Pergamon

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Tetrahedron Letters 44 (2003) 77–79

TETRAHEDRON LETTERS

Indium-mediated one-pot reductive conversion of nitroarenes to *N*-arylacetamides

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Received 17 October 2002; accepted 5 November 2002

Abstract—*N*-Arylacetamides were prepared in excellent yields from nitroarenes in the presence of acetic anhydride, acetic acid and indium by a one-pot procedure.

Amides are important constituent of many biologically significant compounds. In general, the preparation of *N*-arylacetamides involves two steps, i.e. reduction of nitroarenes to *N*-arylamines followed by the acylation of *N*-arylamines to the corresponding *N*-arylacetamides. Thus, a variety of methods for the reduction of nitro groups to amines have been developed. These methods generally use metal catalysts, such as platinum oxide,[1] rhodium–platinum oxide,[1a] palladium,[1a,2] Raney nickel,[3] copper,[4] ruthenium sulfide,[5] zinc,[6] and iron.[7] In addition, the reduction of nitro groups using samarium,[8] indium,[9] or Bakers' yeast[10] has recently been reported. However, there have been few reports on the one-pot conversion of nitroarenes to the corresponding

Table 1. Indium-mediated reductive acylation of nitrobenzene under various reaction conditions at room temperature

1a **2** **3a** **4a**

Entry	Molar ratio	Solvent	Time (h)	Yield (%)[a]		
	1a:**2**:AcOH:In			**1a**	**3a**	**4a**
1	1:2.5:0:5	EtOH/aq. NH_4Cl (v/v = 3:1)	4	0	34[b]	5
2	1:2.5:0:5	MeOH	48	70	Trace	Trace
3	1:2.5:5:5	THF	48	34	2	11
4	1:2.5:5:5	THF/MeOH (v/v = 2:1)	48	4	7	9
5	1:2.5:5:5	MeOH	5	0	83	14
6	1:2.5:10:5	MeOH	2	0	95 (92)[c]	4
7	1:10:10:5	MeOH	2	0	86	7
8	1:2.5:10:5	EtOH	2.5	0	64	6

[a] GC yield with an internal standard.
[b] 4% of azobenzene and 15% of aniline were determined by GC.
[c] Isolated yield.

Keywords: acylation; amides; indium and compounds; reduction; nitro compounds.
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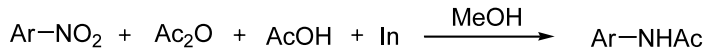
0040-4039/03/$ - see front matter
PII: S0040-4039(02)02479-6

N-arylacetamides. While the reductive acylation of nitrobenzene using Ac_2O–$SnCl_2{\cdot}2H_2O$[11] produced undesired *p*-chloroacetanilide, one-pot conversion of nitroarenes using acetic anhydride–zinc–aluminum oxide[12] produced the corresponding *N*-arylacetamides along with the *N*,*O*-diacylated products that were observed as the major products in our previous report.[13] Thus, neither of these approaches seems to be suitable for synthetic application.

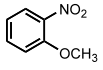
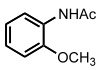
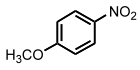
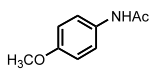
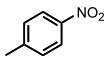
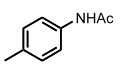
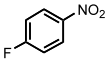
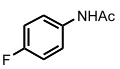
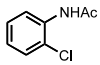
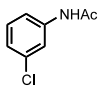
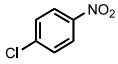
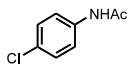
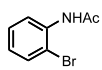
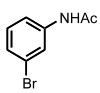
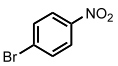
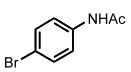
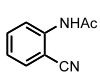
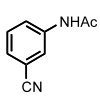
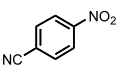
During our study of metal-mediated reductive reactions of nitroarenes, we developed a method for the *N*,*O*-diacylation of nitroarenes using zinc or indium/$InCl_3$ under mild conditions.[13] As the one-pot conversion of nitroarenes to the corresponding *N*-arylacetamides is not well documented, we believe it would be worthwhile to develop an indium-mediated methodology for facile synthetic transformation since indium has desirable chemical properties for organic synthesis[14] and becoming widely used as a reducing reagent in various reductive reactions.[10] We report here an efficient reductive one-pot *N*-acylation reaction of nitroarenes using indium in the presence of acetic acid–acetic anhydride.

As control experiments, various reaction conditions were examined to determine the optimum conditions for indium-mediated reductive acylation, and the results are summarized in Table 1. The reaction using indium

Table 2. Reductive acylation of nitrobenzenes in the presence of Ac_2O (2.5 equiv.)/AcOH (10 equiv.)/In (5 equiv.) in MeOH at room temperature



1 **2** **3**

Entry	1	Time (h)	3	Isolated yield (%)
1		2.0		92[b]
2		1.0		96
3		2.0		94
4		1.5		94
5		1.5		91[b]
6		1.0		99
7		1.5		93
8		1.0		90[b]
9		0.5		81
10		0.5		77
11		1.0		73
12		1.5		100
13		1.0		95
14		2.0		96
15		1.5		98
16		1.0		100
17		1.5		96[b]
18		1.5		76[c]
19		1.5		100
20		1.5		73[c]
21		1.0		79[b]
22		2.0		93

[a]All reactions were carried out with 0.3 mmol of reactant.

[b]Trace of *N*,*O*-diacetylated product was observed.

[c]3-5% of azobenzene was observed.

in the presence of Ac_2O in aqueous ethanol containing ammonium chloride (Moody's indium-mediated reductive condition)[9] gave *N*-phenylacetamide in relatively low yield, along with aniline, *N*,*O*-diacylated *N*-phenylhydroxylamine, and azobenzene (Table 1, entry 1). The reaction of nitrobenzene using Ac_2O–In in MeOH also did not proceed well also, as expected (Table 1, entry 2). However, the addition of AcOH to the reaction mixture gave better results. Although the reactions of nitrobenzene (**1a**) using Ac_2O–AcOH–In in THF solvent or THF–MeOH co-solvent gave the desired *N*-phenylacetamide (**3a**) in low yield (Table 1, entries 3 and 4), the reactions in MeOH solution with suitable amounts of Ac_2O–AcOH–In were drastically improved (Table 1, entries 5–7). The best results were obtained with nitrobenzene/Ac_2O (2.5 equiv.)/AcOH (10 equiv.)/In (5 equiv.) in MeOH at room temperature (Table 1, entry 6).

Using the optimized reaction conditions, we investigated the scope of *N*-arylacetamide derivative synthesis, and the results are summarized in Table 2. The reaction appears to be generally applicable, since all of the substrates were consumed within 0.5–2 h to give the corresponding *N*-arylacetamide (**3**) in excellent yield. Fluoro-substituted nitrobenzenes (Table 2, entries 9–11) or *o*-, *p*-cyano substituted nitrobenzenes (Table 2, entries 18 and 20) produced relatively low yields of the desired product compared to others presumably because of the strong inductive effect of fluoro group or resonance effect of the *o*-, *p*-cyano group that may reduce the nucleophilic character of the intermediate toward acetic anhydride electrophile. Compared to our previous procedure for the *N*,*O*-diacylation of nitroarenes using Ac_2O–In–$InCl_3$–MeOH in $CHCl_3$ solution, the present procedure is superior in that the *N*-arylacetamide (**3**) can be efficiently prepared without forming undesired by-products. The method using Pd/C catalyst for reduction of halo-substituted nitroarene to the corresponding *N*-arylamine, which is a precursor of *N*-arylacetamide, maynot be used since Pd/C-catalyzed reduction is known to be effective sometimes for removing halogen from chloro or bromo-substituted nitroarenes.[15] However, dehalogenation was not observed in our mild one-pot reductive reactions (Table 2, entries 12–17).

Typical procedure for the reductive acylation: Acetic acid (0.172 mL, 3.0 mmol) was added to a mixture of indium powder (172 mg, 1.5 mmol), nitroarene derivative (0.3 mmol) and acetic anhydride (0.071 mL, 0.75 mmol) in MeOH (1.5 mL). The reaction mixture was stirred for a fixed time. After the reaction was complete, the reaction mixture was poured into saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was eluted with ethyl acetate/hexane (v/v = 10/90–30/70) through a silica gel column to give the corresponding *N*-arylacetamide (**3**).

In conclusion, we have described a simple and efficient method for the one-pot preparation of *N*-arylacetamides from nitroarenes using Ac_2O–AcOH–In in MeOH under mild conditions.

Acknowledgements

This work was supported by the Brain Korea 21 Project and partly by Kwangwoon University in the year 2002.

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