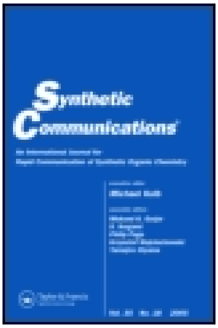

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Mild and Useful Method for N-Acylation of Amines

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Mild and Useful Method for N-Acylation of Amines

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Abstract: Iodine is found to promote quantitative N-acylation of primary and secondary amines (aliphatic and aromatic) in a very short time with an equimolar amount of acetyl chloride and benzoyl chloride under solvent-free conditions at room temperature. This catalytic acylation of amines offers an additional useful method for the acetylation using acetyl chloride instead of acetic anhydride and other acetylating agents. This method is also useful in the N-acylation of heterocycles. Mild reaction condition, high selectivity, efficiency, and good yields are some of the major advantages of the procedure.

Keywords: Acetamide, acetyl chloride, N-acylation, benzamides, benzoyl chloride, iodine

The acetylation and benzoylation of primary and secondary amines are among the most widely used transformations in organic synthesis. N-Acyl derivatives of amines are used widely in the synthesis of amides and their derivatives, as starting materials for various organic transformations, and in protection of –NH and OH- groups.[1,2] In practical terms, acylation involves the following categories: (a) direct reaction of an amine and an acid, (b) reaction of a readily available acid derivative (e.g., simple methyl ester) with an amine, (c) formation of an activated carbonyl compound (e.g., acid chloride, anhydride, or active ester) followed by condensation with an amine, and (d) one-pot reaction of a carboxylic acid with an amine in which a coupling reagent activates the acid component in situ. Acid halides[3] and acid anhydrides are commonly

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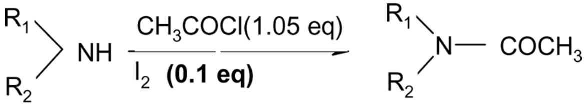
used as acylating agents in various solvent systems in the presence of a protic or Lewis acid catalyst.[1] Novel catalysts used are a basic, aqueous alkali like sodium hydroxide (Schotten–Bauman condition) or a tertiary amine (py or Et_3N). $Cp_2Sn(THF)_2$,[4] tetrabutyl ammonium salts,[5] and cyanide anion[6] have been reportedly used as catalysts in the acetylation of amines with esters. 18-Crown-6 has also been reportedly used in the selective acylation of secondary amines.[7] All these existing procedures have some drawbacks, such as the rquirement of more expensive reagents, relatively harsh reaction conditions, and long reaction times. The widely used Schotten–Baumann condition suffers from the drawback that hydrolysis of acetyl chloride and benzoyl chloride is a significant competing side reaction, so a strict maintenance of pH is required. Otherwise, acetic anhydride is recommended. However, this is highly expensive and creates technical problem so. Thus, there is still a great need to find better alternatives to make use of the high reactivity of acyl chlorides toward the acylation of amines, which might proceed under mild, environmentally benign, efficient, clean, and economically much cheaper reaction conditions. In recent years, iodine has been used as a Lewis acid catalyst for various organic transformations.[8] Use of iodine in catalyzing the Mukaiyana aldol condensation reaction[9] and in acetylation of alcohols[10] has been reported. Herein we report a general, rapid, and one-pot convenient procedure for N-acetylation and N-benzoylation of amines using acetyl chloride and benzoyl chloride respectively under solvent-free conditions catalyzed by iodine (Scheme 1).

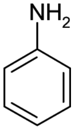
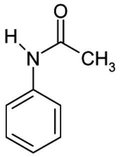
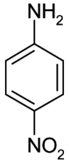
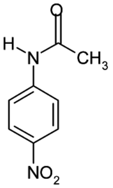
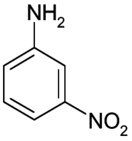
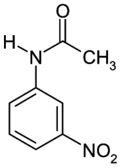
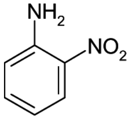
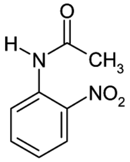
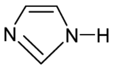
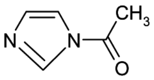
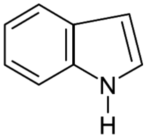
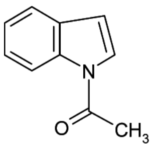
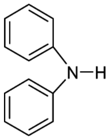
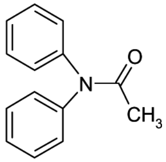
The general efficiency of this reaction is evident from the variety of amino compounds including aliphatic, aromatic, and heterocyclic amines (primary and secondary), which react in excellent yields within a very short time; simple primary amines are acylated within 1 min. First, we have tried to optimize the reaction conditions for acetylation of aniline. At room temperature, use of 0.1 mmol of I_2 with 1 mmol of aniline and 1.05 mmol of acetyl chloride gave 95% of acetanilide. Similarly, we have converted various primary and secondary amines to respective amides in relatively good yields under identical reaction conditions (Table 1). The



1 2

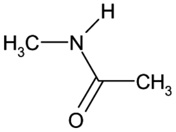
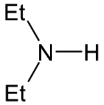
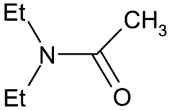
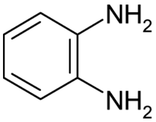
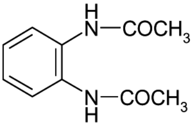
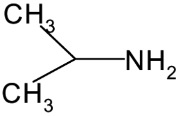
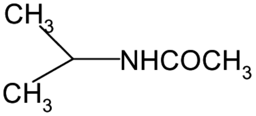
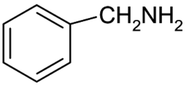
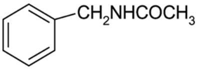
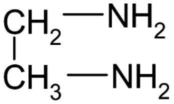
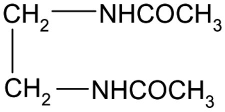
Scheme 1. (i) $R_1 = H$, $R_2 = $ alkyl, aryl; (ii) $R_1 = R_2 = $ alkyl; (iii) $R_1 = R_2 = $ aryl; (iv) $R_1 = $ imidazolyl, $R_2 = -$; and (v) $R_1 = $ indole residue, $R_2 = -$.

Table 1. Acetylation of primary and secondary amines using iodine as a catalyst[a]

Entry	Substrate 1	Time (min)	Product 2[b]	Yield[c]/%
A		1		94.5
b[d]		5		60.3
c[d]		8		68.5
d[d]		10		64.6
e[d]		7		74.7
f[d]		10		77.09
g[d]		5		97.58

(*Continued*)

Table 1. Continued

Entry	Substrate 1	Time (min)	Product 2[b]	Yield[c]/%
H	$H_3C–NH_2$	1		70.87
I		1		86.3
j[d]		15		84.9
K		2		75.0
L		5		78.00
M		2		75.5

[a] Reaction condition: substrate = 1 mmol, AcCl = 1.05 mmol, iodine = 0.1 mmol, 25°C.

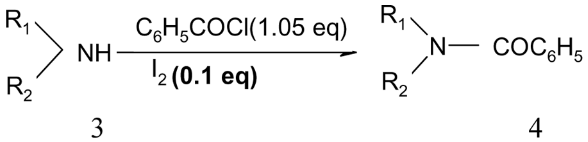
[b] Products have been characterized by melting points, chemical tests, IR, and ^1H NMR data.

[c] Isolated yield.

[d] AcCl (3.5 eq) was used.

products are fully characterized by ^1H NMR, infrared (IR), and melting points.

Encouraged by the results of acetylation, we have extended the process to benzoylation of the same substrates using benzoyl chloride in place of acetyl chloride, keeping all other conditions identical (Scheme 2). Both aromatic and aliphatic primary and secondary amines



Scheme 2. (i) $R_1 = H$, $R_2 =$ alkyl, aryl; (ii) $R_1 = R_2 =$ alkyl; (iii) $R_1 = R_2 =$ aryl; (iv) $R_1 =$ imidazolyl, $R_2 = -$; and (v) $R_1 =$ indole residue, $R_2 = -$.

as well as the heterocycles were found to be N-benzoylated in good yields. Table 2 shows representative results of the benzoylation of various amines with benzoyl chloride using iodine as catalyst.

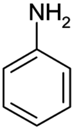
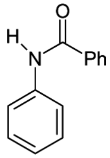
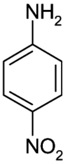
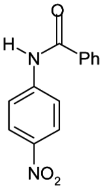
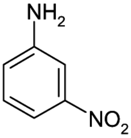
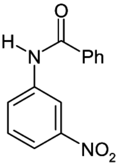
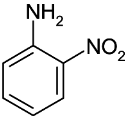
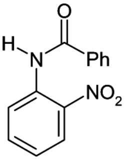
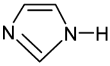
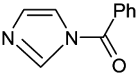
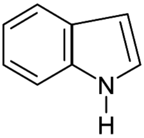
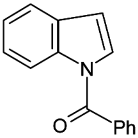
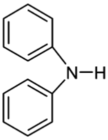
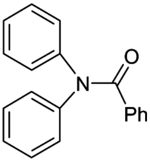
In conclusion, iodine shows a very strong catalytic activity toward general acylation of primary and secondary amines including N-containing heterocycles with actyl and benzoyl chloride. The merits of this method are that (a) it is a very simple, one-pot, rapid, high-yielding process, (b) iodine is cheap and easily available as compared to other catalysts, (c) the method is environmentally benign because it does not require any solvent, and (d) iodine is not moisture sensitive, and reactions are carried out in air at room temperature. Near equimolar acyl chlorides are typically used, avoiding waste and providing very simple experimental and workup procedure. It is significant to note that neither the substituted groups like the nitro group nor the aromatic ring is acylated under the experimental conditions. Because of its simplicity, generality, efficacy, and cost-effectiveness, this method is expected to have wide applicability for N-acylation of primary and secondary amines. This method is also useful in the N-acylation of heterocycles.

EXPERIMENTAL

General Procedure for N-Acylation

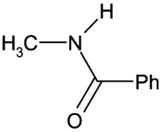
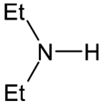
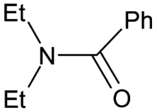
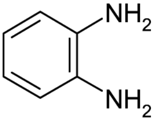
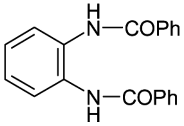
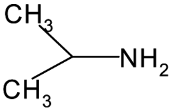
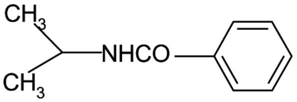
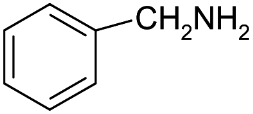
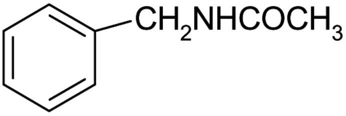
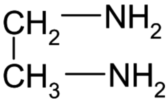
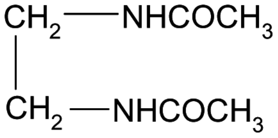
Acyl chloride (acetyl or benzoyl chloride) (1.05 mmol) was added to a stirred mixture of the amine **1** or **2** (1 mmol) and iodine (1 mmol), and stirring continued between two additions at room temperature for the appropriate time as monitored by thin-layer chromatography (TLC). In case of solid substrate, 3.5 eqv of the acyl chloride were used to solubilize the substrate. After completion of the reaction, iodine was destroyed by adding saturated $Na_2S_2O_3$ solution (5 ml). Diethyl ether (10 ml) was added, and the two phases were separated. The organic phase was washed with saturated $NaHCO_3$ solution (2.5 ml) and brine (2.5 ml), dried (Na_2SO_4), and concentrated to give the pure product.

Table 2. Benzoylation of primary and secondary amines using iodine as a catalyst[a]

Entry	Substrate 3	Time (min)	Product 4[b]	Yield[c]/%
A		1		95.66
b[d]		10		65.32
c[d]		12		90.05
d[d]		8		62.12
e[d]		14		97.32
f[d]		10		62.72
g[d]		5		99.19

(*Continued*)

Table 2. Continued

Entry	Substrate 3	Time (min)	Product 4[b]	Yield[c]/%
h	$H_3C–NH_2$	1		54.29
i		1		88.34
j[d]		13		92.03
k		2		82.5
l		5		78.0
m		2		75.5

[a] Reaction condition: substrate = 1 mmol, PhCOCl = 1.05 mmol, iodine = 0.1 mmol, 25°C.

[b] Products have been characterized by melting points, chemical tests, IR, and ^1H NMR data.

[c] Isolated yield.

[d] AcCl (3.5 eq) was used.

^1H NMR spectroscopic data of compound (**2h**): (liquid) 2.0 and 2.1 (2s, 3H), 2.8 (d, 3H), 4.7 (s, 1H). ^1H NMR spectroscopic data of compound (**4e**): (melting point 100°C) 7.25 (s, 1H), 7.5 (m, 1H), 7.65 (m, 1H), 8.1 (m, 5H). ^1H NMR spectroscopic data of compound (**4i**): (semisolid) 1.1 (t, 6H), 3.5 (q, 4H), 7.1 (s, 1H), 7.3 (m, 4H).

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