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Mono-acylation of symmetric diamines in the presence of water

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ABSTRACT

Simply reacting equal equivalents of symmetric diamines with esters or carbonates in the presence of a suitable amount of water gave mono-acylated products in good to quantitative yields.

Because of the high stability of amide bonds and the ease of their formation, symmetric diamines, many of which are commercially available with different lengths and different solubility properties, are widely used as linkers in solid-phase synthesis, surface chemistry, bioconjugate chemistry, medicinal chemistry, and in other areas.[1] In most cases, two different moieties have to be attached to the two amino groups; as a result, mono-acylation is required in the first step during the formation of the linkage. Statistically, the reaction of 1 equiv diamine with 1 equiv acylating agent such as acid chloride, acid anhydride, and activated ester should provide 50% yield of the desired mono-amide, 25% yield of di-amide, and 25% yield of unreacted diamine. Unfortunately, this is not the case; under many reported conditions, reacting a diamine with an acylating agent gave predominantly or exclusively di-acylated product. Moreover, the yield of mono-acylated product could not be improved significantly by using a large excess (e.g. 10 equiv) of diamine, including using the diamine as the solvent for the reaction.[2]

In order to develop simple methods for the preparation of mono-acylated diamines, several strategies have been reported. For example, using a less reactive acylating agent such as acid anhydride (compared with acid chloride), under high dilution and slow addition conditions, Sayre's group achieved better than statistical yields of mono-acylated diamines.[2] Schwabacher's group developed a method to prepare amino azides by selective reduction of symmetric di-azides; after acylation of the amino group, the remaining azide group was reduced to an amine under mild conditions to give exclusively mono-acylated diamines.[3] Wang's group reported two approaches to achieve mono-acylation by either selectively activating or deactivating one of the two amino groups of a diamine; the former was realized by treating the diamine with 2 equiv strong base such as BuLi;[4] the latter was realized by covering one nitrogen atom with 9-BBN.[5] Christensen's group desymmetrized diamines using alkyl phenyl carbonates; in most cases, more than statistical yields (46–86%) of mono-acylated products were obtained.[6] More recently, Lee et al. developed a method for mono-Boc protection of diamines under acidic conditions.[7] Pringle reported mono-acylation of piperazine and homopiperazine via ionic immobilization of the diamines to a sulfonic acid functionalized silica gel.[8] Other reported methods include performing the reaction under acidic conditions or in the presence of a metal cation and employing different acylating agents; these have been reviewed by Bender et al.[1] According to our experience,[9] one of the most reliable and relatively simple methods in the literature for linking two different molecules with a diamine is to prepare a mono-Boc protected diamine under high dilution and slow addition conditions (5 equiv diamine, 1 equiv Boc_2O, 1,4-dioxane, rt, 12 h) developed by Krapcho and Kuell[10] followed by acylation, deprotection, and second acylation.

Despite the rich literature on the development of methodologies for mono-acylation of symmetric diamines, all reported methods have various drawbacks such as complicated manipulation including using high dilution and slow addition techniques, multistep synthesis, harsh reaction conditions, limited substrate scope, and low yields, and in some cases, expensive acylating agents had to be used. Consequently, an efficient, general, and simple method for mono-acylation of symmetric diamines would be highly welcomed by the scientists working in areas such as solid-phase synthesis, nanotechnology, surface chemistry, bioconjugate chemistry, and medicinal chemistry. To meet this demand, here

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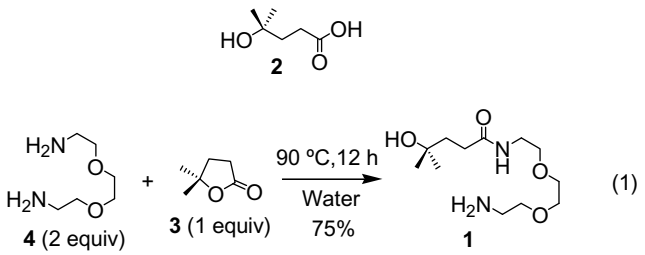
we report an efficient and simple method for mono-acylation of symmetric diamines using the environmentally benign water as the reaction medium and the readily available stable carboxylic acid esters or carbonates as the acylating agents.



In 2003, for one of our projects we needed to link biotin to nucleosides, which required the amino alcohol **1** (see Eq. 1 for structure).[11] All known methods for mono-acylation of diamines were not ideal for the preparation of this simple compound due partially to the difficulty in preparing **2** (it slowly converts to lactone **3**) and its other forms of carboxylic acid derivatives. We first attempted to accomplish this by heating the lactone **3** in a large excess of diamine **4** in the absence of any solvent; consistent with the literature information discussed in the introduction section, di-acylated product was formed exclusively. Because these conditions could be considered as hydrophobic, without any strict reasoning, we were curious to see if hydrophilic conditions could reverse the selectivity to form the desired mono-acylated product **1**. This was indeed the case, at 90 °C in the presence of 10 mL water, reacting **3** (9.5 g, 1 equiv) with **4** (24 mL, 2 equiv) gave **1** exclusively along with unreacted starting materials (Eq. 1); after flash column chromatography, pure **1** was obtained in 75% yield (based on **3**, 16.3 g).[11] In this Letter, we report the details of this diamine mono-acylation reaction including optimization of reaction conditions, substrate scope studies, and procedures for product purification.

Because no di-acylated product was detected in the reaction between **4** and **3**, we were interested to further challenge the mono-acylation reaction conditions by reducing the amount of the diamine from 2 equiv to 1 equiv. In order to find out the amount of water that was optimum for mono-acylation, at the beginning of the study, we increased the amount of water by 10 times. Therefore, 20 mmol 1,3-diaminopropane (**5**) was reacted with 20 mmol EtOAc in the presence of 10 mL water at reflux temperature for 24 h. Under these conditions, although no di-acylated product was detectable, the yield of mono-acylated product (**6**) was only about 10% (Table 1, entry 1,). Under the same conditions, using a lactone (**7**) as the acylating agent, which was more structurally similar to previously used **3** than EtOAc, similar yields of mono-acylated product (**8**) were obtained (entry 2). These indicated that the amount of water was important and too much water was not favorable for the reaction. As a result, we reduced the amount of water from 10 mL to 1 mL, which was at the same level we used previously,[11] and repeated the two reactions under otherwise identical conditions. Gratifyingly, under these conditions (20 mmol diamine, 20 mmol acylating agent, 1 mL water, reflux, 24 h), mono-acylated products **6** and **8** were obtained in 85% and 60% yields, respectively (entries 3 and 4); and in both cases, no di-acylated products were detectable on TLC plate.[12]

It was reported that with short spacer between the two amino groups, the newly formed amide function could reduce the reactivity of the second amino group, and therefore mono-acylation was favored.[2] This means that diamines with long spacer between the two amino groups could be more difficult for mono-acylation. Based on this consideration, we next used the reaction between **9** and BuOAc to optimize the amount of water for the reaction. Under anhydrous conditions, the desired mono-acylated product **10** was formed in 50% yield (entry 5) along with starting materials and 12% di-amide. This result was not consistent with our previous results for the reaction between **3** and **4**, in which case, in the absence of water di-acylated product was formed exclusively. To ensure the accuracy of these observations, the two reactions were repeated two times using carefully dried **4** and **9**, and distilled **3** and BuOAc; the same results were observed. When 0.5 mL water was added to the reaction mixture, the yield of mono-acylated product **10** was dropped to 28% (entry 6). However, when 1 mL water was used, the yield was improved to 72% (entry 7). But when the amount of water reached 2 mL and 3 mL, the yield of **10** was reduced to 52% and 19%, respectively (entries 8 and 9). These studies indicated that the optimum amount of water for the reaction between **9** and BuOAc to give **10** was 1 mL.

Although the optimum amount of water for mono-acylation of diamines may vary with the diamine and the acylating agent, in our substrate scope studies, we consistently used the amount identified using the reaction between diamine **9** and the acylating agent BuOAc, which was 1 mL for 20 mmol substrates. Under these

Table 1
Mono-acylation of symmetric diamines: optimization of reaction conditions[a]

Entry	Diamine	Acylating agent	Amount of water (mL)	Product	Yield[b] (%)	Ref.
1	H_2N NH_2 (**5**)	EtOAc	10	H_2N N Me (**6**)	~10	2
2	**5**	O O (**7**)	10	H_2N N OH (**8**)	~10	19
3	**5**	EtOAc	1	**6**	85	2
4	**5**	**7**	1	**8**	60	19
5	H_2N $_8$ NH_2 (**9**)	BuOAc	0	H_2N $_8$ N Me (**10**)	50[c]	13
6	**9**	BuOAc	0.5	**10**	28	13
7	**9**	BuOAc	1	**10**	72	13
8	**9**	BuOAc	2	**10**	52	13
9	**9**	BuOAc	3	**10**	19	13

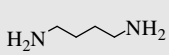
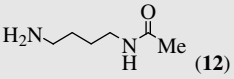
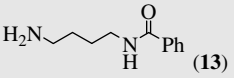
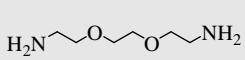
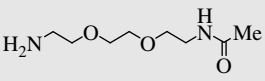
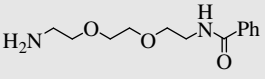
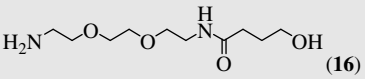
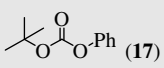
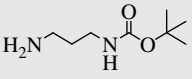
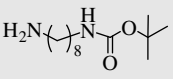
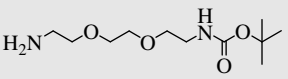
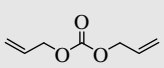
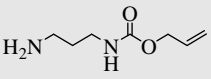
[a] Reaction conditions: diamine (20 mmol), acylating agent (20 mmol), water, reflux, 24 h.
[b] Isolated yield.
[c] Di-acylated product was formed in 12% yield.

optimized conditions (see Supplementary data for experimental details), reaction of **11** with EtOAc gave mono-acylated **12** in 56% yield (Table 2, entry 1). Next, we were interested to know if our method was effective for mono-acylation of diamines with esters of phenyl carboxylic acid such as $PhCO_2Me$; therefore, diamine **11** was heated with $PhCO_2Me$ in the presence of water, and the desired product **13** was obtained in 60% yield (entry 2). The highly hydrophilic diamine **4** with a long spacer, which was widely used as linkers and was mono-acylated with lactone **3**,[11] could also be acylated with other agents such as EtOAc, $PhCO_2Me$, and lactone **7** under our conditions to give mono-acylated products **14**–**16** in good to excellent isolated yields (entries 3–5).

Next, we were interested in using our method to selectively protect one of the two amino groups of a diamine with the acid-removable Boc and the palladium-removable allyl carbonate groups. In the literature, the resulting mono-protected diamines have found wide applications, but a simple, efficient, and general method for their preparation is unavailable. Because phenoxide is a better leaving group than an alkoxide, when the *tert*-butyl phenyl carbonate (**17**) was used as the acylating agent, the reactions were performed at rt. Therefore, 20 mmol diamine **5**, 20 mmol **17**, and 1 mL water were stirred vigorously at rt; after 24 h, the mono-acylated product **18** was isolated in quantitative yield (Table 2, entry 6). When the reaction time was shortened to 3 h, a lower yield was obtained (entry 7). Under these conditions, diamines with longer spacer also gave excellent yields of mono-acylated products; reaction of **9** with **17** gave **19** in 69% yield (entry 8). These simple reaction conditions are also highly effective for protecting one end of the diamines that have a long hydrophilic spacer by a Boc group; for example, stirring **4** with **17** in the presence of water at rt for 24 h gave **20** in 81% yield (entry 9). Finally, we tested to selectively protect one of the two amino groups of a diamine by the palladium-removable allyl carbonate group; the high efficiency was demonstrated by stirring equal equiv of **5** and **21** in the presence of water at rt, and within 3 h the mono-acylated **22** was obtained in 92% yield (entry 10).

Most of the mono-acylated diamine products in Tables 1 and 2 have been reported previously. However, these compounds were prepared using complicated procedures, and in some cases they were prepared under harsh conditions and in low yields. For example, compounds **6** and **12** were prepared by slow addition of *p*-nitrophenyl acetate to a large excess of diamine under high dilution conditions.[2] Compound **10** was prepared in only 28% yield by slow addition of acetic anhydride to **9** followed by aqueous

Table 2
Mono-acylation of symmetric diamines: substrate scope study[a]

Entry	Diamine	Acylating agent	Product[b]	Yield[c] (%)	Ref.
1	 (**11**)	EtOAc	 (**12**)	56	2
2	**11**	$PhCO_2Me$	 (**13**)	60	5,20
3	 (**4**)	EtOAc	 (**14**)	57	17
4	**4**	$PhCO_2Me$	 (**15**)	65	18
5	**4**	**7**	 (**16**)	92	–
6	**5**	 (**17**)	 (**18**)	99[d]	7,14
7	**5**	**17**	**18**	62[d,e]	7,14
8	**9**	**17**	 (**19**)	69[d]	14,15
9	**4**	**17**	 (**20**)	81[d]	7,17
10	**5**	 (**21**)	 (**22**)	92[d,e]	6

[a] Reaction conditions: diamine (20 mmol), acylating agent (20 mmol), water (1 mL), reflux, 24 h.
[b] In all cases, di-acylated product is negligible, and can be easily removed by flash column chromatography.
[c] Isolated yield.
[d] Reaction was performed at rt.
[e] Reaction time was 3 h.

workup and ion-exchange column chromatography.[13] To prepare compound **13**, Wang's group used the expensive 9-BBN to cover one of the two amino groups of the starting diamine and the reaction had to be performed under carefully controlled anhydrous conditions.[5] Compound **18** appeared in many literatures; recently it was prepared in 95% yield by slow addition of Boc_2O in $CHCl_3$ (1 equiv, 0.5 M) to **5** (in $CHCl_3$, 5 equiv, 0.25 M) over 2 h by Dardonville et al.[14] Other compounds including **19**[14,15] and **20**[7,16] were also prepared under high dilution and slow addition conditions using excess diamines. We believe that the method described in this Letter will be preferred for preparing these and related compounds in the future.

Different methods have been used in the literature for isolation and purification of the mono-acylated products, which can be found in the references cited in the above discussions. In our experiments, we did not resolve to aqueous workup with only a few exceptions; after cooling the reaction mixture to rt under inert atmosphere, it was dissolved in a suitable amount (roughly three times the volume of the reaction mixture) of the solvent mixture of the non-polar component Et_2O and the polar component MeOH/MeCN/Et_3N (2:2:1). The ratio of the two components was determined by TLC (SiO_2) so that the R_f value of the mono-acylated product fell between 0.2 and 0.4; under these conditions, on TLC plate the unreacted diamine normally remained at the origin and the di-acylated product (if any) had a R_f above 0.5. Then, the reaction mixture in these solvents was loaded directly on a silica gel column and pure mono-acylated product was collected by eluting with the same solvent system. To reduce the size of the column, part of water and diamine in the reaction mixture may be removed before chromatography. The unreacted diamine and mono-acylated product can be visualized by rinsing the TLC plate in ninhydrin solution briefly followed by heating with a heat gun. In a few cases, the side product PhOH was not completely removed by column chromatography; a partition between CH_2Cl_2 and 10% NaOH was needed.

In conclusion, we have developed a new method for mono-acylation of symmetric diamines. It is particularly important that the method can be used to make compounds such as **1**, **8**, and **16** in one pot, which otherwise need multiple steps to synthesize. The method does not need the use of high dilution and slow addition techniques, and employs equal equiv of diamine and acylating agent; the acylating agents are simple, stable, and are commercially available; and only the environmentally benign water is used as the reaction medium. We expect that the method will find wide applications for linking different functionalities together in areas such as solid-phase synthesis and bioconjugate chemistry.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.174.

References and notes

1. Bender, J. A.; Meanwell, N. A.; Wang, T. *Tetrahedron* **2002**, *58*, 3111–3128.
2. Jacobson, A. R.; Makris, A. N.; Sayre, L. M. *J. Org. Chem.* **1987**, *52*, 2592–2594.
3. Schwabacher, A. W.; Lane, J. W.; Schiesher, M. W.; Leigh, K. M.; Johnson, C. W. *J. Org. Chem.* **1998**, *63*, 1727–1729.
4. Wang, T.; Zhang, Z. X.; Meanwell, N. A. *J. Org. Chem.* **1999**, *64*, 7661–7662.
5. Zhang, Z. X.; Yin, Z. W.; Meanwell, N. A.; Kadow, J. F.; Wang, T. *Org. Lett.* **2003**, *5*, 3399–3402.
6. Pittelkow, M.; Lewinsky, R.; Christensen, J. B. *Synthesis-Stuttgart* **2002**, 2195–2202.
7. Lee, D. W.; Ha, H.-J.; Koo, L. W. *Synth. Commun.* **2007**, *37*, 737–742.
8. Pringle, W. *Tetrahedron Lett.* **2008**, *49*, 5047–5049.
9. Fang, S. Y.; Bergstrom, D. E. *Tetrahedron Lett.* **2004**, *45*, 8501–8504.
10. Krapcho, A. P.; Kuell, C. S. *Synth. Commun.* **1990**, *20*, 2559–2564.
11. Fang, S. Y.; Bergstrom, D. E. *Nucleic Acids Res.* **2003**, *31*, 708–715.
12. The role of water in this mono-acylation reaction is unknown at this time. One hypothesis is that diamines form clusters through intermolecular hydrogen bonding in organic solvents like those formed by BuLi in hexane. This cluster formation lowers the reactivity of the diamine toward acylating agents. Compared to diamine, the mono-acylated product is associated with the clusters to a lesser degree and is therefore more reactive. As a result, di-acylated product is favored over mono-acylated product in organic media. In the presence of water, the clusters may be broken by hydrogen bonding between the diamine and water, and the reactivity of diamine is increased. This would lead to a 50% theoretical yield of mono-acylated product. The higher than 50% yield may be attributed to the reduced reactivity of the second amino group in mono-acylated diamine caused by the electron-withdrawing amide group, lower solubility of mono-acylated diamine than diamine in the reaction media and the solid state of the mono-acylated product and the liquid state of diamine at the reaction temperature.
13. Dredar, S. A.; Blankenship, J. W.; Marchant, P. E.; Manneh, V.; Fries, D. S. *J. Med. Chem.* **1989**, *32*, 984–989.
14. Dardonville, C.; Fernandez-Fernandez, C.; Gibbons, S. L.; Ryan, G. J.; Jagerovic, N.; Gabilondo, A. M.; Meana, J. J.; Callado, L. F. *Bioorg. Med. Chem.* **2006**, *14*, 6570–6580.
15. Morrell, A.; Placzek, M. S.; Steffen, J. D.; Antony, S.; Agama, K.; Pommier, Y.; Cushman, M. *J. Med. Chem.* **2007**, *50*, 2040–2048.
16. (a) Pastorin, G.; Wu, W.; Wieckowski, S.; Briand, J. P.; Kostarelos, K.; Prato, M.; Bianco, A. *Chem. Commun.* **2006**, 1182–1184; (b) Beer, P. D.; Cadman, J.; Lloris, J. M.; Martinez-Manez, R.; Soto, J.; Pardo, T.; Marcos, M. D. *J. Chem. Soc., Dalton Trans.* **2000**, *11*, 1805–1812; (c) Mart, R. J.; Liem, K. P.; Wang, X.; Webb, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 14462–14463.
17. Xie, Q.; Wenkert, D.; Shen, Y.; Vande Woude, G. F.; Hay, R. PCT Int. Appl. WO 2005095347, 2005; 89 pp.
18. Min, J.; Kim, Y. K.; Cipriani, P. G.; Kang, M.; Khersonsky, S. M.; Walsh, D. P.; Lee, J.-Y.; Niessen, S.; Yates, J. R., III; Gunsalus, K.; Piano, F.; Chang, Y.-T. *Nat. Chem. Biol.* **2007**, *3*, 55–59.
19. Lagerman, R.; Clancy, S.; Tanner, D.; Johnston, N.; Callian, B.; Friedli, F. *J. Am. Oil Chem. Soc.* **1994**, *71*, 97–100.
20. Zaragozadorwald, F.; Vonkiedrowski, G. *Synthesis-Stuttgart* **1988**, 917–918.