Phenyl esters, preferred reagents for mono-acylation of polyamines in the presence of water

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ABSTRACT

In the presence of water, several diamines and one triamine were mono-acylated at ambient to moderate temperatures using phenyl esters and a phenyl carbonate as acylation agents in good to excellent isolated yields. Both linear and cyclic polyamines were suitable substrates, and the acylating agents can be aryl and alkyl carboxylic acid esters.

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The formation of an amide bond between an amine and a carboxylic acid derivative is one of the most studied reactions in organic chemistry. However, the selective acylation of one amino group in the presence of others in a polyamine remains difficult.[1] Statistically, with equal moles of diamine and acylating agent, it is possible to obtain the desired mono-acylated product in 50% yield, which is acceptable in most cases.[2] Unfortunately, these statistically predicted results are not easy to be achieved. For example, when a polyamine such as 1,4-diaminobutane, 2,2′-(ethylenedioxy)bis(ethylamine), piperazine, 1,2-cyclohexane diamine, or diethylenetriamine is reacted in organic solvents with a carboxylic acid anhydride or chloride, even with more than 1 equiv polyamine, di-acylated product is formed predominantly or exclusively. Sayre and co-workers attributed this phenomenon to the inefficient mixing of reactants during the addition of acylating agent to the diamine.[2] More specifically, when a drop of acylating agent contacts the solution of the diamine, the acylation reaction is so fast that before additional diamines reach the reaction site, the mono-acylated products continue to react with the locally excess acylating agent, and therefore di-acylated product predominates. This hypothesis is supported by the fact that the yields of mono-acylation products can be increased by using the less reactive acid anhydrides as opposed to acid chlorides under high dilution conditions at low temperature in the presence of excess diamine. Under these conditions, mono-acylation of 1,2-ethanediamine and 1,4-butane-

diamine could be achieved in close to or slightly higher than statistical yields.[2] Later, many other research groups continued to approach the problem with the goal of developing more practically useful methods as well as to extend the scope of diamines to cyclic ones and ones that have longer spacer between the two amino groups.[1] For example, Wang's group treated diamines with 2 equiv BuLi and reacted the resulting di-anions with 1 equiv acylating agents to give mono-acylated products.[3] The same group also achieved mono-acylation using 9-BBN to protect one of the two amino groups followed by acylation.[4] Christensen's group used alkyl phenyl carbonates for selective acylation of polyamines.[5] Other reported methods include performing the reaction under acidic conditions,[6] using metal cations to protect one of the two amino groups and using special acylating agents.[1] Simple mix and react procedures were available for mono-acylation of diamines with short spacer between the two amino groups such as piperazine and ethylenediamine.[7] Unfortunately, the methods were not applicable to diamines with long spacers due to the similarity of the two pK_as of the diamines and limited reduction of the reactivity of the second amino group upon acylation of the first amino group.[2] The protocol developed by Krapcho and Kuell for selective protection of some diamines using Boc_2O under high dilution and slow addition conditions in 1,4-dioxane is quite simple to follow and good yields of desired product can be obtained.[8] More recently, Pringle reported a new mono-acylation method using ionic immobilization of diamines to sulfonic acid-functionalized silica gel. The method worked well for mono-acylation of piperazine and homopiperazine, but failed to give useful yields for other polyamines.[9]

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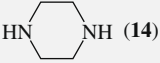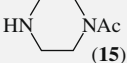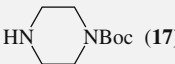 E-mail address: shifang@mtu.edu (S. Fang).

We recently found that diamines could be mono-acylated with lactones, alkyl esters, and phenyl and allyl carbonates in good to quantitative yields in the presence of suitable amount of water.[10,11] We hypothesized that the disruption of the hydrogen bonds between diamines by water along with other factors might be responsible for the good selectivity of mono-acylation.[10] The method has the following advantages. (a) No organic solvent is used. (b) The acylating agents are stable, inexpensive, and readily available. (c) Only 1 equiv diamine is required. (d) There is no need to use high dilution and slow addition techniques, which is particularly significant for large-scale synthesis. However, the method has one drawback. In some cases, to drive the reaction to completion, the reaction mixture must be heated to high temperature (more than 100 °C).[10] In order to lower the temperature, we recently tested using phenyl esters as the acylating agent for the reaction. We found that the reaction could proceed with useful rates at 50 °C and give mono-acylated products in good to excellent yields. In this Letter, we report our results on this study.

In a typical experimental procedure, 20 mmol polyamine, 20 mmol acylating agent, and 1 mL water were combined in a round-bottomed flask. The mixture was stirred under a moderate nitrogen flow for about 30 min. After stopping the nitrogen flow, the reaction was continued for 24 h either at room temperature or at other temperatures as indicated in Table 1. A small portion of the mixture was then taken out and dissolved in methanol for TLC analysis. We found that the solvent system MeOH/MeCN/Et$_3$N/Et$_2$O (2:2:1:5) was excellent for separation of the mono-acylated products from the remaining polyamines on silica gel, which could be easily visualized by staining with a ninhydrin solution (ninhydrin 4.5 g, BuOH 300 mL, AcOH 9 mL) followed by gentle heating with a heat gun. Under these conditions, the desired mono-acylated products have an R_f between 0.2 and 0.6 and the polyamines remained at the origin. In some cases, the blue color of the mono-acylated product was significantly lighter than that of the unreacted polyamine; this did not mean that the yield was low. The reaction mixture was dissolved in the same solvents and loaded on a flash chromatography silica gel column, which was packed with the same solvent system. Alternatively, the mixture was first concentrated under reduced pressure and then loaded onto column in the same manner. If the mixture did not dissolve well in the solvent system, it was dissolved in methanol and applied on a small amount of silica gel in a Petri dish. After air drying, the silica gel was loaded onto the column. The fractions containing the mono-acylated products were combined. Evaporating of solvents under reduced pressure gave pure products. In some cases, the products contained small amount of phenol. This was removed by partition between methylene chloride and 10% NaOH followed by drying with Na$_2$SO$_4$ and evaporating the solvent.

The procedure worked well on linear diamines, a triamine and the cyclic diamine piperazine. The results are summarized in Table 1.[12] The reaction was first tested on 1,4-butanediamine (**1**) using phenyl acetate (**2**) as the acylating agent. Using the general procedure described above, at 50 °C the desired mono-acylated product **3** was obtained in 56% isolate yield (entry 1). Although the yield was only slightly higher than the statistically predicted 50%, the result was significant because the procedure was simple and no excess diamine was needed. The reaction could also be carried out at room temperature but the rate was low. Because 4-nitrophenoxide is a better leaving group than phenoxide, we also tested using 4-nitrophenyl acetate (**4**) as the acylating agent (entry 2). However, lower yield was obtained (22%). One reason might be the hydrolysis of **4** before its reaction with the diamine, but we believe that the solid nature of **4** (melting point 75 °C) and its low solubility in the mixture might play a more important role. From this observation, we used phenyl esters in our next studies. The reaction between **1** and phenyl benzoate (**5**) also proceeded smoothly at 50 °C. The mono-acylated product **6** was obtained in 63% isolated yield (entry 3). It was reported that diamines with longer spacer between the two amino groups are more difficult for mono-acylation.[2] However, under our conditions, 1,8-octanediamine (**7**) was mono-acylated with equal efficiency to give product **8** in 62% yield (entry 4). Under similar conditions, the more hydrophilic 2,2′-(ethylenedioxy)bis(ethylamine) (**9**), which also contains a long spacer between the two amino groups, was mono-acylated with **2** and **5** to give products **10** and **11**, respectively, in acceptable yields (entries 5 and 6). A triamine was also tested for the reaction. At room temperature using the general procedure, **12** was acylated to give **13** in 56% isolated yield (entry 7). The cyclic diamine piperazine (**14**), which was recently mono-acylated with the more expensive ionic immobilization approach,[9] was also shown to be a good substrate for our simple and inexpensive procedure. By simply mixing **14** with **2** and suitable amount of water, the mono-acylated product **15** was obtained in 39% yield at room temperature and in 69% yield at 55 °C (entries 8 and 9). It should be pointed out that there was an excellent procedure for mono-acylation of piperazine, in which the substrate was treated with 2 equiv of BuLi and the

Table 1
Mono-acylation of polyamines using phenyl esters and a phenyl carbonate in water[a]

Entry	Amine	Acylating agent	Product	Temperature	Yield[b] (%)	Ref.
1	H$_2$N(CH$_2$)$_4$NH$_2$ (**1**)	PhOAc (**2**)	H$_2$N(CH$_2$)$_4$NHAc (**3**)	50 °C	56	2
2	**1**	4-NO$_2$-PhOAc (**4**)	**3**	50 °C	22	
3	**1**	PhCO$_2$Ph (**5**)	H$_2$N(CH$_2$)$_4$NHBz (**6**)	50 °C	63	4
4	H$_2$N(CH$_2$)$_8$NH$_2$ (**7**)	**2**	H$_2$N(CH$_2$)$_8$NHAc (**8**)	50 °C	62	10
5	[H$_2$N(CH$_2$)$_2$OCH$_2$]$_2$ (**9**)	**2**	H$_2$NCH$_2$(CH$_2$OCH$_2$)$_2$CH$_2$NHAc (**10**)	rt	42	10
6	**9**	**5**	H$_2$NCH$_2$(CH$_2$OCH$_2$)$_2$CH$_2$NHBz (**11**)	50 °C	33	13
7	[H$_2$N(CH$_2$)$_2$]$_2$NH (**12**)	**2**	H$_2$N(CH$_2$)$_2$NH(CH$_2$)$_2$NHAc (**13**)	rt	56	14
8	HN⌬NH (**14**)	**2**	HN⌬NAc (**15**)	rt	39	15
9	**14**	**2**	**15**	55 °C	69	
10	**14**	PhOBoc (**16**)	HN⌬NBoc (**17**)	rt	68	9
11	**14**	**16**	**17**	55 °C	87	
12	**14**	**16**	**17**	Reflux	71	

[a] Reaction conditions: amine (20 mmol), acylating agent (20 mmol), water (1 ml), 24 h.
[b] Isolated yields.

resulting dianion was then acylated with 1 equiv acylating agent. Excellent yields were obtained.[3] However, this method was only demonstrated for mono-benzoylation. Obviously, when acylating agents that contain acidic protons such as acetic anhydride are used, side reactions will occur. This problem does not exist while using our method. Finally, we tested the mono-Boc protection of **14**. Using **16** as the acylating agent, compound **17** was obtained in 68% yield at room temperature, 87% yield at 55 °C, and 71% yield at reflux temperature (entries 10–12).

In summary, using water as the reaction medium and phenyl esters and carbonates as acylating agents, we were able to mono-acylate linear and cyclic polyamines at room temperature or moderate temperature in good to excellent isolated yields. The procedure is simple and environmentally benign, the starting materials are commercially available and inexpensive, and the substrate scope is broader than that of reported methods.[3,9] We expect that the method will become a favorite choice for organic and medicinal chemists and other scientists to prepare mono-acylated diamines.

Acknowledgments

References and notes

1. Bender, J. A.; Meanwell, N. A.; Wang, T. *Tetrahedron* **2002**, *58*, 3111.

2. Jacobson, A. R.; Makris, A. N.; Sayre, L. M. *J. Org. Chem.* **1987**, *52*, 2592.
3. Wang, T.; Zhang, Z. X.; Meanwell, N. A. *J. Org. Chem.* **1999**, *64*, 7661.
4. Zhang, Z. X.; Yin, Z. W.; Meanwell, N. A.; Kadow, J. F.; Wang, T. *Org. Lett.* **2003**, *5*, 3399.
5. Pittelkow, M.; Lewinsky, R.; Christensen, J. B. *Synthesis-Stuttgart* **2002**, 2195.
6. Lee, D. W.; Ha, H.-J.; Koo, L. W. *Synth. Commun.* **2007**, *37*, 737.
7. (a) Hall, H. K. *J. Am. Chem. Soc.* **1956**, *78*, 2570; (b) Hill, A. J.; Aspinall, S. R. *J. Am. Chem. Soc.* **1939**, *61*, 822.
8. (a) Krapcho, A. P.; Kuell, C. S. *Synth. Commun.* **1990**, *20*, 2559; (b) Fang, S.; Bergstrom, D. E. *Tetrahedron Lett.* **2004**, *45*, 8501.
9. Pringle, W. *Tetrahedron Lett.* **2008**, *49*, 5047.
10. Tang, W.; Fang, S. *Tetrahedron Lett.* **2008**, *49*, 6003.
11. In our previous work,[10] only linear diamines were used as substrates. We recently found that the method was also useful for mono-acylation of cyclic diamines using the same procedure. For example, piperazine was mono-acylated with diallyl carbonate at rt to give piperazine-1-carboxylic acid allyl ester[16] in 59% yield. The racemic *trans*-1,2-cyclohexanediamine was mono-acylated with the same reagent at 55 °C to give *trans*-1-(*N*-allyloxycarbonyl)-cyclohexane-1,2-diamine (**18**) in 63% yield. Compound **18** (racemic): ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.83–5.73 (m, 1H), 5.40 (br d, 1H, J = 8.4 Hz), 5.15 (dt, 1H, J = 17.2, 0.4 Hz), 5.05 (d, 1H, J = 10.4 Hz), 4.41 (d, 2H, J = 5.2 Hz), 3.10–2.98 (m, 1H), 2.31–2.25 (m, 1H), 1.86–1.79 (m, 2H), 1.68 (br s, 2H), 1.58–1.55 (m, 2H), 1.18–0.97 (m, 4H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 156.2, 132.8, 117.2, 65.1, 57.7, 54.9, 34.7, 32.4, 24.8, 24.7; HRMS (ESI) *m/z* [M+H]$^+$ calcd for C$_{10}$H$_{19}$N$_2$O$_2$: 199.1447, found 199.1445.
12. All products are known, references are given in Table 1.
13. Min, J.; Kim, Y. K.; Cipriani, P. G.; Kang, M.; Khersonsky, S. M.; Walsh, D. P.; Lee, J.-Y.; Niessen, S.; Yates, J. R.; Gunsalus, K.; Piano, F.; Chang, Y.-T. *Nat. Chem. Biol.* **2007**, *3*, 55.
14. Kuswikrabiega, G.; Bruenger, F. W.; Miller, S. C. *Synth. Commun.* **1992**, *22*, 1307.
15. Ferroud, C.; Godart, M.; Ung, S.; Borderies, H.; Guy, A. *Tetrahedron Lett.* **2008**, *49*, 3004.
16. Sutton, J. C.; Bolton, S. A.; Davis, M. E.; Hartl, K. S.; Jacobson, B.; Mathur, A.; Ogletree, M. L.; Slusarchyk, W. A.; Zahler, R.; Seiler, S. M.; Bisacchi, G. S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2233.