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Tetrahedron Letters 49 (2008) 1531–1533

Tetrahedron Letters

Efficient reductive acylation of 3-nitroindoles

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Received 13 September 2007; accepted 19 December 2007
Available online 25 December 2007

Abstract

3-Nitroindoles are catalytically reduced by hydrogen on palladium/carbon to furnish the relatively unstable aminoindoles, which in the presence of carboxylic acid anhydrides afford good to excellent yields of the corresponding *N*-acylaminoindoles. 2-Nitroindoles give lower yields of N-acylated 2-aminoindoles.

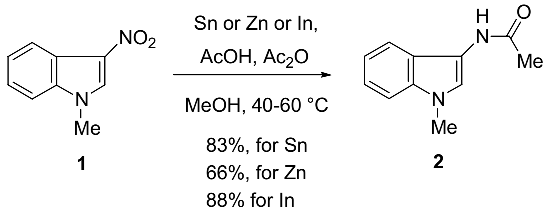
Keywords: Aminoindoles; Acylaminoindoles; Reduction; Nitroindoles; Hydrogenation

Although the indole nucleus is found in myriad alkaloids and biologically active heterocycles, 3- and 2-aminoindoles are virtually unexplored as novel heterocyclic enamines due to their relative instability.[1–3] Nevertheless, these aminoindoles could potentially serve as important vehicles for the synthesis of other indoles and fused indole heterocycles. For example, in a reported synthesis of δ-carbolines,[4] the requisite 3-aminoindoles were generated and suitably trapped by in situ hydrolysis of 3-acetylaminoindoles, which were prepared via a Beckmann rearrangement of the corresponding 3-acetylindole oximes. An efficient and direct synthesis of derivatized 3- and 2-aminoindoles would be of enormous value for the study of their chemistry.

In this regard, and in connection with our interest in the chemistry of nitroindoles,[5] we recently reported a one-pot indium-mediated reductive acylation of 3- and 2-nitroindoles affording the respective 3- and 2-acylaminoindoles.[1] Although several reducing conditions are available for the reduction and subsequent acylation of nitro compounds, the reports of achieving this two-step conversion in a one-pot procedure are limited. Such methods include $PtCl_2(PPh_3)_2$–$SnCl_4$ in the presence of CO and carboxylic acids,[6a] Fe(III)-exchanged montmorillonite with NaI and carboxylic acids,[6b] $Ni(CO)_4$ with carbon monoxide and acetic or propionic acid,[6c] $Ru_3(CO)_{12}$ with methyl formate or formic acid,[6d] molybdenum hexacarbonyl and carboxylic acids,[6e] and iodine or iodides with red phosphorus and carboxylic acids.[6f] Most of these methods require high temperatures, toxic reagents, and/or expensive catalysts.

Because our indium-mediated reduction of nitroindoles requires an excess of expensive indium,[1] we have examined tin and zinc with acetic anhydride as cheaper alternatives in this reductive acylation (Scheme 1). Although the desired product **2** is obtained with both metals, the yields are lower than the indium-mediated reduction.

Therefore, we turned to catalytic hydrogenation using palladium on carbon to accomplish this one-pot reductive acylation of 3- and 2-nitroindoles, which were synthesized



Scheme 1.

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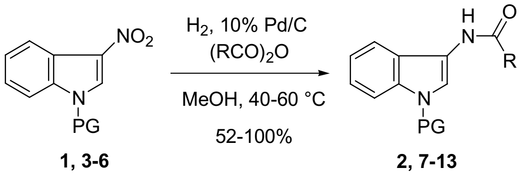
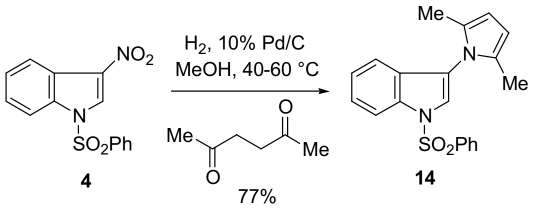
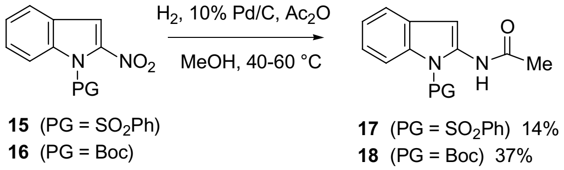
0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.12.108



Scheme 2.



Scheme 3.



Scheme 4.

Table 1
Synthesis of acetylaminoindoles (**2**, **7**–**13**) from nitroindoles (**1**, **3**–**5**) using H_2, Pd/C

3-Nitroindole	PG	Anhydride used	Product	R	Yield (%)
1	Me	Ac_2O	**2**	Me	100
1	Me	Boc_2O	**7**	Boc	99
1	Me	$(C_6H_{11}O)_2O$	**8**	$(CH_2)_4CH_3$	95
1	Me	$(PhCO)_2O$	**9**	Ph	91
3	Bn	Ac_2O	**10**	Me	76
4	SO_2Ph	Ac_2O	**11**	Me	52
5	CO_2Et	Ac_2O	**12**	Me	61
6	Boc	Ac_2O	**13**	Me	80

as described earlier.[7] In the event, treatment of 1-methyl-3-nitroindole (**1**) with hydrogen on 10% Pd/C in methanol in the presence of acetic anhydride afforded **2** in nearly quantitative yield (Scheme 2, Table 1).[8,9] In contrast to the corresponding 3-aminoindole, **2** is quite stable and can be stored indefinitely, but, as reported by Dupas and co-workers,[4] can be readily converted in situ to the 3-aminoindole by methanolic HCl as necessary. This simple reductive-acylation of 3-nitroindoles is quite general. Thus, as shown in Table 1, the reaction of **1** with H_2 and Pd/C in the presence of Boc-anhydride provides Boc-protected amine **7** in 99% yield.[10] Similarly, hexanoic anhydride and benzoic anhydride furnish **8** and **9**, respectively, in excellent yield.

Treatment of different N-protected 3-nitroindoles **3**–**6** affords the corresponding acetylated amines **10**–**13** in 52–80% yield.[10,11]

The Paal–Knorr pyrrole synthesis[12] is widely used to prepare pyrroles from amines and 1,4-dicarbonyl compounds, and a multitude of acidic and other conditions (*p*-TSA,[13] Al_2O_3,[14] zeolites,[15] montmorillonite clay,[16] and microwave,[17] to name a few) have been used to promote this simple and general pyrrole synthesis. As might be anticipated, the treatment of 3-nitro-1-(phenylsulfonyl)-indole (**4**) under our reductive acylation conditions gives the novel 3-(1-pyrrolyl)indole **14** in 77% yield (Scheme 3).[18,19] Pyrrolylindole **14** is relatively unstable and was stored under −4 °C.

Although 2-nitroindoles **15** and **16** also undergo this reductive-acylation, the yields of **17** and **18** are lower (Scheme 4),[10] which is a result similar to our previous observations for the indium-mediated reduction of these 2-nitroindoles.[1]

The advantages of this catalytic hydrogenation method are mild and neutral conditions, in contrast to the acidic conditions using In, Sn, and Zn, and higher yields in all cases. Moreover, the catalytic hydrogenation method precludes the formation of mixed anhydrides that are generated in situ when other anhydrides are used in the presence of acetic acid as in, for example, the indium-mediated reduction. At this point, the method is less useful for the reductive acylation of 2-nitroindoles.

In summary, we have found an efficient method for the catalytic reduction of 3-nitroindoles and their subsequent acylation in the same reaction vessel. The resulting N-acylated 3-aminoindoles are obtained in good to excellent yield.

Acknowledgments

This work was supported by the Donors of the Petroleum Research Fund (PRF), administered by the American Chemical Society, and by Wyeth.

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8. *Representative procedure*: To a solution of 1-methyl-3-nitroindole (**1**) (44 mg, 0.25 mmol) and acetic anhydride (77 mg, 0.75 mmol) in anhydrous methanol (3 mL) was added 10% palladium on carbon (10 mg). Using a hydrogen filled balloon, the atmosphere of the flask was replaced by hydrogen gas. After three vacuum/hydrogen cycles to remove air from the reaction flask, the reaction mixture was heated at 40 °C (60 °C for other cases) at atmospheric pressure for 1 h, maintaining the hydrogen atmosphere with a balloon. The catalyst was removed by filtration through Celite. The filtrate was evaporated and the crude product was purified by column chromatography (hexanes/ethyl acetate = 1:5) to give the desired product **2** (47 mg, 100%) as a white solid: mp 189–191 °C (lit.[9] mp 191–192 °C); spectral data are identical to our previously reported values.[1]
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11. Compound **12**: mp 148–150 °C; ^{1}H NMR (acetone-d_6): δ 9.43 (br s, 1H), 8.27 (s, 1H), 8.21 (d, 1H, $J = 7.6$ Hz), 7.81 (d, 1H, $J = 7.9$ Hz), 7.38 (t, 1H, $J = 7.8$ Hz), 7.27 (t, 1H, $J = 7.5$ Hz), 4.49 (q, 2H, $J = 7.0$ Hz), 2.18 (s, 3H), 1.45 (t, 3H, $J = 7.0$ Hz); ^{13}C NMR (acetone-d_6): δ 168.6, 151.7, 134.2, 125.9, 125.2, 123.4, 121.1, 118.7, 115.9, 114.4, 63.9, 23.4, 14.7; LRMS (EI): *m*/*z* 246 (M^+), 204, 176, 159, 131 (100%), 103, 77; HRMS (EI): calcd for $C_{13}H_{14}N_2O_3$: 246.1005, found: 246.1004.
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19. Compound **14**: oil; ^{1}H NMR (DMSO-d_6): δ 8.15 (s, 1H), 8.03–8.07 (m, 3H), 7.69 (t, 1H, $J = 7.3$ Hz), 7.59 (t, 2H, $J = 7.3$ Hz), 7.43 (t, 1H, $J = 7.8$ Hz), 7.28 (t, 1H, $J = 7.2$ Hz), 7.07 (d, 1H, $J = 7.6$ Hz), 5.85 (s, 2H), 1.85 (s, 6H); ^{13}C NMR (DMSO-d_6): δ 136.5, 134.8, 133.5, 129.8, 128.4, 127.9, 126.8, 125.8, 124.5, 121.9, 118.8, 113.8, 106.4, 12.2; LRMS (EI): *m*/*z* 350 (M^+), 322, 209 (100%), 181, 168; HRMS (EI): calcd for $C_{20}H_{18}N_2O_2S$: 350.1089; found: 350.1084.