Green Chemistry

Cite this: *Green Chem.*, 2012, **14**, 326

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CDI-mediated monoacylation of symmetrical diamines and selective acylation of primary amines of unsymmetrical diamines†

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Received 21st October 2011, Accepted 18th November 2011
DOI: 10.1039/c1gc16314k

A highly efficient and green protocol for monoacylation of symmetrical diamines and chemoselective acylation of primary amines of unsymmetrical diamines has been developed.

Highly selective reactions capable of selecting one functionality in the presence of others have applications in a number of synthetic strategies.[1] Such selectivity becomes more challenging when two functionalities are the same or have very little reactivity difference. These kinds of selectivities mainly occur with living organisms/enzymes and have always attracted synthetic chemists.[2] Chemoselective monoacylation of symmetrical diamines[3] or chemoselective acylation of primary amines in the presence of secondary amines[4] are important examples. Selective monoacylation of diamines is important as the monoacylated diamines are intermediates for several well-established drugs.[5] The main challenge associated with such selectivity is a tendency for bis-acylation even with an excess (10 equiv.) of diamine.[3] A number of attempts have been carried out to solve the problem.[3–5] However, till date the most simple and practical method of monoacylation is selective monoprotection of one nitrogen atom with BOC in acidic medium,[5] followed by acylation of another nitrogen and finally deprotection to afford the desired product. However by this method, the overall yield of the reaction is reduced.

In such a scenario, monoacylation of diamine is of great interest. It would be a win–win situation from a green chemistry perspective if the above reaction can be carried out in the presence of a green solvent or with minimum use of industrially accepted organic solvents (ethyl acetate or ethanol).[6d–e] Herein, we report a highly efficient, scalable, and practical protocol for monoacylation of symmetrical diamines in brine solution.

Recently, we have developed a protocol for monoacylation of symmetrical diamines.[7] The protocol has lot of advantages; however the overall yield decreased due to a two step synthesis of acyl imidazole from carboxylic acid by acyl chloride intermediate and dry organic solvent was required. Further the synthesis of acyl chloride for reactants with active methylene group, *e.g.* phenyl acetic acid and derivatives, involves various side chain reactions causing reduction in yield. In order to overcome these limitations and to develop a new green protocol, CDI-mediated one-step synthesis of acyl imidazole from carboxylic acid was attempted.

N,*N*-Carbonyldiimidazole (CDI) is widely used for the synthesis of amides from carboxylic acids and amines.[8] It is synthesized by the reaction of phosgene and imidazole in highly leak-proof systems in industry. It is easy to handle and is less toxic compared to phosgene or thionyl chloride. The synthesis of amides using CDI is mainly carried out in one-pot two-step reactions of acid and amine mediated by CDI. The first step of the reaction involves the reaction of carboxylic acid and CDI in dry aprotic solvent (*e.g.* dry THF or toluene) under nitrogen atmosphere until release of CO_2 gas ceases and the intermediate acyl imidazole is formed (step 1, Scheme 1). The reaction mainly completed in 2–4 h depending upon the reactant and the solvent used.[4,9]

In order to increase the efficiency of the process and to look for greener alternatives, the reaction was attempted without solvent and in different organic solvents.[10] Phenyl acetic acid was chosen as model reactant. The progress of the reaction was monitored with ^{1}H NMR and the disappearance of peak corresponding to CH_2 (δ 3.46) was considered as reference. A very encouraging result was observed. Reaction was fastest without any solvent. The reaction completed in 5 min and peak corresponding to CH_2 of phenyl acetic acid disappeared and new peak (δ 4.18) corresponding to acyl imidazole appeared. The stability of acyl imidazole formed was also checked with NMR. It was found that the product remained stable for 20 min, after which it started hydrolysing to give parent reactant.

Various acyl imidazoles **1a–10a** (aliphatic, aromatic and with active methylene group, *e.g.* derivatives of phenyl acetic acids **6–10**) were synthesised using hte optimized protocol (Table 1). It is noteworthy that we were able to prepare imidazole carboxylic esters **11a–12a** by the reaction of alcohols and CDI with 100% conversion within 10 min. The same protocol in dry toluene required four hours under nitrogen atmosphere.[9]

After accomplishment of acyl imidazoles **1a–10a** and imidazole carboxylic esters **11a–12a**, the next step involves reaction of acyl imidazoles with diamines dihydrochloride to give monoacylated diamines.[7]

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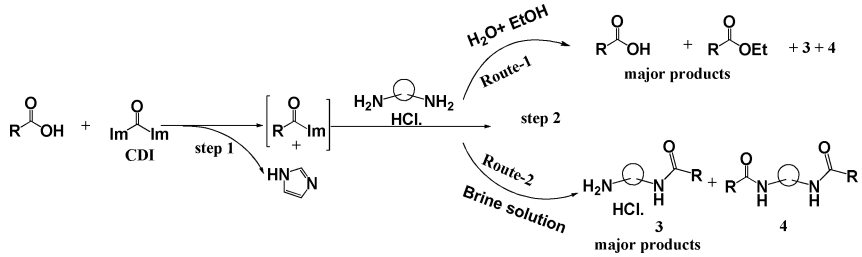
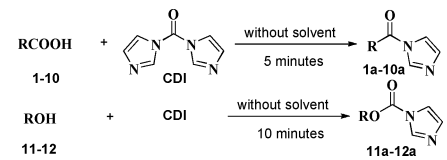
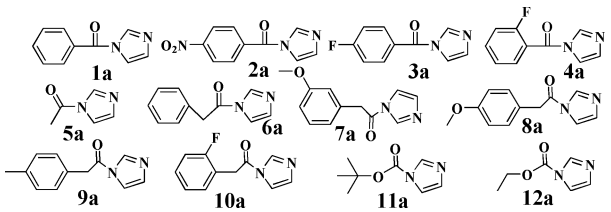
† Electronic supplementary information (ESI) available: Experimental procedures and NMR spectra for compounds.See DOI: 10.1039/c1gc16314k



Scheme 1

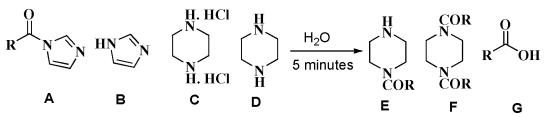
Table 1 Synthesis of acyl imidazole and Imidazole carboxylic esters





Acid/alcohol: CDI (1 : 1.2). **1–10** not isolated and used within 20 min. **11**, **12** were isolated.

Table 2 Effect of NaCl and imidazole concentration on selectivity



Entry	**B** (mol%)	NaCl (%)	**C** : **D**	**E** (%)	**F** (%)	**G** (%)
1	0.1	0	1 : 0	90	10	0
2	0.2	0	1 : 0	80	10	10
3	0.4	0	1 : 0	70	5	25
4	0.8	0	1 : 0	40	2	58
5	1	0	1 : 0	28	2	70
6	1	0	1 : 0.5	35	25	40
7	1	0	1 : 1	40	40	20
8	1	0	1 : 2	20	40	40
9	1	0	0 : 1	10	90	0
10	1	10	1 : 1	60	30	10
11	1	20	1 : 1	90	10	0
12	1	25	1 : 1	90	10	0

HPLC yield.

Piperazine dihydrochloride and benzoyl imidazole were selected as model reactants and were reacted in ethanol–water mixture (step 2, route 1 of Scheme 1), as reported earlier.[7] To our disappointment, the major products were esters and acids of the corresponding benzoyl imidazole (step 2, route 1 of Scheme 1). The result was entirely different from our earlier report[7] where N-selective monoacylation was observed. From these results and from our earlier report[7] it was clear that imidazole/imidazole HCl concentration played an important role in N-selective monacylation.[11]

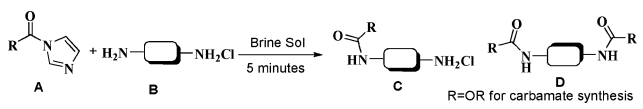
In order to study the effect of imidazole on N-selective acylation in aqueous medium, acyl imidazole was synthesized by the reaction of acyl chloride and imidazole[7] and subjected to reaction with piperazine dihydrochloride with different mol% of imidazole (Table 2, entries 1–5).[7] It was observed that acyl imidazole preferred hydrolysis over amide formation as the amount of imidazole was increased in the reaction mixture. We attempted a number of theoretically possible protocols to reduce imidazole concentration.[12] However, all the methods failed. The reaction was further attempted by using piperazine and piperazine dihydrochlorides in different ratios (Table 2 entries 6–8). Entry 9, Table 2, indicates N-acylation (**E** and **F**) dominates as the concentration of free piperazine increases in reaction mixture. The ratio of mono and diacylated product (**E** : **F**) was maximum at 1 : 1 ratio of piperazine and piperazine dihrochloride (entry 7, Table 2).[13] No further improvement was observed by changing ratio of piperazine and piperazine dihrochloride (entries 5–9, Table 2).

Recently, brine solution has been reported to influence various organic transformations by increasing or decreasing the reaction rates.[14] It is expected to decrease ion exchange process because of common ion effect. In order to achieve chemoselectivity by decreasing proton exchange between monoacylated/monoprotonated diamines and imidazole, we attempted the reaction in different concentrations of brine solution (entries 10–12, Table 2). To our surprise, the ratio of mono to diacylated product started increasing with the increasing concentration of salt along with decrease in reaction rate. At 20% NaCl solution, chemoselective monoacylation of piperazine was observed (route 2, Scheme 1). Further increase in NaCl concentration was found to have no improvement.

The optimized conditions were attempted for a variety of different reactants (**1a** to **12a** of Table 1) and diamines **13–23** of Fig. 1 for monoacylation and monocarbamate formation (Table 3). Entries 1–11, 15 and 19–21 of Table 3 indicate good conversion with secondary cyclic and acyclic diamines, while entries 12, 14 and 16–18 of Table 3 indicate good conversion with primary diamines. Entries 6–10 of Table 3 indicate good result with reactants having active methylene group. The protocol was also attempted for carbamate formation, it was observed from entry 21 and 22 that the protocol gave chemospecific monocarbamate formation. All the results indicate that the protocol is effective for cyclic, acyclic, primary as well as secondary diamines for chemoselective benzoylation and carbamate formation.

The scope of the reaction was further explored for the highly selective acylation of primary amines in the presence of secondary amines (Table 4). It is clear from Table 4 that selectivity is maintained for small alkyl chains as well as for

Table 3 Chemoselective monoacylation and carbamate formation



Entry	A	B	Yield[a] C (%)	Yield[a] D (%)	Total yield[a]
1	**1a**	**13**	83	5	88
2	**2a**	**13**	90	0	90
3	**3a**	**13**	88	4	92
4	**4a**	**13**	80	8	88
5	**5a**	**13**	70	23	94
6	**6a**	**13**	88	4	92
7	**7a**	**13**	84	5	89
8	**8a**	**13**	80	5	84
9	**9a**	**13**	87	5	92
10	**10a**	**13**	68	20	88
11	**1a**	**14**	80	12	92
12	**1a**	**15**	92	0	92
13	**1a**	**16**	0	0	0
14	**1a**	**17**	68	25	93
15	**1a**	**18**	90	0	90
16	**1a**	**19**	88	4	92
17	**1a**	**20**	80	10	90
18	**1a**	**21**	72	20	92
19	**1a**	**22**	90	2	92
20	**1a**	**23**	88	4	92
21	**11a**	**1a**	95	0	95
22	**12a**	**1a**	96	0	96

[a] isolated yield.

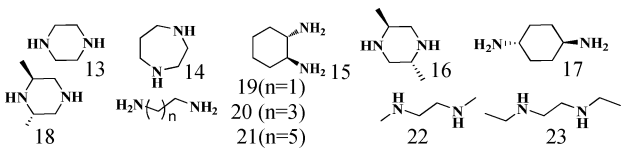


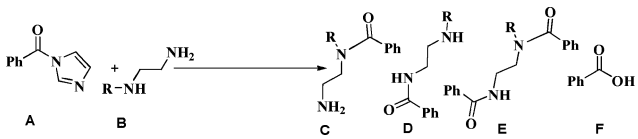
Fig. 1 Amines selected for monoacylation/monocarbamate formation.

sterically hindered isopropyl groups. No acylation of secondary amine was observed. In line with our anticipation, selectivity of the present protocol (method 1) was compared with our earlier report (method 2).[7] It was observed that both the methods were highly efficient for selective acylation of primary amines.

On the basis of these results and literature precedents, a plausible mechanism for the observed mono-selectivity is proposed. The acyl imidazole preferred hydrolysis over amide formation with the reaction of diamine dihydrochloride in aqueous medium. This may be due to higher reactivity of acyl imidazole in excess of imidazole, where acyl imidazole hydrolyses before *in situ* generation of piperazine monohydrochloride. It has been verified with NMR that acyl imidazole hydrolyses within 2 min with piperazine dihydrochloride and water. The maximum conversion was observed with piperazine and piperazine dihydrochloride (1 : 1 ratio) as it has one free nitrogen available for acylation.[13] Increase in selectivity with brine solution may be attributed to a decrease in reaction rate or decrease in rate of proton exchange between diamine monohydrochloride or monoacylated piperazine with excess of imidazole.

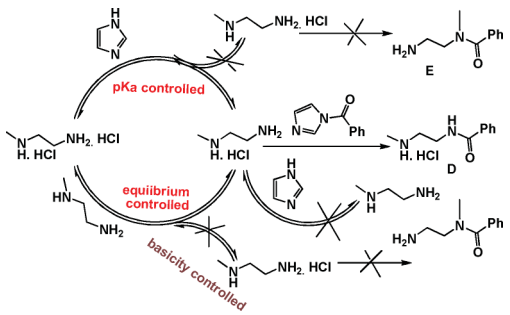
The chemoselective acylation of primary amines is explained in Scheme 2. The dihydrochloride salt of unsymmetrical diamines give monohydrochloride diamines either because of pK_a-controlled selective deprotonation in the presence of a catalytic

Table 4 Acylation of primary amines in the presence of secondary amines



Entry	R	C* % c′(c″)	D* % d′(d″)	E* % e′(e″)	Total yield g′(g″)
1	methyl	0(0)	88(90)	6(3)	94(93)
2	ethyl	0(0)	90(92)	5(2)	95(94)
3	propyl	0(0)	92(90)	2(0)	94(90)
4	isopropyl	0(0)	96(94)	0(0)	96(94)
5	4-amino piperidine	0(0)	94(92)	0(0)	94(92)

c′, d′, e′,g′: isolated yield by method 1: acyl imidazole was synthesized by the reaction of benzoic acid and CDI and was reacted with diamine monohydrochloride in 20% brine solution. c″, d″, e″,g″: isolated yield by method 2: acyl imidazole was synthesized by the reaction of acyl halide and imidazole and was reacted with piperazine dihydrochloride in ethanol–water mixture.



Scheme 2 Monoacylation of primary amines in the presence of secondary amines.

amount of imidazole[7] or because of equilibrium reaction with diamine.[13] Deprotonation always occurs at primary amines because they are less basic than secondary amines. The monoprotonated diamines have only primary free nitrogen, Hence, chemoselectivity is observed. The diacylation is also controlled because of slow proton exchange between monoprotonated diamine or monoacyl diamine with imidazole in brine solution.

In conclusion, we have developed a simple protocol for monoacylation of symmetrical and unsymmetrical diamines. It is particularly noteworthy that this protocol is the first example of monoacylation of symmetrical diamines in brine solution and selective acylation of primary amines. The protocol is applicable for monoacylation of a wide variety of substrates. The protocol is green in nature as it uses only industrially preferred organic solvents (ethyl acetate and ethanol),[6d,6e] and further no dry organic solvent at any stage of reaction is used.

Experimental section

General procedure 1: Synthesis of phenyl-piperazin-1-yl-methanone

In a round bottom flask add 0.01 mole (1.36 g) phenyl acetic acid and 0.012 moles (1.94 g) of CDI. Mix the reaction mixture with spatula to start the reaction. CO_2 gas starts releasing with exothermic reaction. Leave the reaction mixture at room

temperature for 5 min till solid reaction mixture turned to pale yellow liquid. In a separate round bottom flask add 0.05 moles (0.43 g) of piperazine and 0.05 moles (0.80 g) of piperazine dihydrochloride in 20 ml of water. Stir the reaction mixture for 5 min and add 4 g of NaCl. Add this brine solution to the round bottom flask containing acyl imidazole. Stir the reaction mixture for half hour. The aqueous layer was washed with 4 × 5 ml of ethyl acetate to remove diacylated product. 10 ml of saturated solution of NaOH was added to the aqueous layer and washed with ethyl acetate (4 × 10 ml). The aqueous layer was discarded. The organic layer was washed with water (4 × 10 ml), dried over anhydrous Na_2SO_4 and concentrated to give pale yellow coloured liquid. The pure product 2-phenyl-1-(piperazin-1-yl)ethanone was purified by flash chromatography as a colourless liquid.

General procedure 2: Synthesis of N-BOC piperazine (monocarbamate of diamines)

The synthesis is mainly carried out in two steps. **First step, synthesis of tert-butyl 1H-imidazole-1-carboxylate:** In a round bottom flask add 0.01 mol (0.75 g) of t-butanol and 0.012 mole (1.94 g) of CDI. Stir the reaction mixture for 10 min at 40 °C. Add 10 ml of ethyl acetate in it. Wash the organic layer with 2 × 5 ml of 0.1 N HCl and 2 × 10 ml of water. Dry organic layer over anhydrous Na_2SO_4 and concentrated to give coloured liquid. The product formed is enough pure to be used for next step. **Second step, synthesis of N-BOC piperazine:** In a separate round bottom flask add 0.05 mol (0.43 g) of piperazine and 0.005 mol (0.80 g) of piperazine dihydrochloride in 20 ml of water. Stir the reaction mixture for 5 min and add 4 g of NaCl. Add tert-butyl 1H-imidazole-1-carboxylate from first step to the brine solution. Stir the reaction mixture for half hour. 10 ml of saturated solution of NaOH was added to the aqueous layer and washed with ethyl acetate (4 × 15 ml). The aqueous layer was discarded. The organic layer was washed with water (4 × 5 ml), dried over anhydrous Na_2SO_4 and concentrated to give pale yellow coloured liquid. The pure product N-BOC piperazine was purified by flash chromatography as a colourless liquid.

General procedure 3: Monoacylation of unsymmetrical diamines

Monoacylation of unsymmetrical diamines has been achieved following general procedure 1 and general procedure of our earlier report.[7]

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10 $CDCl_3$, DMSO, C_6D_6 and neat. In neat conditions, the reaction was performed without solvent and NMR was recorded in $CDCl_3$.
11 Route 1 of Scheme 1 gave one mole of imidazole for every mole of acyl imidazole formed, while in an earlier report[7] imidazole HCl formed was filtered off and catalytic amount of imidazole HCl left in reaction mixture.
12 For example, use of acid, solid supports and imidazole complexing agents.
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