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Selective Monoacylation of Symmetrical Diamines via Prior Complexation with Boron

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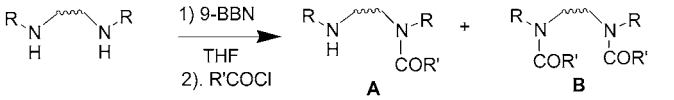
ABSTRACT

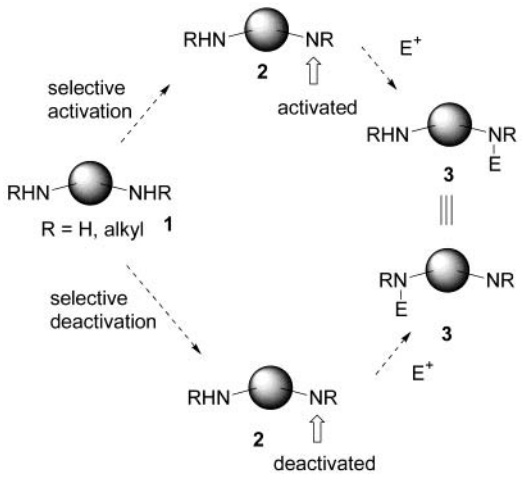


Pretreatment of a symmetrical primary or secondary diamine with 9-BBN prior to the addition of an acyl chloride significantly suppressed undesired diacylation, and the product of monoacylation predominated. The reactive preference is interpreted as the result of a selective deactivation of one nitrogen atom of the diamine by 9-BBN.

The monoacylation of symmetrical diamines continues to be a remarkably simple and fundamental transformation that is bereft of a generally applicable solution.[1] In the absence of reactivity modified by interactions unique to specific structural motifs, it has proven to be quite difficult to selectively control the extent of acylation and the majority of procedures afford predominantly diacylated product. In a conceptual sense, there are two possible approaches to resolve this problem that rely upon the complementary strategies of either selectively activating or deactivating one of the nitrogen atoms, as summarized in Scheme 1. The notion of enhancing the reactivity of one nitrogen atom is exemplified by our previous work in which a diamine is treated with 2 equiv of a strong base (*n*-butyllithium) to generate a dianion.[2] Selective monoacylation is then dependent upon the rapid consumption of the electrophile, added in a limited quantity, by a markedly more nucleophilic species, as summarized in Scheme 2.

Accordingly, acceleration of the first acylation in the presence of limiting substrate promotes monoacylation as

Scheme 1



the predominant process. However, it has been our experience that the scope of this procedure has limitations associated with both partners. More specifically, only secondary diamines have been found to be useful substrates, while

(1) Bender, J.; Meanwell, N. A.; Wang, T. *Tetrahedron* **2002**, *58*, 3111.
(2) (a) Wang, T.; Zhang, Z.; Meanwell, N. A. *J Org. Chem.* **2000**, *65*, 4740. (b) Wang, T.; Zhang, Z.; Meanwell, N. A. *J. Org. Chem.* **1999**, *64*, 7661.

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Scheme 2

acylating agents that possess acidic protons are subject to proton transfer as a consequence of the highly basic nature of doubly deprotonated diamines. While the latter limitation is readily understood, the reason behind the observation that only secondary amines participate in this process remains somewhat enigmatic.

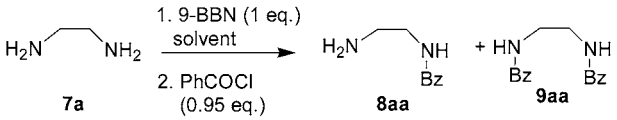
In an effort to circumvent these restrictions and identify a process with applicability to a broader range of reaction partners, the concept of complexation of one nitrogen atom as a means of selective deactivation was examined. Since neither the nucleophilicity or basicity of the diamine would be enhanced, it was anticipated that this strategy would not only provide an alternate approach to selective monoacylation but would be more generally applicable, particularly with respect to acylating agents containing acidic hydrogen atoms.

It is well established in the fields of both organic and inorganic chemistry that nitrogen atoms can coordinate with a variety of metals and Lewis acids.[1,3] Simple associative complex formation between amines and reagents based on B, Si, Al, Mg or a transition metal under circumstances where further reaction does not occur provides a species in which the both the nucleophicity and basicity of the Lewis acid-complexed nitrogen atom is attenuated.[3,4] In the case at hand, selective complexation of a diamine would leave the remaining nitrogen atom free to react with an acylating agent and control of chemical reactivity would depend on the stability of the complex.

As an initial step toward the objective of identifying a suitable process for the monoacylation of diamines, a survey of the benzoylation of ethylenediamine or piperazine pre-complexed with a series of commercially available reagents was conducted.[5] While most of the conditions examined provided some control of chemical reactivity, boron-based reagents generally provided the best results. In particular, complexes of ethylenediamine or piperazine with 9-BBN provided a 2:1 ratio of monoacylated:diacylated product and prompted a more detailed investigation.[4]

The dependence of the ratio of products on solvent was studied in the context of the complex of ethylenediamine (**7a**) and 9-BBN, utilized either as a solution in hexane or THF, reacting with benzoyl chloride (Table 1). The ratio of mono- to diacylation varied from 1:1 in hexane to 6:1 in THF (with 9-BBN added as a solution in hexane), indicating that more polar solvents provided for better selectivity.[6] When pyridine was used as a solvent, complex mixtures resulted, presumably because the nitrogen atom of the heterocycle interfered with the formation or stability of the complex between ethylenediamine and 9-BBN.

Table 1. Solvent and Reagent Effect on Monobenzoylation of Diamines



entry	solvent	9-BBN in[a]	**8aa**:**9aa**[b]
1	CH_2Cl_2	hexane	2:1
2	THF	hexane	6:1
3	ether	hexane	4:1
4		hexane	2:1
5	hexane	hexane	2:1
6	pyridine	hexane	complicated mixture
7	ether	THF	1:2.5
8	THF	THF	1:4

[a] From ref 6. [b] Ratios were determined by LC-MS.

The scope of the 9-BBN-enhanced monoacylation process (entry 2, Table 1) was examined by pretreating a panel of primary and secondary symmetrical diamines dissolved in THF with 9-BBN in hexane followed by the addition of benzoyl chloride or phenylacetyl chloride. The latter was selected as a representative example of an acyl chloride incorporating acidic hydrogen atoms designed to determine the compatibility of the process with sensitive substrates. In both cases, a control arm, in which the reaction was conducted in the absence of 9-BBN, was included. As shown in Tables 2 and 3, precomplexation of a range of diamines with 9-BBN effectively modulated the chemical reactivity toward acylation. Without precomplexation with 9-BBN, the

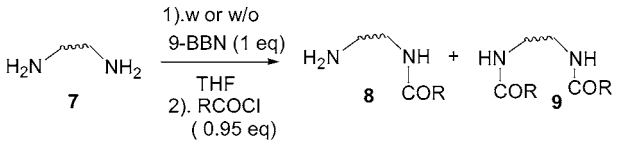
(3) (a) Ham, J.-Y.; Kang, H.-S. *Bull. Korean Chem. Soc*. **1994**, *15*, 1025. (b) Shaw, S. Y.; Neilson, R. H. *Inorg. Chem*. **1994**, *33*, 3239. (c) Lee, S. H.; Cheong, C. S. *Tetrahedron* **2001**, *57*, 4801. (d) Overman, L. E.; Flippin, L. A. *Tetrahedron Lett.* **1981**, *22*, 195. (e) Nakai, K.; Ibuka, T.; Otaka, A.; Tamamura, H.; Fujii, N.; Yamamoto, Y. *Tetrahedron Lett*. **1995**, *36*, 6247. (f) Yamamoto, H.; Maruoka, K. *J. Org. Chem*. **1980**, *45*, 2739. (g) Magrane, P. L.; Jensen, M.; Livinghouse, T. *J. Am. Chem. Soc*. **1992**, *114*, 5459. (h) Snieckus, V.; Reed, J. N.; Iwao, M. *J. Am. Chem. Soc.* **1982**, *104*, 4. 5531. (i) Clarke, P. A. *Tetrahedron Lett*. **2002**, *43*, 4761.

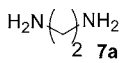
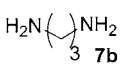
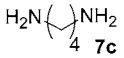
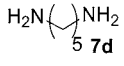
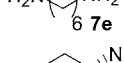
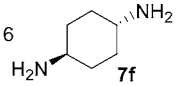
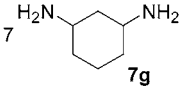
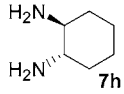
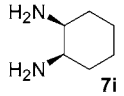
(4) The following competitive reactivity studies confirmed that amines were deactivated via pretreatment with 9-BBN (1 h, room temperature). **Experimental A:** (a) *n*-$PrNH_2$ (1 equiv) and $PhCH_2CH_2NH_2$ (1 equiv) were treated with BzCl (1 equiv) to provide *n*-PrNHBz and $PhCH_2CH_2NHBz$ (1:1.4); (b) *n*-$PrNH_2$−9-BBN (1 equiv) and $PhCH_2CH_2NH_2$ (1 equiv) were treated with BzCl (1 equiv) to provide *n*-PrNHBz and $PhCH_2CH_2NHBz$ (1:3); (c) *n*-$PrNH_2$ (1 equiv) and $PhCH_2CH_2NH_2$−9-BBN (1 equiv) were treated with BzCl (1 equiv) to provide *n*-PrNHBz and $PhCH_2CH_2NHBz$ (1:1). **Experimental B:** (a) BnNHMe (1 equiv) and BnNHBn (1 equiv) were treated with BzCl (1equiv) to provide BnN(Me)Bz and BnN(Bn)Bz (3:1); (b) BnNHMe−9-BBN (1 equiv) and BnNHBn (1 equiv) were treated with BzCl (1 equiv) to provide BnN(Me)Bz and BnN(Bn)Bz (4:3); (c) BnNHMe (1 equiv) and BnNHBn−9-BBN (1 equiv) were treated with BzCl (1 equiv) to provide BnN(Me)Bz and BnN(Bn)Bz (4:1). All ratios are based on LC-MS spectra.

(5) Other agents screened include Ph_2PbCl_2, Ph_3SbCl_2, $PhBCl_2$, Catechol-BCl, Catechol-BH, Me_2BBr, $(cyclohexyl)_2BCl$, Et_2BOMe, 9-BBN−OMe, $B(OEt)_3$, Et_3B, BF_3−Et_2O, BH_3−Et_2O, (*R*)-Alpine-Boramine, SmI_2, $CeCl_3$, $CuCl_2$, CuBr, $InCl_3$, $(NH_4)_2MoO_4$, $Pd(OAc)_2$, $ZnCl_2$, $TiCl_4$, $Ti(O\text{-}^iPr)_4$, $Cl_2Ti(O\text{-}^iPr)_2$, $ClTi(O\text{-}^iPr)_3$, Me_3Al, Me_2AlCl, $MeAlCl_2$, $AlCl_3$, Bu_3SnCl, Bu_3SnH, Bu_2SnO, Bu_2SnCl_2, $SnCl_2$, Et_3SiCl, Et_3SiH.

(6) It should be noted that 9-BBN in hexane obtained from Fluka Chemical Company (a part of Aldrich, Co.) enhanced monobenzoylation significantly (entries 1−6, Table 1), while 9-BBN in THF procured from the Aldrich Chemical Co. only offered minor improvements (entries 7 and 8, Table 1).

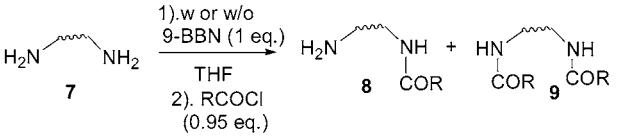
Table 2. Acylation of Symmetrical Primary Diamines

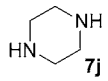
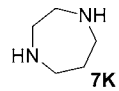
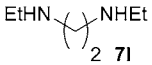
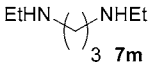
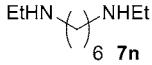
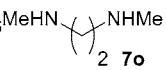
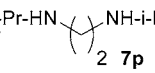
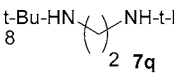


entry	diamine	PhCOCl with 9-BBN **8:9** (yield)	PhCOCl without 9-BBN **8:9** (yield)	BnCOCl with 9-BBN **8:9** (yield)	BnCOCl without 9-BBN **8:9** (yield)
1	 **7a**	9.2:1 (96%[a]) 6.1:1 (87%)	<1:20 (72%[a]) 1:16.5 (94%)	27.2:1 (84%[a]) 6.9:1 (68%)	<1:20 (96%[a]) 1:5.1 (90%)
2	 **7b**	5.0:1 (80%)	<1:20 (94%)	5.3:1 (75%)	<1:20 (94%)
3	 **7c**	9.3:1 (88%)	<1:20 (97%)	>20:1 (71%)	1:14.5 (98%)
4	 **7d**	12.2:1 (95%)	<1:20 (94%)	>20:1 (85%)	<1:20 (95%)
5	 **7e**	9.7:1 (91%)	1:10.1 (86%)	12.4:1 (94%)	<1:20 (100%)
6	 **7f**	14.6:1 (92%)	3.1:1 (55%)	3.2:1 (85%)	1:6.9 (75%)
7	 **7g**	10.3:1 (88%)	1:8.6 (90%)	16.3:1 (76%)	1:4.3 (79%)
8	 **7h**	19.7:1 (90%)	2.5:1 (61%)	3.5:1 (95%)	1:3.9 (96%)
9	 **7i**	3.0:1 (93%)	1.6:1 (96%)	5.7:1 (95%)	1.7:1 (95%)

[a] Isolated yields. All other yields were determined by LC-MS.

Table 3. Acylation of Symmetrical Secondary Diamines[a]



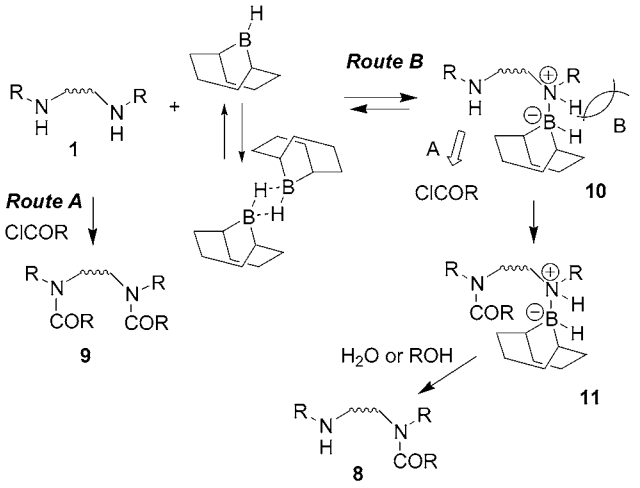
entry	diamine	PhCOCl with 9-BBN **8:9** (yield)	PhCOCl without 9-BBN **8:9** (yield)	BnCOCl with 9-BBN **8:9** (yield)	BnCOCl without 9-BBN **8:9** (yield)
1	 **7j**	5.3:1 (84%)	1:6.9 (94%)	2.3:1 (89%)	1:14.5 (93%)
2	 **7K**	1.3:1 (95%)	<1:20 (99%)	1.5:1 (89%)	1:20 (97%)
3	 **7l**	1.3:1 (96%)	1:3 (97%)	1.1:1 (93%)	1:7.8 (99%)
4	 **7m**	1.8:1 (96%)	1:6.4 (99%)	2.7:1 (96%)	1:6.8 (99%)
5	 **7n**	1.6:1 (91%)	1:5.2 (98%)	1.7:1 (93%)	1:7.9 (98%)
6	 **7o**	6.9:1:1 (88%)	1:7 (94%)	2.4:1 (83%)	1:19.9 (95%)
7	 **7p**	1.4:1 (83%)	1:7.8 (94%)	1.2:1 (88%)	1:1.1 (97%)
8	 **7q**	1.4:1 (80%)	1.1:1 (91%)	>20:1 (89%)	20:1 (90%)

[a] All yields were determined by LC-MS.

major product in most cases resulted from diacylation. Notable exceptions are entries 8 and 9 in Table 2 and entry 8 in Table 3. In contrast, pretreatment with 9-BBN remarkably enhanced the formation of monoacylated products, a bias more prominent with the primary diamines compiled in Table 2 than with secondary diamines assembled in Table 3. This result complements the results obtained with the nucleophilic dianion activation strategy examined earlier.[4] Moreover, phenylacetyl chloride, which is a chemically sensitive substrate due to the presence of acidic α-protons and which provided poor results when exposed to dianions of diamines, afforded similar results to benzoyl chloride. This demonstrates a clear and significant advantage for this selective deactivation process compared to the previous approach.[4]

The results associated with the acylation of diamines after 9-BBN pretreatment compiled in Tables 2 and 3 can be summarized as follows. (1) The acylation of primary diamines was subject to a higher degree of control than the acylation of secondary diamines. (2) The preference shown for the monoacylation of secondary diamines was dependent upon the nature of the N substituent: smaller groups provided better selectivity. For the homologous series of substituted 1,2-diaminoethanes summarized in entries 3 and 6−8 of Table 3, the methyl derivative **7o** (entry 6, Table 3) provided the highest ratio of mono- to di-acylation. However, the selectivity declined as the size of alkyl group increased (entries 3 and 7, Table 3), diminishing considerably in the case of the *tert*-butyl derivative **7q** (entry 8, Table 3). (3) For both acyclic primary and secondary diamines, the number of intervening methylene groups did not influence selectivity. On the basis of these results and literature precedent, a plausible mechanism for the observed mono-selectivity for the acylation of alkyl diamines is proposed in Scheme 3. The coordination of one of the two nitrogens of diamine **1** with 9-BBN, dissociated from its dimer form via either first-order or second-order kinetics,[8e] results in the formation of a complex, **10**. This process does not entail the generation of H_2 gas, a hypothesis consistent with previous studies[7−10] and with direct observation of the reaction mixtures. The uncomplexed nitrogen atom remains free to react with the

Scheme 3. Possible Mechanism



acyl chloride to generate the acylated intermediate **11**, which is decomposed during workup when either alcohol or water is added, liberating the desired monoacylated product **8**. However, if complexation was either incomplete or readily reversible, both nitrogen atoms of the diamine would be available for reaction with the acyl chloride, leading to the diacylated product **9**. The control of chemical reactivity thus depends on the ability of the nitrogen atom of diamines to form a stable complex with the boron atom of 9-BBN. The stability of the complex would be expected to be sensitive to the steric environment surrounding the nitrogen atom, with less sterically encumbered substituents favoring complexation. This would rationalize the observations described herein in which primary diamines generally performed better than secondary diamines and that bulky groups attenuated monoacylation at the expense of diacylation. The observation that the number of intervening methylene units did not strongly influence selectivity further suggests that a cyclic complex in which both nitrogen atoms coordinate to the boron does not play a significant role.

In summary, a general strategy has been developed that allows the selective monoacylation of diamines through a process that appears to rely upon the deactivation of one nitrogen atom. While absolute control of chemical reactivity has not been achieved, this process provides an improved procedure that favors the selective functionalization of symmetrical diamines and is compatible with chemically sensitive acylating agents.

Acknowledgment. The authors are very grateful to Professor Gilbert Stork and Dr. Kap-Sun Yeung for valuable advice. The authors are also very grateful to Dr. Li Pan for assistance in obtaining exact mass spectral data.

Supporting Information Available: ^{1}H and ^{13}C spectra and HRMS data of compounds **8aa**, **9aa**, **8ab**, and **9ab**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) (a) Singaram, B. *Heteroat. Chem*. **1992**, *3*, 245. (b) Brown, H. C.; Pai, G. G. *J. Org. Chem*. **1981**, *46*, 4713.

(8) (a) Booth, B. L.; Lawrence, N. J.; Pritchard, R. G.; Rashid, H. S. *J. Chem. Soc., Chem. Commun.* **1995**, 287. (b) Booth, B. L.; Lawrence, N. J.; Rashid, H. S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 287. (c) Lalor, F. J.; Paxson, T.; Hawthorane, M. F. *J. Am. Chem. Soc.* **1971**, 3156. (d) Couturier, M.; Tucker, J. L.; Andresen, B. M.; Dube, P.; Negri, J. T. *Org. Lett*. **2001**, *3*, 465. (e) Brown, H. C.; Chandrasekharan, J.; Wang, K. K. *J. Org. Chem*. **1983**, *48*, 3689. (f) Brown, H. C.; Wang, K. K. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 117.

(9) Some stable borane−amine complexes are commercially available. Examples are borane−dimethylamine complex (74-94-2), borane−morpholine complex (4856-95-5), and borane−*tert*-butylamine complex (7337-45-3).

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