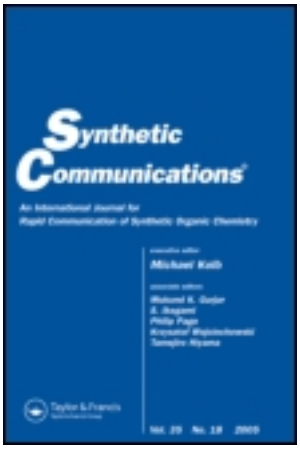

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Convenient, Cost-Effective, and Mild Method for the N-Acetylation of Anilines and Secondary Amines

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Convenient, Cost-Effective, and Mild Method for the *N*-Acetylation of Anilines and Secondary Amines

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Abstract: An efficient, cost-effective, and mild method for the *N*-acetylation of anilines and secondary amines with ammonium acetate in acetic acid media at reflux temperature in good yield is described.

Keywords: *N*-Acetylation, ammonium acetate, anilines, secondary amines

INTRODUCTION

The *N*-acetylation of amino groups is an important fundamental transformation in organic chemistry.[1,2] The most common reagents employed for *N*-acetylation of amines are acetic anhydride and acetyl chloride. Acetic anhydride is used as a *N*-acetylating agent in the presence of basic catalysts, such as pyridine, 4-pyrrolidinopyridine, and 4-dialkylaminopyridine.[3] A variety of other catalysts such as $Cu(OTf)_2$,[4] basic alumina,[5] $In(OTf)_3$,[6] montmorillonite K-10 and KSF,[7] ruthenium(III)chloride,[8] and zeolite H-FER[9] in -the presence of acetic anhydride and with various reagents under microwave irradiation,[10] were also used for *N*-acetylation of amines. Further, the *N*-acetylation of primary and secondary amines can be achieved by the methods such as ethyl trifluoroacetate,[11] pentafluorophenylacetate,[12]

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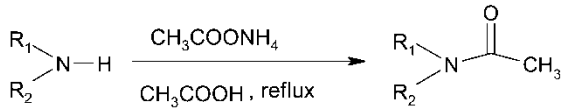
Address correspondence to D. Channe Gowda, Department of Studies in Chemistry, University of Mysore, Manasagangotri, , Mysore, Karnataka 570 006, India. Fax: 091-0821-2421263/2518835; E-mail: dcgowda@yahoo.com

N-methoxydiacetamide,[13] poly(3-acyl-2-oxazolone),[14] *N*-acyl-*N*-(2,3,4,5,6-pentafluorophenyl)methanesulfonamides,[15] *ortho*-substituted *N,N*-diacetylaniline,[16] and *N*-acetyl-*N*-acyl-3-aminoquinazolinones.[17] At the same time, selective *N*-acetylation of the primary amine moiety in the presence of secondary amine moiety can also be achieved by these methods. However, many of the earlier methods suffer from certain drawbacks. The catalysts are rather expensive and toxic, and require not-readily-available reagents. Thus, an efficient, convenient, and mild method is still desirable. To this end, we developed a convenient and mild method (Scheme 1) for the *N*-acetylation of anilines and secondary amines in good yields using ammonium acetate, which is a very useful reagent in the synthesis of many organic compounds,[18–21] including β-amino acids.[22]

As shown in Table 1, a number of substituted anilines and secondary amines underwent *N*-acetylation smoothly with ammonium acetate in presence of acetic acid at reflux temperature in good yields. The course of the reaction was monitored by thin layer chromatography (TLC) and IR spectra. The workup and isolation of the products were easy. All the acetylated products were characterized by comparison of their TLC, IR spectra, ^{1}H-NMR spectra, and melting points with authentic samples.

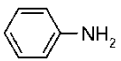
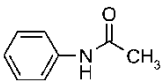
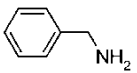
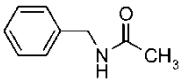
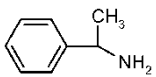
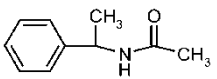
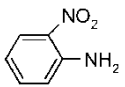
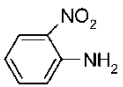
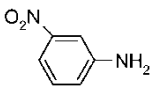
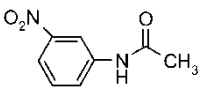
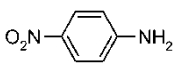
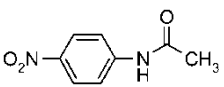
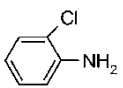
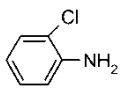
With this present method, only *N*-acetylated products were observed. The generality of this methodology was examined using other functionally and sterically hindered amines. The presence of electron-withdrawing groups such as nitro and chloro groups in anilines slow down the acetylation (entries 4–9 in Table 1), whereas the electron-releasing group facilitates the process (entries 10, 11, 13–16). The operation of both the electron-withdrawing effect and the steric effect completely stop the process of acetylation (entries 4, 7). It was also observed that the acetylation reaction is fast in acetic acid, but it was very slow in acetonitrile or methanol. A control experiment was carried out using an amino compound with acetic acid, in the absence of ammonium acetate, and conversion of amino to *N*-acetylated product was observed to be less than 5%.

In conclusion, this new method does not require any expensive catalysts or reagents such as $Cu(OTf)_2$,[4] basic alumina,[5] $In(OTf)_3$,[6] montmorillonite K-10 and KSF,[7] ruthenium(III)chloride,[8] or zeolite H-FER.[9] The ease of product separation, safe reaction medium, high selectivity, and low cost of the reagents promote this method as a promising alternative to the other existing methods.



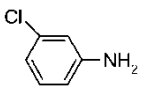
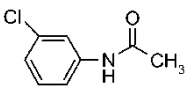
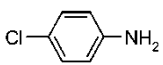
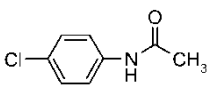
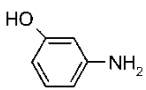
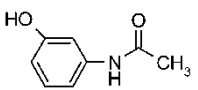
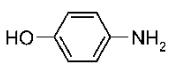
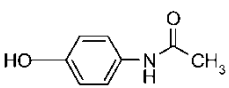
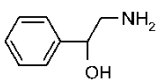
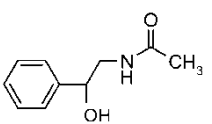
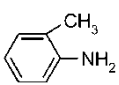
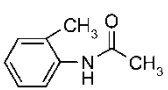
Scheme 1. For anilines, R_1 = aryl, R_2 = H; for secondary amines, R_1, R_2 = alkyl.

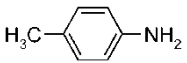
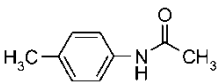
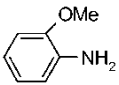
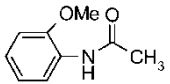
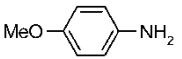
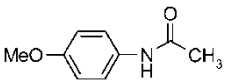
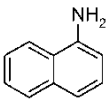
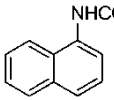
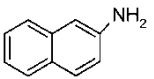
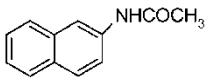
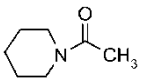
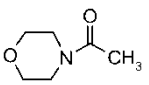
Table 1. *N*-Acetylation of anilines and secondary amines with CH_3COONH_4/CH_3COOH

Entry	Substrate	Product[a]	Time (h)	Yield (%)[b]	Melting point (°C) Found	Melting point (°C) Lit.
1			0.75	75	113–115	114[23]
2			2.5	86	57–59	60[24]
3			2.0	88	77–79	79–80[15]
4			24.0	100[c]	—	—
5			4.5	60	153–155	155[23]
6			6.0	36	214–215	216[23]
7			24.0	100[c]	—	—

(*continued*)

Table 1. Continued

Entry	Substrate	Product[a]	Time (h)	Yield (%)[b]	Melting point (°C) Found	Melting point (°C) Lit.
8			16.0	40	77–79	79[23]
9			8.0	48	177–178	179[23]
10			2.0	82	147–149	149[23]
11			1.5	88	167–168	168[23]
12			2.0	89	115–117	118–119[13]
13			2.0	67	123–124	125[23]

14			1.5	82	144–146	146[23]
15			5.0	89	86–87	88[23]
16			0.5	91	129–131	130[23]
17			15.0	34	161–162	163[23]
18			13.0	52	168–170	171[23]
19			11.0	82	224–226[d]	226–227[5]
20			1.5	85	Oil	14[5]

[a]All products were identified by their ^{1}H-NMR, IR spectra, mp, or bp with authentic samples.
[b]Isolated yields are based on single experiment and the yields were not optimized.
[c]Based on recovery of the starting material, no acetylation was observed even after 24 reflections.
[d]Boiling point.

EXPERIMENTAL

Materials

All the anilines and secondary amines were purchased from Aldrich Chemical Company (USA). Ammonium acetate and acetic acid were purchased from SISCO Research Laboratories Pvt. Ltd., Bombay (India). All of the solvents used were analytical grade or were purified according to standard procedures. Thin layer chromatography was carried out on silica-gel plates obtained from Whatman Inc. The melting points were determined by using a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FTIR-8300 spectrometer. ^{1}H-NMR spectra were recorded on an AMX-400 MHz spectrometer using $CDCl_3$ as the solvent and TMS as internal standard.

General Procedure for the *N*-Acetylation of Anilines and Secondary Amines

To a mixture of ammonium acetate (15 mmol) and acetic acid (5 ml), the substrate (amine, 5 mmol) was added and the reaction mixture stirred at 95 °C for a length of time indicated in Table 1. After completion of the reaction (monitored by TLC), the reaction mixture was neutralized with saturated $NaHCO_3$ solution. The obtained product was extracted with chloroform (3 × 15 ml) and the combined organic extracts were washed with cold water and dried over Na_2SO_4. The product obtained, after removal of the solvent under reduced pressure, was crystallized from a suitable solvent.

ACKNOWLEDGMENTS

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