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Highly rapid and direct synthesis of monoacylated piperazine derivatives from carboxylic acids under mild conditions

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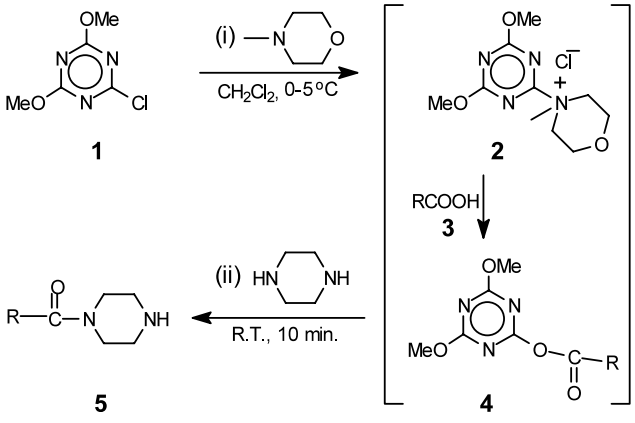
This paper is dedicated to Professor R. B. Mane on occasion of his 61st birthday

Abstract—A series of monoacylated piperazine derivatives were obtained by the reaction of carboxylic acids with 2-chloro-4,6-dimethoxy-1,3,5-triazine in dichloromethane at room temperature. Good to excellent yields, short reaction times and mild reaction conditions are important features of this methodology. © 2003 Published by Elsevier Science Ltd.

The amide unit is one of the most widely occurring functional groups. It is present as a key feature in many important natural products and man-made compounds.[1] Azo-dye liquid crystalline molecules containing a piperazine moiety are useful for low power consumption reflective liquid crystal devices.[2] These liquid crystal molecules, as three-layered guest–host (G–H) systems with substrate color mixing of yellow, magenta and cyan are expected to be used for developing full-color reflective displays.[3] The materials containing a piperazine moiety are useful in the application of anti-ferroelectric or ferroelectric liquid crystal displays.



Scheme 1.

In the G–H system, the dye molecules are mixed with liquid crystals to increase the desired mesogenic phase or other physical properties.[4] However, the phase separation between the guest and host materials are serious issues in developing liquid crystal devices. Intermediates containing the O=C–piperazine unit are not only versatile for synthesizing various kinds of liquid crystals,[5a,b] but are also useful in drug chemistry.[5c,d,6,7]

The amide functionality is highly thermostable and is one of the most important factors to be considered in designing photoelectric materials. However, direct monoacylation of symmetrical diamines becomes frequently problematic due to competitive bisacylation.[8] For instance, under normal basic conditions, the bisadduct is isolated as the major product. A possible explanation of the uncontrollable bisacylation of the symmetrical secondary diamines under these conditions is that the monobenzoylated intermediate is more soluble in the solvent than piperazine and it reacts preferentially with the arylcarboxyl derivative to provide the observed bisacylated product. Therefore, a number of indirect, multistep processes have been developed.[9a–d] The problem of bisacylation can be somewhat circumvented using recently reported methods.[10–12] However, the reported methods suffer from several drawbacks such as the use of a strong lithium reagent, drastic reaction conditions, long reaction times, the use of aggressive and expensive reagents, application to limited substrates and difficulties in separation/purification of the products. Therefore, it is of interest to develop an alternative process for efficient, rapid and selective preparation of the desired monoacylated piperazine derivatives under mild conditions.

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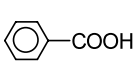
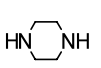
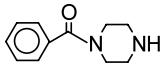
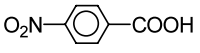
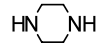
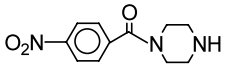
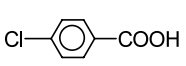
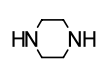
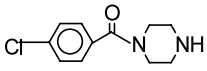
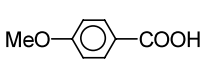
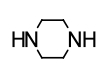
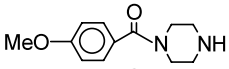
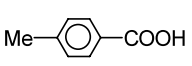
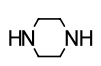
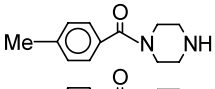
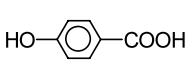
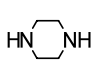
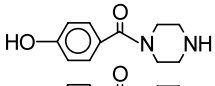
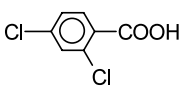
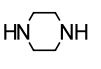
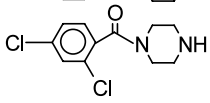
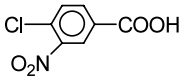
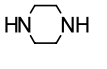
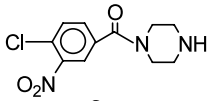
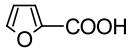
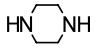
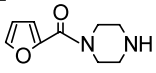
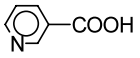
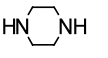
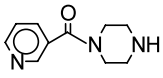
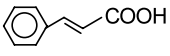
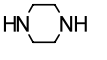
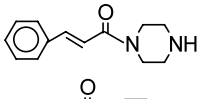
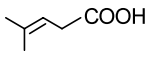
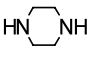
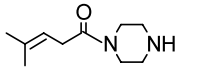
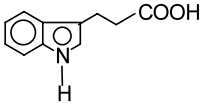
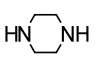
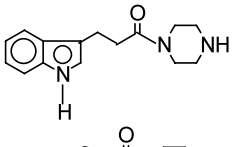
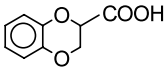
Over the last few years there has been a considerable growth in interest in the use of cyanuric chloride or its derivatives in organic synthesis.[13,14] We now report the use of 2- chloro-4,6-dimethoxy-1,3,5-triazine for the direct conversion of carboxylic acids and piperazine into monoacyl piperazine derivatives (Scheme 1).

Our strategy involves enhancement of the reactivity of the carbonyl group of the acid moiety using the 4,6-dimethoxy-1,3,5-triazine group. The carboxylic acid was first allowed to react with 2-chloro-4,6-dimethoxy-1,3,5-triazine in dichloromethane in the presence of *N*-methylmorpholine; the hydrogen chloride generated is absorbed by the amine. The resulting reaction mixture was further treated with piperazine at room temperature to afford the monoacylated product **5**.

In comparison with other methods, our method is superior because the carboxylic acid group can be converted to the amide moiety via a one-pot synthesis at room temperature without converting the carboxylic acid to an acyl chloride, mixed anhydride, ethyl/methyl

Table 1. Synthesis of monoacylated piperazine derivatives from carboxylic acids using 2-chloro-4,6-dimethoxy-1,3,5-triazine under mild conditions

Entry	Acid	Amine	Piperazine	Yield (%)[a,b]
a				93
b				88
c				91
d				82
e				88
f				92
g				63
h				67
i				92
j				76
k				92
l				72
m				60
n				95
o				92

a. Yield of isolated pure product b. Products were characterized by IR, ^{1}H NMR, elemental analysis and by comparison with authentic samples.

ester or by using a strong lithium reagent. The desired monoacylated product, **5** can easily be purified by simple recrystallization or using column chromatography (pet. ether:ethyl acetate = 8:2) and by-products such as *N*-methylmorpholine hydrochloride and the triazine derivative easily removed by aqueous work-up. Due to the steric hindrance present in the 4,6-dimethoxy-1,3,5-triazine intermediate **4**, the reaction with a second amino group is prevented and, therefore, no bisadduct was detected. ^{1}H NMR spectroscopy revealed that the monoacylated piperazine derivatives thus prepared were the desired products. The methodology was found to be general, a variety of carboxylic acids such as aliphatic, unsaturated, aromatic and heterocyclic were smoothly converted into the corresponding monoacylated piperazine derivatives. It is interesting to note that even the hydroxy group on the side chain of 2-hydroxyethylpiperazine did not interfere with the amidation reaction (entry o, Table 1).

In conclusion, a convenient and straightforward protocol has been developed to convert piperazine into monosubstituted piperazine derivatives. The reaction product can easily be purified by recrystallization or column chromatography. Furthermore, this process is amenable to scale-up. All the chemicals used are commercially available and inexpensive. The selective preparation of monoacylated piperazine, short reaction times, mild reaction conditions and the use of inexpensive and easily available reagents are noteworthy advantages of this method.

In a typical procedure, to a solution of 2-chloro-4,6-dimethoxy-1,3,5-triazine (5 mmol) in CH_2Cl_2 (20 ml), *N*-methylmorpholine (15 mmol) was added at 0–5°C under continuous stirring. A white suspension was formed after 30–40 min and to this mixture 2,3-dihydrobenzo[1,4]dioxin–carboxylic acid (5 mmol) in CH_2Cl_2 (10 ml) was added resulting in the formation of a clear solution. After stirring the mixture for 1 h, piperazine (5 mmol) was added at room temperature. After completion of the reaction (TLC, 10 min), the mixture was washed with 10% aqueous $NaHCO_3$ solution (2×10 ml) followed by H_2O (3×10 ml). The organic layer was dried over anhydrous sodium sulfate and removal of the solvent under reduced pressure furnished a crude product which was further purified by recrystallization or column chromatography (pet. ether:ethyl acetate = 8:2).

N-(2,3-Dihydrobenzo[1,4]dioxin-2-carbonyl)piperazine (**5n**): mp = 85°C; IR (KBr): 1640, 3450 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.15 (s, 1H, NH), 2.8–2.9 (m, 2H), 2.95–3.00 (m, 2H), 3.5–3.65 (m, 2H), 3.7–3.8 (m, 2H), 4.4 (dd, J = 12, 8.5 Hz, 1H), 4.5 (dd, J = 12, 2.5 Hz, 1H), 4.9 (dd, J = 8.5, 2.5 Hz, 1H), 6.9–7.1 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$); δ = 40.2, 45.7, 50.3, 65.1, 70.5, 115.1, 120.2, 122.4, 123.9, 144.2, 145.6, 170.2; mass: m/z (%) = 248 (M^+, 25), 111 (100). Anal. calcd for $C_{13}H_{16},N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 63.02; H, 6.41; N, 11.35.

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