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Imidazole-Catalyzed Monoacylation of Symmetrical Diamines

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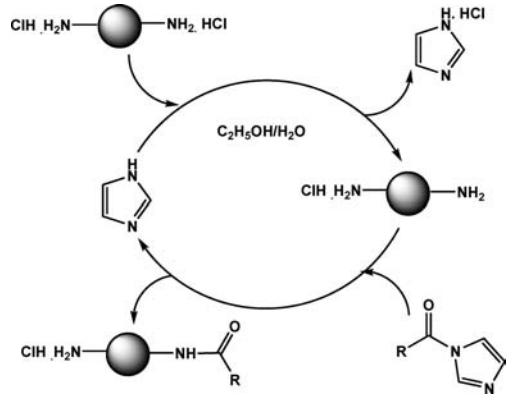
ABSTRACT



An imidazole-catalyzed protocol for monoacylation of symmetrical diamines has been developed. The protocol gave selective monoacylation of aliphatic (cyclic and acyclic) primary and secondary diamines. In the reaction, imidazole acts as both catalyst and a leaving group. Different monoacylated piperazines and other diamines were synthesized at room temperature in an ethanol/water solvent system.

Monoacylated symmetrical diamines are building blocks[1] or intermediates[2] of several well-established drugs such as cardiotonic agent vesnarinone and the antihypertensive agent prazosin.[3] The synthesis of these compounds involves chemoselective acylation on one nitrogen of symmetrical diamines. However, the direct monoacylation of symmetrical diamines is frequently fraught with a complication associated with the tendency for bisacylation even with a large excess (10 equiv) of diamine to acyl halides in aprotic solvent.[4a] A possible explanation of the uncontrollable diacylation under these conditions is that the monoacylated intermediate is more soluble in the solvent (aprotic) than the original diamine.[4] Plethoras of indirect[5,6] and direct[4,7] syntheses of monoacylated symmetric diamines are reported. However, the reported methods either use dry conditions at very low temperature (−78 °C)[7] or have used reactants not readily available or difficult to synthesize.[8] Some polymer-supported reactions[9] are also reported; however, all these methods did

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(2) (a) Williams, L.; Booth, S. E.; Undheim, K. *Tetrahedron* **1994**, *50*, 13697. (b) Li, R.-T.; Ding, P.-Y.; Han, M.; Cai, M.-S. *Synth. Commun.* **1998**, *28*, 295.

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(4) (a) Wang, T.; Zhang, Z.; Meanwell, N. A. *J. Org. Chem.* **1999**, *64*, 7661. (b) Zhang, Z.; Yin, Z.; Meanwell, N. A.; Kadow, J. F.; Wang, T. *Org. Lett.* **2003**, *5*, 3399. (c) Luna, A.; Alfonso, I.; Gotor, V. *Org. Lett.* **2002**, *4*, 3627. (d) Kelly, T. R.; Cavero, M. *Org. Lett.* **2002**, *4*, 2653.

(5) (a) Manoury, P. M.; Binet, J. L.; Dumas, A. P.; Lefevre-Borg, F.; Cavero, I. *J. Med. Chem.* **1986**, *29*, 19. (b) Dhawan, B.; Southwich, P.N. L. *Org. Prep. Proced. Int.* **1975**, *7*, 85. (c) Southwich, P. L.; Dhawan, B. *Org. Prep. Proced. Int.* **1976**, *8*, 205. (d) Lyle, R. E.; Coppola, B. P.; Saavedra, J. E.; Lyle, G. G. *Org. Prep. Proced. Int.* **1978**, *10*, 304.

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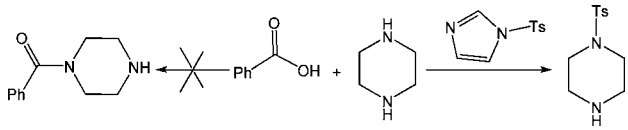
not have synthetic applicability. Due to these limitations, a simple and direct monoacylation of symmetrical diamines was required to be developed. To date, the most simple and practical method of monoacylation is selective monoprotection of one nitrogen atom with BOC in acidic medium, followed by acylation of another nitrogen and finally deprotection to afford the desired product.[5] However, by this method, the overall yield of the reaction is reduced.

In continuation of our work on the synthesis of bioactive compounds, we required the quantitative scale syntheses of a library of monoacylated diamines as reaction intermediates. Since no method was available in the literature, a new method was required. Herein, we report the monoacylation of symmetrical diamines by the use of imidazole as a leaving group as well as a catalyst in the water/ethanol system.

Tosyl imidazole is a well-known reagent used for esterification reactions.[10] Because of the lesser reactivity of the reagent, it is also used for selective esterification between two diols.[11] The same method was attempted for selective amide formation by the reaction of benzoic acid and piperazine in the presence of tosyl imidazole (Scheme 1).

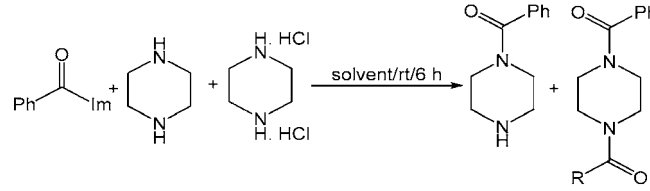
Scheme 1



Interestingly, instead of attaining the amide of acid, a selective tosyl group transfer on one NH bond of the piperazine was observed. When the same reaction was repeated without the use of an acid source, predominately ditosylated product was obtained. This observation gave us an idea that selective monoacylation can be carried out by the reaction of acyl imidazole and diamines in the presence of an acid source.

The reaction of benzoyl imidazole and piperazine in the presence of benzoic acid was attempted for a selective N-acylation reaction.[12] To our disappointment, the reaction gave only 30% monoacylated product, and no improvement in the result was observed with the change of reaction conditions. The reaction was then attempted between benzoyl imidazole and piperazine and piperazine dihydrochloride (1:1) in different solvent systems (DCM, acetonitrile, ethanol, water, and ethanol−water mixture) (entries 1−5, Table 1).

Table 1. Standardization of Reaction Conditions



1 2 3 4 5

entry	diamine ratio (**2**:**3**)	solvent	ratio[a] (**4**:**5**)	yield[b] (**4**) %
1	1:1	DCM	1:1	10
2	1:1	acetonitrile	2:3	10
3	1:1	ethanol	3:2	30
4	1:1	water	3:1	40
5	1:1	ethanol + water (1:1)	4:1	50
6	1:2	ethanol + water (1:1)	4:1	57
7	1:4	ethanol + water (1:1)	5:1	65
8	1:6	ethanol + water (1:1)	5:1	71
9	1:8	ethanol + water (1:1)	7:1	74
10	0:1	ethanol + water (1:1)	9:1	80
11	2:1	ethanol + water (1:1)	4:1	40
12	4:1	ethanol + water (1:1)	3:1	38
13	8:1	ethanol + water (1:1)	1:2	25
14	1:0	ethanol + water (1:1)	1:4	10

[a] Determined by LC-MS. [b] LC-MS yield of monoacylated product.

An improvement in results with 50% monoacylation was observed with the ethanol−water (1:1) mixture as a solvent system. A mixture of piperazine and piperazine dihydrochloride was used to synthesize the monohydrochloride salt of piperazine by an equilibrium reaction.[13] The ethanol−water system (1:1) was found to be the best solvent, essentially because all the components of the reaction, e.g., piperazine, piperazine dihydrochloride, and acyl imidazole, are soluble. After optimizing the solvent system, the reaction parameters were standardized by changing the ratio of piperazine to piperazine dihydrochloride (entries 6−14, Table 1). It was observed that a direct correlation exists between yield and molar ratio of piperazine dihydrochloride. Surprisingly, 80% monoacylation was observed with 100% piperazine dihydrochloride (entry 10, Table 1).

(6) Dorokhova, M. I.; Alekseeva, E. N.; Kuznetsova, I. A.; Portnov, M. A.; Rozanova, Y. M.; Tikhnova, O. Y.; Mikhalev, V. A. *Pharm. Chem. J.* **1974**, 737, and references therein.

(7) (a) Jacobi, K. *Ber. Chem.* **1933**, *66*, 113. (b) Cymerman-Craig, J.; Rogers, W. P.; Tate, M. E. *Aust. J. Chem.* **1956**, *9*, 397. (c) Desai, M.; Watthey, J. W. H.; Zuckerman, M. *Org. Prep. Proced. Int.* **1976**, *8*, 85. Masaguer, C. F.; Ravina, E. *Tetrahedron Lett.* **1996**, *37*, 5171.

(8) Picard, C.; Arnaud, N.; Tisnes, P. *Synthesis* **2001**, *10*, 1471.

(9) Wang, Y.; Jin, J.; Moore, M. L.; Graybill, T. L.; Wang, F.; Wang, M. A.; Wang, B.; Jin, Q.; Rivero, R. A. *Tetrahedron Lett.* **2004**, *45*, 6645.

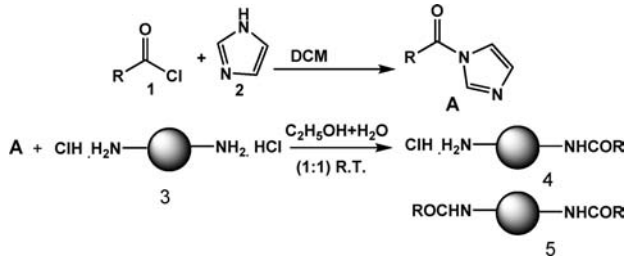
(10) Soltani, M. N. R.; Behrouz, S.; Faghihi, M. A.; Khalafi-Nezhad, A. *Tetrahedron Lett.* **2008**, *49*, 1115.

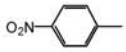
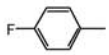
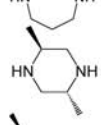
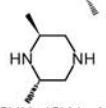
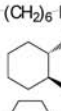
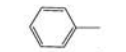
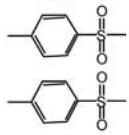
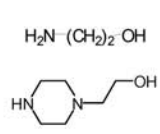
(11) Wang, Z.; He, G.; Lu, R. *Monatsh. Chem.* **2008**, *139*, 1109.

(12) The benzoyl imidazole for the reaction was synthesized by the reaction of benzoyl chloride and imidazole in 1:2 ratios in DCM. The imidazole hydrochloride formed in the reaction was filtered off, and the organic layer was concentrated under vacuum and used as such.

(13) Craig, J. C.; Young, R. J. *Org. Synth., Coll.* **1973**, *5*, 88.

Table 2. Acylation of Symmetrical Diamines and Amino Alcohols



entry	R	amine 3	ratio[a] (4:5)	yield c(b)
1			9:1	88(80)
2			1:0	92(84)
3			13:1	90(83)
4			8:1	82(76)
5			7:1	70(70)
6			1:0	96(85)
7			9:1	85(78)
8			0:0	0[c]
9			1:0	90(82)
10		$H_3CHN-(CH_2)_2-NHCH_3$	12:1	85 (75)
11		$C_2H_5HN-(CH_2)_2NHC_2H_5$	10:1	75(70)
12		$C_2H_5HN-(CH_2)_3NHC_2H_5$	8:1	70(64)
13		$H_2N-(CH_2)_2-NH_2$	14:1	70(68)
14		$H_2N-(CH_2)_3-NH_2$	8:1	62(58)
15		$H_2N-(CH_2)_4-NH_2$	4:1	55(50)
16		$H_2N-(CH_2)_6-NH_2$	3:1	45(40)
17			12:1	85(78)
18			9:1	75(70)
19			1:2	40(30)
20		$H_2N-(CH_2)_2-OH$	1:0	90(88)
21		$H_2N-(CH_2)_2-OH$	1:0	97(92)
22			1:0	97(92)

[a] **4**:**5** LC-MS ratio. [b] Isolated yield of monoacylated product. [c] LC-MS yield. R is RCO for tosyl group.

The standardized reaction condition was attempted with a wide variety of the reactant and is presented in Table 2. It is observed from Table 2 that the protocol gave a good result for a wide range of substrates. Entries 1−7 and 9 indicate good yield for the monoacylation of cyclic secondary diamines with substituated benzoyl chlorides and ethanoyl chloride. Entry 8 shows that no reaction was observed when an alkyl group is present adjacent to a secondary amine. This might be attributed to steric hindrance around the amine. This phenomenon was expoited to examine acylation of unsymmetrical 2,6-dimethylpiperazine, for which only monoacylated product was formed (entry 9, Table 2). Similar to this, when tosylation was carried out on symmetrical diamine, chemospecific tosylation on one nitrogen was obsereved with no sign of ditosylated product.

Selectivity for monoacylation was found to decrease for both primary and secondary diamines with an increase in carbon chain length (entries 10−12 and 13−16, Table 2). This led to the decrease in yield for monoacylated products. Probably, the amino groups of diamine behave more as amino groups of monoamine with an increase in chain length.

The protocol for monoacylation was also attempted for chemoselective acylation and tosylation of the NH group in aminoalcohols. In this case, chemospecific acylation and tosylation were observed only at nitrogen. However, when the same reaction was attempted with a conventional method, the reaction gave a mixture of O-acylated, N-acylated, and diacylated product.[14] All the results indicate that the protocol is effective for cyclic and acyclic aliphatic diamines and aminoalcohals for acylation, benzoylation, and tosylation, respectively.

After standardization of the reaction conditions, the upscaling of the reaction with benzoyl imidazole and piperazine dihydrochloride as model reactant was carried out. It was observed that the reaction gave good results with 0.1 mol of benzoyl imidazole with 74% (14 g) of isolated monacylated product.

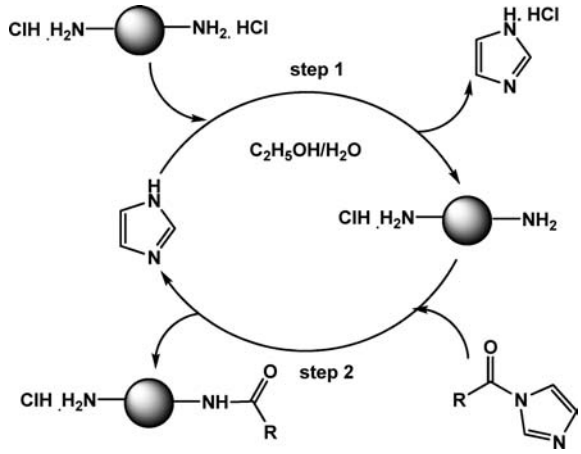
On the basis of the above observations and literature reports, a plausible mechanism for the observed selectivity for the monoacylation of symmetrical diamines (considering piperazine as the model substrate) is proposed in Scheme 2. Selective formation of piperazine monohydrochloride and the lower pK_a of imidazole (pK_a = 6.95)[15] than monobenzoylated piperazine hydrochloride (pK_a =7.78)[16] are the key factors for monobenzoylation. To validate our hypothesis, pure benzoyl imidazole was reacted with piperazine dihydrochloride under the same reaction conditions. Surprisingly, no benzoylation was observed. This is because in piperazine dihydrochloride both the nitrogens are protected and hence not available for reaction. However, when a catalytic amount of imidazole was added, good yield was observed. Imidazole (pK_a = 6.95)[15] can abstract the proton from piperazine dihydrochloride (pK_a = 9.82)[15] to give piperazine monohy-

(14) Reaction of benzoyl chloride with aminoalcohols in DCM at 0 °C.

(15) Albert, A.; Serjeant, E. P. *The Determination of Ionization Constants*, 2nd ed.; Chapman and Hall Ltd.: London; 1971; Chapter 8, pp 94−95.

(16) Hall, H. K., Jr. *J. A.m. Chem. Soc.* **1957**, *79*, 5441.

Scheme 2. Mechanism of Monoacylation



drochloride ($pK_a = 5.68$)[15] in situ (step 1, Scheme 2). The free nitrogen atom reacts with benzoyl imidazole to generate the *N*-benzoyl piperazine monohydrochloride and an imidazole molecule (step 2, Scheme 2). The free imidazole again follows step 1. In this way, the process undergoes a cyclic pathway of in situ generation of imidazole and piperazine monohydrochloride. Furthermore, due to lower pK_a value, imidazole could not abstract the proton from *N*-benzoyl piperazine hydrochloride ($pK_a = 7.78$). In the reported process, this catalytic amount of imidazole was present as an impurity when we used the benzoyl imidazole produced by the reaction of benzoyl chloride and imidazole as such without purification.

When a mixture of piperazine and piperazine dihydrochloride was used, a significant amount of diacylated products were obtained with an increase in the molar ratio of piperazine (Table 1, entries 11−14). This might be attributed to the reaction of acyl imidazole with free piperazine present in an equilibrium mixture of piperazine, piperazine monohydrochloride, and piperazine dihydrochloride.

Acyl imidazole is highly essential in the reaction system for two reasons. First, it is the source of imidazole, a weak base which primarily converts piperazine dihydrochloride to monohydrochloride. Second, imidazole is a better leaving group and weaker nucleophile than piperazine monohydrochloride which facilitates the formation of acyl piperazine from acyl imidazole.

In conclusion, a novel, simple, and scalable method for monoacylation of symmetrical diamines was developed. The protocol has a wide range of applicability and is also useful for chemoselective tosylation of symmetrical amines and aminoethanols.

Supporting Information Available: General experimental procedures for monoacylation and ^1H and ^{13}C spectra for the representative compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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