Pd/C was added to the reaction mixture and it was heated at 140 °C in the microwave cavity for 30 min (reduction). A CEM Focused Microwave System, Discover S-Class was used (temperature measurements were conducted using an IR sensor located below the microwave-cavity floor, and reaction time refers to the total hold time at the indicated temperature; the maximum wattage supplied was 80 W).
13. The likely intermediate 5,7-dinitroindoles **8** were detected by GC-MS but after completion of the cyclization, only the final 7-amino-5-nitroindoles **9** were isolated.
14. Typical procedure for the synthesis of 2-substituted 7-amino-5-nitroindole derivatives **9**; synthesis of 7-amino-5-nitro-2-phenyl-1*H*-indole (**9a**; Table 2, entry 1): A mixture of 2-bromo-4,6-dinitroaniline **1f** (262 mg, 1 mmol), phenylacetylene **2a** (153 mg, 1.5 mmol), $PdCl_2(PPh_3)_2$ (21 mg, 0.03 mmol), CuI (9.5 mg, 0.05 mmol), and Et_2NH (110 mg, 1.5 mmol) in DMF (3 mL) was stirred under N_2 at 70 °C for 2 h (the consumption of the starting material was monitored by GC-MS). Then, freshly powdered NaOH (400 mg, 10 mmol) was added to the reaction mixture, and it was heated to 140 °C for 3 h (the end of the cyclization was monitored by GC-MS). The reaction was cooled to rt. and then, CH_2Cl_2 (20 mL) was added. The separated aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were washed with water (2 × 60 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (eluent: hexane/EtOAc, 3/2) to afford **9a** (116 mg, 46%) as a brown solid; mp 244–246 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.58 (s, 1H), 7.88–7.79 (m, 3H), 7.48 (t, J = 7.5 Hz, 2H), 7.39–7.31 (m, 1H), 7.24 (d, J = 2.0 Hz, 1H), 7.02 (s, 1H), 5.82 (br s, 2H); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ = 142.5 (C), 139.5 (C), 134.4 (C), 131.4 (C), 129.4 (C), 129.1 (2 × CH), 128.1 (CH), 127.8 (C), 125.1 (2 × CH), 105.8 (CH), 101.5 (CH), 98.6 (CH); EI-LRMS m/z 253 (M^+, 9), 231 (44), 207 (100), 191 (12); HRMS calcd for $C_{14}H_{11}N_3O_2$, 253.0851; found, 253.0854.
15. CCDC 725042 contains the supplementary crystallographic data for compound **11**·Et_2NH. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
16. See, also: Saleha, S.; Siddiqui, A. A.; Khan, N. H. *Indian J. Chem.* **1980**, *19B*, 81–82.