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MILD, SIMPLE, AND EFFICIENT METHOD FOR *N*-FORMYLATION OF SECONDARY AMINES VIA REIMER–TIEMANN REACTION

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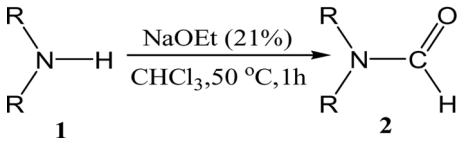
GRAPHICAL ABSTRACT



1 **2**

Abstract *A rapid and easy route for the* N*-formylation of secondary amines using chloroform and sodium ethoxide via dichlorocarbene by the Riemer–Tiemann reaction with excellent yield is reported.*

Keywords Dichlorocarbene; *N*-formylation; Reimer–Tiemann; secondary amines; sodium ethoxide

INTRODUCTION

A number of formylating methods have been reported in the literature. Acetic formic anhydride[1,2] continues to be the most widely used formylating reagent, but it is sensitive to decomposition to acetic acid and carbon monoxide. Many other useful formylation reagents have been reported such as chloral,[3] activated formic acid using N,N′-dicyclohexylcarbodiimide (DCC)[4] or EDCI,[5] activated formic esters,[6–8] PGE-400,[9] and ammonium formate.[10] Despite the usefulness of these reactions, such as excellent yields and mild conditions, they are less practical: they are either toxic or expensive and the preparation and use of these reagents require strictly anhydrous conditions. Moreover, the formyl group is a useful amino-protecting group in peptide synthesis[11] and *N*-formylamino acid esters can, for

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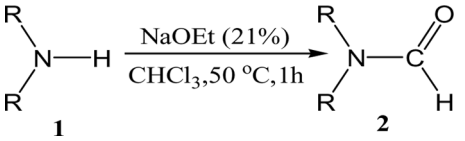
example, serve as starting materials for peptide synthesis.[12] Thus, in a few minutes on a multiple-gram scale, primary and secondary amines have been subjected to *N*-formylation by microwave irradiation.[13,14] Alcohols and amines have been formylated and acetylated in the presence of Silphos [$PCl_{3-n}(SiO_2)_n$] in good yield,[15,16] and various cyclic and aliphatic amines have been *N*-formylated using dense carbon dioxide and ruthenium as catalyst.[17] The effect of solvent on *N*-formylation[18] using aqueous formic acid have been reported. *N*-Formylation under solvent-free conditions with excellent yields has been achieved using ZnO as catalyst.[19] In our previous work, we reported the *N*-acylation of primary and secondary amines using acetic, propionic acid, and hydrazine hydrate.[20] We now report a mild and simple N-formylation procedure using chloroform and sodium ethoxide.

RESULTS AND DISCUSSION

Though numerous methods have been reported in the literature for formylation of primary and secondary amines, there are several factors in some cases that limit their applications, for example, thermal instability, formation of by-products, and difficult preparation of the formylating agents. The present formylation procedure via dichlorocarbene seems to be unknown for amines in the literature. Here, we are reporting a general and very efficient procedure, which accommodates practicality and functionality. This particular procedure has high specific importance for



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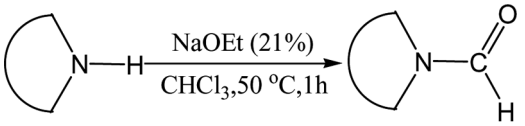
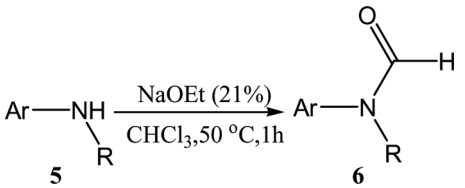
Scheme 1. R=CH_3, C_2H_5, isopropyl.



3 **4**

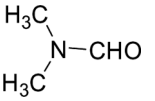
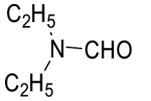
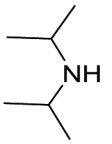
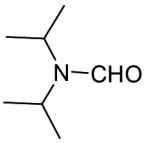
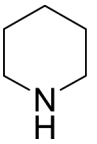
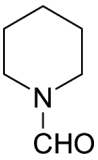
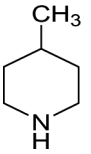
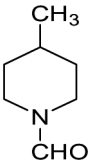
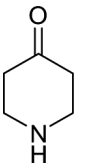
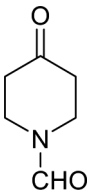
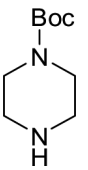
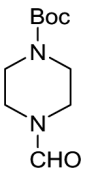
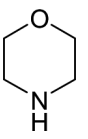
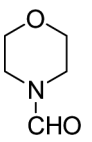
Scheme 2. NH = Piperidine, 4–CH_3-piperidine, 4–piperidone, 4–ph-piperidine, pyrrolidin, N-Boc-piperzine, morpholine.



5 **6**

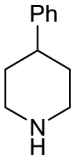
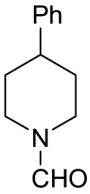
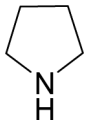
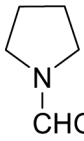
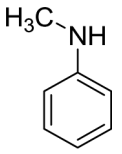
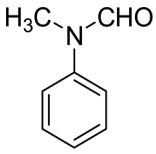
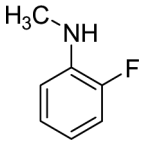
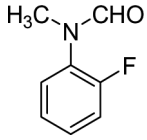
Scheme 3. R=CH_3.

Table 1. *N*-Formylation from chloroform and NaOEt (21%) via Riemer–Teimann reaction

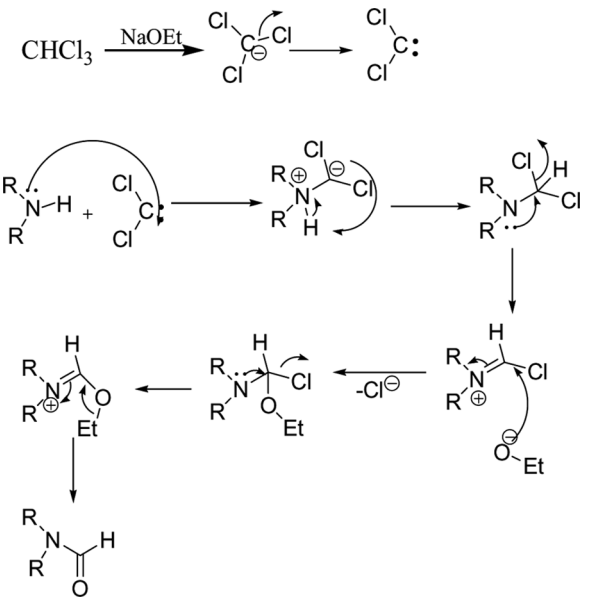
Entry	Substrate	Product		Yield (%)
		Structure	Entry code	
1a			**2a**	68
1b			**2b**	62
1c			**2c**	65
3a			**4a**	92
3b			**4b**	94
3c			**4c**	95
3d			**4d**	96
3e			**4e**	95

(*Continued*)

Table 1. Continued

Entry	Substrate	Product		Yield (%)
		Structure	Entry code	
3f			**4f**	96
3g			**4g**	94
5a			**6a**	65
5b			**6b**	68

potential reactants. At the onset of our work, we explored the utility of the Riemer–Teimann reaction via dichlorocarbene with secondary amines. We were surprised to find *N*-formylated products with good yields. Absence of a NH stretching band and presence of aldehyde carbonyl stretching band in the infrared (IR) spectrum could be easily confirmed. Thus, among the obtained products there are very common solvents synthesized such as *N,N*-dimethylformamide (**2a**) and *N,N*-diethylformamide (**3b**) from *N,N*-dimethylamine and *N,N*-diethyl amine respectively. The spectral data for the synthesized compounds are in good agreement with the reported literature. We thought this procedure could be expanded to an array of amines. A series of aliphatic open chain (Scheme 1), cyclic (Scheme 2), and aromatic (Scheme 3) secondary amines were converted into the corresponding *N*-formyl amines in good yields (Table 1). The present reaction conditions for aliphatic open-chain amines and aromatic amines afforded the *N*-formylation product in relatively poor yield, while the cyclic amines undergo very good conversion, more than 90%. The formylation reaction could be considered to proceed through the Riemer–Teimann reaction. The formylating agent chloroform excess was treated with a base such as sodium ethoxide (21%) at 50 °C to give chloroform carbanion, which quickly undergoes α-elimination to afford dichlorocarbene. Dichlorocarbene reacts with a secondary amine, and a plausible mechanism is depicted in Scheme 4.



Scheme 4. General mechanism. R,R = alkyl or cyclic aliphatic secondary amines.

The applications in organic synthesis have not yet been fully explored. The present conversion has been utilized efficiently for the preparation of *N*-formylation of secondary amines without further purification. The experimental procedure is highly convenient. In a forthcoming work, we will report results for primary amines. The structures of the products were established from their spectral [IR, ^{1}H NMR, ^{13}C NMR, and, liquid chromatographic–mass spectrometric (LCMS)] data.

EXPERIMENTAL

General Experimental Information

All reactions were performed in flame-dried glassware under a nitrogen atmosphere. Reagents were used as purchased from Aldrich, and ^{1}H and ^{13}C NMR spectra were obtained on a Varian VI-300 and Bruker 300- and 400-MHz spectrometers using dimethylsulfoxide (DMSO-d_6) and $CDCl_3$ with tetromethylsilane (TMS) or residual solvent as standard unless otherwise noted. IR spectra were obtained on a Bruker Equinox 55 Fourier transform (FT)–IR instrument. Thin-layer chromatography (TLC) analysis was performed using Aldrich 254, nm polyester-backed plates (60 Å, 250 μm) and visualized using ultraviolet and $KMnO_4$ stains. LCMS mass spectra were obtained using an MPS-SCIEX-API-2000 Instrument.

General Procedure for *N*-Formylation of Secondary Amines for Liquid Compounds

To a mixture of secondary amines (1 eq.) and sodium ethoxide (21% obtained from Sigma-Aldrich) (3 eq.) was added. The mixture was stirred at 50 °C on an oil

bath for 15 min, and excess of chloroform was added slowly. Stirring was continued for another 30 min. The progress of the reaction was monitored by TLC. After completion, the mixture was quenched with 10 mL of water, and stirring continued another for 15 min. The reaction mixture was distilled under reduced pressure, and the pure compound was collected at a constant boiling point. The data obtained for the isolated product was compared with the literature.

Selected Data

***N*-Formyl-*N,N*-dimethyl amine (or *N,N*-dimethylformamide) (2a).** Colorless liquid, boiling point 151–154 °C; IR cm^{-1} 1664, 2865, 2932, (3448 cm^{-1} is due to moisture); ^1H NMR (400 MHz, $CDCl_3$) δ 2.88 and 2.91 (2-s for 2-CH_3), 8.02 (s, 1H, N-CHO); ^{13}C NMR (400 MHz, $CDCl_3$) δ 31.27, 36.32, 162.39; LCMS (method 0.1% HCOOH/ACN) $m/z = 147.2$ (double the mass, instead of m/z 73, 100%). Calcd. for C_3H_7NO: 73.05; found: 147.2.

***N*-Formyl-*N,N*-diethyl amine (or *N,N*-diethylformamide) (2b).** Colorless liquid boiling point 172 to 175 °C; IR cm^{-1} 1658, 2891, 2936; ^1H NMR (400 MHz, DMSO-d_6) δ 1.32 (t, 3H), 1.35 (t, 3H), 2.75 (q, 2H), 2.87 (q, 2H), 8.21 (s, 1H, N-CHO); ^{13}C NMR (400 MHz, DMSO-d_6) δ 13.21, 13.25, 32.30, 35.41, 161,43; LCMS (method 0.1% HCOOH/MeOH) $m/z = 203.06$ (98.6%). Calcd. for $C_5H_{11}NO$: 101.08; found: 203.06.

***N*-Formyl-*N,N*-diisopropyl amine (or *N,N*-diisopropylformamide) (2c).** Colorless liquid boiling point 194 to 198 °C; IR cm^{-1} 1664, 2871, 2982; ^1H NMR (400 MHz, DMSO-d_6) δ 1.21 (t, 6H), 1.29 (t, 6H), 2.91 (m, 1H), 2.98 (m, 1H), 8.03 (s, 1H, N-CHO); ^{13}C NMR (400 MHz, DMSO-d_6) δ 12.13, 12.15, 12.42, 1243, 31.41, 34.87, 162,10; LCMS (method 0.1% HCOOH/MeOH) m/z = 130.08 (99.2%). Calcd. for $C_7H_{15}NO$: 129.12; found: 130.08.

***N*-Formylpiperidine (or 1-formylpiperidine) (4a).** Colorless liquid, boiling point 220–225 °C; IR cm^{-1} 1659, 2860, 2939 (3447 cm^{-1} is due to moisture); ^1H NMR (400 MHz, $CDCl_3$) δ 1.50–1.71 (m, 6H), 3.30 (t, 2H), 3.46 (t, 2H), 8.00 (s, 1H, N-CHO); ^{13}C NMR (400 MHz, $CDCl_3$) δ 24.59, 24.99, 26.48, 40.53, 46.75, 160, 58; LCMS (method 0.1% HCOOH/MeOH) $m/z = 144.2$ (99.0%, m + 1). Calcd. for $C_6H_{11}NO$: 113.08; found: 114.2.

***N*-Formyl-4-methylpiperidine (or 4-methyl-1-formylpiperidine) (4b).** Colorless liquid, boiling point 232–236 °C; IR cm^{-1} 1663, 2872, 2954; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (d, 3H), 1.52 (m, 1H), 1.71–1.78 (m, 4H), 3.62 (t, 2H), 3.68 (t, 2H), 8.12 (s, 1H, N-CHO); ^{13}C NMR (400 MHz, $CDCl_3$) δ 12.31, 22.83, 22.88, 25.92, 41.02, 45.74, 162.31; LCMS (method 0.1% HCOOH/MeOH) $m/z = 128.08$ (98.4%, m + 1). Calcd. for $C_7H_{13}NO$: 127.18; found: 128.08.

General Procedure for *N*-Formylation of Secondary Amines for Solid Compounds: *N*-Formyl-4-piperidone (4c)

To a mixture of secondary amines (1 eq.) and sodium ethoxide (21% obtained from Sigma-Aldrich) (3 eq.) was added. The mixture was stirred at 50 °C on an oil

bath for 15 min, and excess of chloroform was added slowly. Stirring was continued for another 15 min. The progress of the reaction was monitored by TLC. After completion, the mixture was cooled to room temperature, diluted with water (20 mL), and extracted with chloroform. The chloroform layer was washed with 10 mL HCl (1 *N*). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue obtained was pure *N*-formyl amine, which required no further purification. Pale yellow solid, melting point 83–86 °C; IR cm^{-1} 1720, 1657, 2867, 2985; ^1H NMR (400 MHz, $CDCl_3$) δ 2.47 (t, 2H), 2.49 (t, 2H), 3.10 (t, 2H), 3.15 (t, 2H) 8.02 (s, 1H, N-CHO); ^{13}C NMR (400 MHz, $CDCl_3$) δ 39.16, 39.18, 40.32, 45.53, 161.75, 192.53; LCMS (method 0.1% HCOOH/MeOH) $m/z = 128.2$ (97.8%, m + 1). Calcd. for $C_6H_9NO_2$: 127.06; found: 128.2.

Selected Data

***N*-Boc-4-formylpiperazine (4d).** Colorless solid, melting point 121–125 °C; IR cm^{-1} 1682, 1648, 2861, 2978; ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 6H), 2.76 (t, 2H), 2.79 (t, 2H), 3.52–3.58 (m, 4H), 8.00 (s, 1H, N-CHO); ^{13}C NMR (400 MHz, $CDCl_3$) δ 23.25, 40.02, 40.41, 44.48, 46.01, 158.96, 161.92; LCMS (method 10 mM NH_4OAc/MeOH) $m/z = 216.02$ (96.7%, m + 2). Calcd. for $C_{10}H_{18}N_2O_3$: 214.13; found: 216.02.

***N*-Formylmorpholine (4e).** Colorless liquid boiling point 234–238 °C; IR cm^{-1} 1663, 2857, 2991; ^1H NMR (400 MHz, DMSO-d_6) δ 3.36 (t, 4H), 3.50 (t, 2H), 3.56 (t, 2H), 8.02 (s, 1H, N-CHO); ^{13}C NMR (400 MHz, $CDCl_3$) δ 40.20, 45.86, 66.87, 67.08, 161.23. LCMS (method 10 mM NH_4OAc/MeOH) $m/z = 116.2$ (96.6%, m + 1). Calcd. for $C_6H_9NO_2$: 115.13; found: 116.2.

***N*-Formyl-4-phenylpiperdine (4f).** Pale yellow color solid, melting point 72–75 °C; IR (KBr pellet) cm^{-1} 1665, 2861, 2936 (3433 cm^{-1} is due to moisture); ^1H NMR (400 MHz, DMSO-d_6) δ 1.38–1.53 (2q, 2H), 1.75–1.82 (t, 2H), 2.63–2.68 (t, 1H), 2.77–2.79 (t, 1H), 3.09–3.15 (t, 1H), 3.74–3.78 (d, 1H, J = 16 MHz), 4.27–4.31(d, 1H, $J = 16$ MHz), 7.16–7.30 (m, 5H), 8.01 (s, 1H, N-CHO); ^{13}C NMR (300 MHz, $CDCl_3$) δ 33.30, 33.83, 40.19, 42.82, 46.40, 126.55, 126.58, 128.55, 144.80, 160.80; LCMS (method 0.1% HCOOH/MeOH) $m/z = 190.2$ (98.5%, m + 1), Calcd. for $C_{12}H_{15}NO$: 189.12; found: 190.2.

***N*-Formylpyrrolidine (4g).** Colorless liquid, boiling point 91–95 °C; IR cm^{-1} 1671, 2832, 2946; ^1H NMR (400 MHz, $CDCl_3$) δ 1.80–1.85 (m, 4H), 3.48 (t, 2H), 3.51 (t, 2H), 8.21 (s, 1H, N-CHO); ^{13}C NMR (400 MHz, $CDCl_3$) δ 25.63, 25.86, 41.65, 46.87, 162.51; LCMS (method 0.1% HCOOH/MeOH) $m/z = 99.28$. Calcd. for C_5H_9NO: 99.07; found: 99.28.

***N*-Methyl-*N*-formylaniline (6a).** Colorless liquid, boiling point 242–245 °C; IR cm^{-1} 1683, 2819, 2924 (3432 cm^{-1} is due to moisture); ^1H NMR (400 MHz, DMSO-d_6) δ 3.21 (s, 3H), 7.24–7.45 (m, 5H), 8.53 (s, 1H, N-CHO); ^{13}C NMR (400 MHz, DMSO-d_6) δ 31.80, 121.71, 122.10, 125.91, 128.72, 124.10, 141.80 162,10; LCMS (method 0.1% HCOOH/MeOH) $m/z = 136.2$, (72.7%, m + 1). Calcd. for C_8H_9NO: 135.16; found: 136.2.

***N*-Formyl-*n*-methy-2-flouroaniline (6b).** Colorless liquid, boiling point 128–132 °C; IR cm^{-1} 1677, 2826, 2943; ^1H NMR (400 MHz, DMSO-d_6) δ 2.69 (s, 3H), 6.52 (t, 1H), 6.63 (t, 1H), 6.97 (d, 1H, J = 4.68 Hz), 6.99 (d, 1H, J = 4.88 Hz), 8.24 (s, 1H, N-CHO); ^{13}C NMR (400 MHz, DMSO-d_6) δ 32.73, 121.83, 123.03, 126.86, 130.12, 131.31, 144.62, 162,53; LCMS (method 10 mM NH_4OAc/MeOH) $m/z = 154.2$ (77.9%, m + 1). Calcd. for C_8H_8FNO: 153.15; found: 154.2.

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REFERENCES

1. Strazzolini, P.; Giumanini, A. G.; Cauci, S. Acetic formic anhydride: A review. *Tetrahedron.* **1990**, *46*, 1081–1118.
2. Blicke, F. F.; Lu, C. J. 6-Amino-2,3-dimethylindole. *J. Am. Chem. Soc.* **1952**, *74*, 3933–3934.
3. Waki, J.; Meienhofer, J. Efficient preparation of Na-formylamino acid *tert*-butyl esters. *J. Org. Chem.* **1977**, *42*, 2019–2020.
4. Chen, F. M. F.; Benoiton, N. L. A general method for formylating sensitive amino acid estersy. *Synthesis.* **1979**, 709–710.
5. Yale, H. L. Formylation of amines with phenyl formate. *J. Org. Chem.* **1971**, *36*, 3238–3240.
6. Kisfaludy, L.; Laszlo, O. Rapid and selective formylation with pentafluorophenyl for mate. *Synthesis.* **1987**, 510–511.
7. Neveux, M.; Bruneau, C.; Dixneuf, P. H. Enol formates: Ruthenium-catalysed formation and formylating reagents. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1197–1199.
8. Duczek, W.; Deutsch, J.; Vieth, S.; Niclas, H. J. A simple and convenient synthesis of *N*-formyl amino acid esters under mild conditions. *Synthesis.* **1996**, 37–38.
9. Biswanath, D.; Maddeboina, K.; Boyapati, V.; Balasubramanyam, P.; Nandan Kumar, D. A remarkably simple N-formylation of anilines using polyethylene glycol. *Tetrahedron Lett.* **2008**, *49*, 2225–2227.
10. Reddy, P. G.; Kumar, G. D. K.; Baskaran, S. A convenient method for the *N*-formylation of secondary amines and anilines using ammonium formate. *Tetrahedron Lett.* **2000**, *41*, 9149–9151.
11. Martinez, J.; Laur, J. Active esters of formic acid as useful formylating agents: Improvements in the synthesis of formyl-amino acid esters, *N*-α-formyl-met-leu-Phe-OH, and formyl-Met-Lys-Pro-Arg, a phagocytosis stimulating peptide. *Synthèses* **1982**, 979–981.
12. Floresheimer, A.; Kula, M. R. The application of *N*-formyl amino acid esters in the enzyme-catalyzed peptide synthesis. *Monatsh. Chem.* **1988**, *119*, 1323–1329.
13. Ajay, K. B.; Subhendu, N. G.; Maghar, S. M.; Atri, G.; Esteban, P. V. Microwave-promoted energy-efficient N-formylation with aqueous formic acid. *Tetrahedron Lett.* **2006**, *47*, 4605–4607.
14. Desai, B.; Danks, T. N.; Wagner, G. Thermal and microwave-assisted *N*-formylation using solid-supported reagents. *Tetrahedron Lett.* **2005**, *46*, 955–957.
15. Iranpoor, N.; Habib, F.; Arezu, J. Silphos [$PCl_{3-n}(SiO_2)_n$]: A heterogeneous phosphine reagent for formylation and acetylation of alcohols and amines with ethyl formate and acetate. *Tetrahedron Let.* **2005**, *46*, 7963–7966.
16. Hill, D. R.; Hsiao, C. N.; Kurukulasuriya, R.; Wittenburger, S. J. 2,2,2-Trifluoroethyl formate: A versatile and selective reagent for the formylation of alcohols, amines, and *N*-hydroxylamines. *Org. Lett.* **2002**, *4*, 111–113.

17. Schmid, L.; Canonica, A.; Baiker, A. Ruthenium-catalysed formylation of amines with dense carbon dioxide as C1-source. *Appl. Catal. A.* **2003**, *255*, 23–33.
18. Jung, S. H.; Ahn, J. H.; Park, S. K.; Choi, J. K. A practical and convenient procedure for the *N*-formylation of amines using formic acid. *Bull. Korean Chem. Soc.* **2002**, *23*, 149–150.
19. Savari, M. H.; Sharghi, H. ZnO as a new catalyst for *N*-formylation of amines under solvent-free conditions. *J. Org. Chem.* **2006**, *71*, 6652–6654.
20. Basanagouda, M.; Kulkarni, M. V.; Kalkhambkar, R. G.; Kulkarni, G. M. New, efficient, selective, and one-pot method for acylation of amines. *Synthetic Commun.* **2008**, *38*, 2929–2940.