

Research Article

Benzoylation of Amines *sans* Alkali: A Green Protocol in Neat Phase

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A new procedure for benzoylation of aromatic and aliphatic amines has been developed in neat phase without use of any solvent or alkali.

Protection of functional groups such as amines, phenols, and alcohols is very often employed for multistep reactions and also needed for characterization, resolution, and purification of the said compounds as well. In this respect, benzoylation of aromatic primary or secondary amines [1, 2] or phenols in the presence of alkali [3–5] using commonly available benzoyl chloride is a very attractive and handy methodology known as Schotten-Baumann reaction. [6] However, the product is usually contaminated with traces of benzoyl chloride that requires crystallization from methanol, ethanol, or rectified spirit so as to convert the adhering acid chloride to its ester. Apart from benzoyl chloride, a host of reagents like benzoyl cyanide, [7] benzoic anhydride, [8] *N*-benzoyltetrazole, [9, 10] or 2-benzoylthio-1-methylpyridinium chloride [11] has also been used. The reaction has also been performed in the presence of pyridine, triethyl amine, sodium hydride [12–15], and so forth, and also in solvent-free condition [16–29]. Recently, it has been reported [30] that an acetone solution of amine or amino acids and benzoyl chloride taken in conjunction with brine, when poured over sodium bicarbonate solution gave the benzoylated product.

We wish to report herein an absolutely solvent free green methodology for the benzoylation of both aromatic and aliphatic amines (*primary* and *secondary*) that is devoid of using any alkali and other bases. The overall process affords the product of high purity and in very high yields and in a very short time.

In a typical experimental procedure, exactly equimolar quantities (10 mmol) of amine (*primary* or *secondary*) and benzoyl chloride are mixed in neat phase in a small beaker and stirred with a glass rod in a hood. The reaction mixture instantaneously becomes hot with the evolution of HCl gas and becomes a solid mass or paste that in all likelihood remains as a complex adhering with any unreacted benzoyl chloride or with any hydrochloride formed *in situ*. Crushed ice (*ca.* 10 gm) is then added to the contents of the beaker and stirred well with a glass rod. The thick reaction mixture gradually becomes soft, and product begins to deposit on the walls of the beaker by the dissolution of any hydrochloride adhered with the product or by the gradual dispersion of traces of benzoyl chloride in the aqueous phase during stirring, and finally the supernatant aqueous layer becomes clear when the precipitation of the product is complete as a crystalline product. The product is filtered and washed with water to free it from any adhering amine hydrochloride. It is then dried over anhydrous sodium sulphate and further crystallized from suitable solvents to obtain the benzoylated product in high yield (Table 1). The reaction time usually varies on an average from 3–5 min for aromatic, heterocyclic, aliphatic, and alicyclic primary amines.

While the *primary* amines react easily with benzoyl chloride, the *secondary* amines are reluctant to react under the same condition, and the time required for secondary amines is about 20–25 min. By this protocol, only diphenyl amine (entry 19) and morpholine (entry 20) could be

TABLE 1: Results of benzylation of amines in neat phase (solvent-free condition) *sans* base[#].

Entry	Substrate	Product	Yield ^a (%)	mp °C (lit. [31] mp °C)	Time (min)
1	Aniline	Benzanilide	92	164 (163)	3
2	2-Methylaniline	2-Methylbenzanilide	76	142 (143)	3
3	3-Methylaniline	3-Methylbenzanilide	91	125 (125)	3
4	4-Methylaniline	4-Methylbenzanilide	89	157 (158)	3
5	2-Chloroaniline	2-Chlorobenzanilide	95	99 (100)	3
6	3-Chloroaniline	3-Chlorobenzanilide	76	121 (120)	3
7	4-Chloroaniline	4-Chlorobenzanilide	95	191 (192)	3
8	3-Nitroaniline	3-Nitrobenzanilide	69	156 (155)	10
9	4-Methoxyaniline	4-Methoxybenzanilide	92	153–54 (154)	5
10	2-Aminobenzoic acid	2-(<i>N</i> -benzamido) benzoic acid	76	180 (182)	5
11	4-Aminobenzoic acid	4-(<i>N</i> -benzamido) benzoic acid	73	>250 (278)	5
12	Methyl anthranilate	<i>N</i> -benzoyl methylanthranilate	76	98–99 (100)	5
13	1-Naphthyl amine	1- <i>N</i> -benzamido-naphthalene	66	159 (161)	3
14	4-Amino pyridine	<i>N</i> -(4-pyridyl) benzamide	66	208–209	20
15	2-Amino thiazole	<i>N</i> -(2-thiazolyl) benzamide	70	150 (152 ^[30])	10
16	Benzyl amine	<i>N</i> -benzyl benzamide	88	105 (106)	3
17	Cyclohexyl amine	<i>N</i> -cyclohexyl benzamide	86	147–48 (148)	2
18	<i>N,N</i> -dimethyl hydrazine	<i>N,N</i> -dimethyl benzamide	75	166–67	10
19	Diphenyl amine	<i>N</i> -benzoyl diphenyl amine	67	180 (182)	25
20	Morpholine	<i>N</i> -benzoyl morpholine	58	73 (75)	20

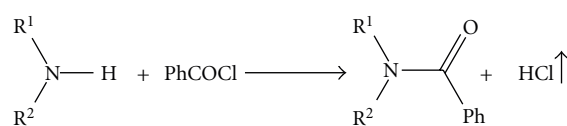
[#] All the compounds give satisfactory spectral data (IR, NMR).^aYield refers to the combined amounts of the first and second crop of crystallized product.R¹ : Ph, R² : HR¹ : Ar, R² : HR¹ : Het, R² : HR¹ : Alkyl, R² : HR¹ : Cycloalkyl, R² : HR¹, R² : PhR¹, R² : -CH₂ - CH₂ - O - CH₂ - CH₂ -

FIGURE 1

benzoylated. The other secondary amines such as indole, imidazole, and carbazole did not react at all with benzoyl chloride under the aforesaid condition and even on reverse addition, that is, *addition* of amine to benzoyl chloride failed to afford the desired product. This is because of the

unavailability of lone pair on nitrogen atom that is involved in the aromaticity of the said substrates.

In this procedure, a large number of *primary* amines have been benzoylated in a very efficient way while the same is not much encouraging for secondary amines. The high efficacy (for *primary* amines) and atom economy of this methodology under solvent-free condition without use of any base or additive coupled with the isolation of the product in pure crystalline form offers an excellent improvement over the conventional methods and may be considered as a green protocol in the true sense of the meaning. The method is free from any unwanted side reactions such as hydrolysis of ester (e.g., methyl anthranilate, entry 12) or acidification (e.g., amino acids, entries 10 and 11) under the reaction condition and is the most practical and easiest way for the synthesis of *N*-substituted amides in an ecofriendly condition.

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