search. The 470-MHz NMR data were obtained through the Purdue University Biological Magnetic Resonance Laboratory (Grant NIH-RR01077) and the GC-MS data were obtained on an instrument provided by NSF Grant CHE-8010832.

Monoacylation of Symmetrical Diamines

Alan R. Jacobson, Angelo N. Makris, and Lawrence M. Sayre*

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106

Received November 25, 1986

Diamines are often used as spacer elements between two dissimilar carboxylic acid components for the synthesis of biologically active agents, such as interconnecting two receptor pharmacophores to form unsymmetrical "bivalent ligands",[1] interconnecting a pharmacophore with an alkylating or photolabile group to form affinity labels,[2] or in the synthesis of unsymmetrically substituted polyamines.[3-6] These syntheses require a strategy which depends upon the selective monoacylation of one end of the diamine. A 1:1 stoichiometry of diamine and acylating agent corresponds to the statistical prediction of 50% yield of the desired monoamide (with 25% yield of both diamide and unreacted diamine), which is synthetically acceptable only if these three materials are easily separated and the acylating component is expendable. On the other hand, the utilization of excess diamine should greatly increase the yield of monoamide based on acylating agent. In cases where the diamine is volatile (e.g., ethylenediamine) or otherwise easily separable, high isolated yields of monoacylated diamine should be readily obtained through this approach. It is thus surprising to note the many examples in the literature wherein it is reported that the employment of excess diamine (sometimes as the solvent) yields inordinately large amounts of diacyl byproduct.[6-10] Such findings prompted these and other investigators to utilize alternative strategies for obtaining the desired monoacyl product, often involving a time-consuming protection–acylation–deprotection sequence[2,4,9-12] or de novo synthesis.[13]

Table I. Yield of Diacyl Product from the Reaction of 1,2-Ethanediamine (EDA) or 1,4-Butanediamine (BDA) (10 mmol) with Various Acylating Agents (2 mmol)[a]

		diacyl product formed,[b] mmol	
diamine	RCOX	"standard"[c]	"high-dilution"[d]
EDA	PhCOCl	0.99	0.22
EDA	$(PhCO)_2O$	0.24	0.14
EDA	$PhCH_2COCl$	0.89	0.56
EDA	$(PhCH_2CO)_2O$	0.29	0.07
EDA	$PhCH_2COOSu$	0.07	0.06
BDA	PhCOCl	0.79	0.35
BDA	$(PhCO)_2O$	0.27	0.09

[a] Data represent the average of two to four experiments. [b] Statistically predicted yield is 0.1 mmol; maximum possible yield is 1.0 mmol. [c] RCOX in 5 mL of CH_2Cl added to diamine in 15 mL of CH_2Cl_2 at -78 °C. [d] RCOX in 100 mL of CH_2Cl_2 added to diamine in 300 mL of CH_2Cl_2 at -78 °C.

Although several possible explanations for the formation of abnormally large amounts of diacyl material are certain to have been considered (e.g., intramolecular catalysis by the first-formed amide group or some other effect that makes the initial monoamide more reactive than unacylated diamine), the invariance of the observed "diacyl effect" with structure of the diamine[6-10] suggests that the only rational explanation is that of a mixing problem. That the limitations of mixing could contribute to the production of difunctionalized diamine in much higher than statistical yield was pointed out many years ago for the reaction of diamines with isocyanates and isothiocyanates,[7] wherein it was shown that the more reactive (former) reagent gave more diacyl product than did the less reactive (latter) reagent. Unfortunately, most organic chemists are unaware of this study and probably believe that a slow dropwise addition of a reasonably dilute solution of an acid chloride to a well-stirred solution of diamine at low temperature (e.g., -78 °C) results in a more-or-less complete dispersion of reactants (at a molecular level) prior to reaction. Once one recognizes that this might not be the case, it is easy to modify reaction conditions to reduce the formation of diacyl material to the statistical limit.

We carried out a simple study comparing the product distribution of a monoacylation experiment as a function of (1) the reactivity of the acylating agent and (2) the concentration of reactants, independently, for two representative amines, 1,2-ethanediamine (EDA) and 1,4-butanediamine (BDA). *Our findings confirm that a typical acylation protocol using an acid chloride results in predominantly diacyl product even though the diamine is present in fivefold excess. On the other hand, the combination of increasing reactant dilution and decreasing reactivity of the acylating agent results in a statistical product distribution.*

Results

Table I lists the results of adding the aryl acylating agents benzoyl chloride or benzoic anhydride to a fivefold excess of either 1,2-ethanediamine or 1,4-butanediamine, under either "standard" or "high-dilution" conditions (see Experimental Section), in CH_2Cl_2 with rapid stirring at -78 °C. In the case of EDA, results were also obtained by using three aliphatic acylating agents, including a *N*-hydroxysuccinimide (HOSu) "active ester" commonly used in peptide chemistry. The 1:5 stoichiometry corresponds to

(1) Triggle, D. J. *Trends Pharmacol. Sci.* **1983**, *4*, 107.
(2) Zioudrou, C.; Varoucha, D.; Loukas, S.; Nicolaou, N.; Streaty, R. A.; Klee, W. A. *J. Biol. Chem.* **1983**, *258*, 10934.
(3) Hansen, J. B.; Nielsen, M. C.; Ehrbar, U.; Buchardt, O. *Synthesis* **1982**, 404.
(4) Jackson, E. L. *J. Org. Chem.* **1956**, *21*, 1374.
(5) Tabor, H.; Tabor, C. W.; De Meis, L. *Methods Enzymol.* **1971**, *17B*, 829.
(6) Bergeron, R. J.; Garlich, J. R.; Stolowich, N. J. *J. Org. Chem.* **1984**, *49*, 2997.
(7) Stoutland, O.; Helgen, L.; Agre, C. L. *J. Org. Chem.* **1959**, *24*, 818.
(8) Moore, T. S.; Boyle, M.; Thorn, V. M. *J. Chem. Soc.* **1929**, 39.
(9) Lawson, W. B.; Leafer, M. D., Jr.; Tewes, A.; Rao, G. J. S. *Hoppe-Seyler's Z. Physiol. Chem.* **1968**, *349*, 251.
(10) Stahl, G. L.; Walter, R.; Smith, C. W. *J. Org. Chem.* **1978**, *43*, 2285.
(11) (a) Schwartz, E.; Shanzer, A. *Tetrahedron Lett.* **1982**, *23*, 979. (b) Barker, P. L.; Gendler, P. L.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 2455.
(12) A polymer-based protecting group strategy has been employed as a method of achieving effective high-dilution (by controlling the average spacing between groups) and, consequently, selective monofunctionalization: Dixit, D. M.; Leznoff, C. C. *J. Chem. Soc., Chem. Commun.* **1977**, 798.
(13) (a) Kunesch, G. *Tetrahedron Lett.* **1983**, *24*, 5211. (b) Kagiya, T.; Izu, M.; Matsuda, T.; Matsuda, M.; Fukui, K. *J. Polym. Sci., Polym. Chem. Ed.* **1968**, *6*, 2059. (c) Nakajima, K.; Shinuchi, T.; Tauchi, M. *Nippon Kagaku Zasshi* **1967**, *88*, 976.

0022-3263/87/1952-2592$01.50/0

Table II. Second-Order Rates for Amine Acylation by 4-Nitrophenyl Acetate[a]

	10^2k, M^{-1} s^{-1} [b]					
	$n = 2$		$n = 3$		$n = 4$	
amine	20 °C	32 °C	20 °C	32 °C	20 °C	32 °C
$H_2N(CH_2)_nNH_2$[c]	0.61	1.5	3.6	4.5	4.3	6.7
$CH_3CONH(CH_2)_nNH_2$	0.22	0.42	0.27	0.54	0.29	0.67
$(CH_3)_2N(CH_2)_nNH_2$	0.71	2.7	4.5	12.	8.2	18.

[a] $[Amine]_0 = 0.0083$ M; $[CH_3COOC_6H_4NO_2]_0 = 0.0017$ M; 0.0083 M Et_3N present as auxiliary base; CH_2Cl_2 solvent. [b] Calculated from the spectrophotometrically determined (at 422 nm, $\epsilon = 1500$) half-life. Each value listed represents the average of two or three experiments. [c] No diacylation was detected under these conditions.

a statistical prediction of 1.8 mmol (90%) of monoacyl product and 0.1 mmol of diacyl product, based on 2.0 mmol of acylating reagent. It was most convenient to measure the yield of diacyl product, and the values given in columns 1 and 2 can be compared with the 0.1-mmol statistical yield and the 1.0-mmol maximum possible yield (if diacylation occurs to the complete exclusion of monoacylation). It can be seen that in a few cases, the yield of diacyl product was less than 0.1 mmol, indicating a better-than-statistical production of monoacyl product, suggesting that the second acylation is actually slower, not faster, than the first. We independently determined the yield of monoacyl product in key experiments to confirm that our measured yields of diacyl material could be directly converted into yields of monoacyl product (viz., that simple hydrolysis of acylating agent did not occur).

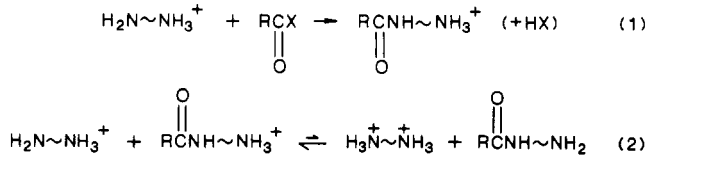
In order to address the possibility that electronic and/or steric effects, or intramolecular catalysis, could contribute to nonstatistical yields of diacyl product, we conducted a brief kinetic study of the reaction of 4-nitrophenyl acetate with primary diamines of two-, three-, and four-carbon spacing, as well as with the corresponding *N*-monoacetyl and *N,N*-dimethyl derivatives. The second-order rate constants, calculated from the spectrophotometrically determined half-lives, are listed in Table II. It can be seen that the three monoacetyl compounds react at similar rates, independent of the spacing between the two nitrogens. These rates are 3 times slower than those of the parent diamine in the case of two-carbon spacing, and 10–15 times slower in the case of three- and four-carbon spacing. Since statistics would predict a twofold rate difference, our results indicate that the intrinsic reactivity of the amino group is greater for the diamines relative to the monoacyl derivatives in the case of three- and four-carbon spacing. The rates for the *N,N*-dimethyl derivatives can all be seen to be somewhat faster than for the parent diamines, though statistics would again predict a twofold rate *decrease*.

Discussion

The results presented above confirm those obtained by others insofar that a typical acylation procedure using an acid chloride (dropwise addition at −78 °C, final concentrations of 0.5 and 0.1 M for diamine and acid chloride, respectively) gives diacyl product nearly exclusively, even though the diamine is present in fivefold excess over the acylating agent. Our data show that the statistically predicted yields are realized by using a less reactive acylating agent (e.g., anhydride) under high-dilution conditions. This is true regardless of whether aryl or alkyl acylating agents are used. The only reasonable explanation for the acid chloride results is that reaction is so rapid that the initial monoamide product molecule formed at the interface between the drop of acid chloride solution and the diamine solution is acylated a second time at this interface before mixing can ensure effective dispersion at the molecular level. Once the mixing problem is effectively eliminated, a high yield of monoacyl product based on acylating agent can be obtained when the diamine is employed in large excess. In this regard, optimum results should be obtained by minimizing the concentration of the acylating agent solution being added, and maximizing the concentration of the diamine solution, though in practice, adding a large volume of solvent to a small volume of solvent will have the desired effect only during the initial stages of the reaction unless special techniques are employed (e.g., continuous evaporation) to maintain the small volume of solvent in the reaction pot.

The kinetic experiments described in Table II (see Results) confirm that the observation of unexpectedly large amounts of diacyl product is not due to intramolecular catalysis *at the N-monoacyl stage*. In fact, for three- and four-carbon (but not two-carbon) spacing, the reactivity of the *N*-monoacetyl compound relative to that of the parent diamine is substantially *less* than the 0.5-fold statistical prediction. The constancy of the rate for all the *N*-monoacetyl compounds suggests to us that these derivatives are exhibiting normal reactivity and that the reactivity of the parent C_3 and C_4 diamines is enhanced due to intramolecular general base catalysis. This interepretation is supported by a previous report by Bruice and Willis,[14] who found that the reactivity of 1,3-propanediamine and 1,4-butanediamine but not 1,2-ethanediamine in water toward phenyl acetate exhibited a substantial positive deviation from a Brønsted plot constructed for simple monoamines and attributed this to intramolecular general base catalysis. Our finding that the *N,N*-dimethyl derivatives are acylated faster than are the parent diamines suggests that the proposed intramolecular general base catalysis by the "second" amino group is enhanced by *N,N*-dimethylation, as would be expected. In conclusion, the kinetic data suggest that better-than-statistical yields of monoacyl product may be obtained in some cases, once the mixing problem is eliminated.

Several procedures exist for obtaining high yields of monoacylation in special situations. For example, using ethylenediamine or other diamines with short hydrocarbon chains, one can take advantage of the differential pK_a effect:[5,8,15] viz., if the acylation is run at a controlled pH which maintains the availability of 1 mol equiv of protons throughout the reaction, then acylation will proceed as in eq 1 and diacylation will be minimized due to the unfavorability of the equilibrium shown in eq 2 for short chains. This strategy will obviously not work for longer chain



(14) Bruice, T. C.; Willis, R. G. *J. Am. Chem. Soc.* **1965**, *87*, 531.
(15) Guggisberg, A.; van den Broek, P.; Hesse, M.; Schmid, H.; Schneider, F.; Bernauer, K. *Helv. Chim. Acta* **1976**, *59*, 3013.

diamines,[9] where the first and second pK_a's are similar. Dynamic protection of diamines using 1 equiv of 18-crown-6 appears to be subject to similar limitations.[16]

Also, one can sometimes find a solvent such that the desired monoamide precipitates from solution as it is formed (thereby taking it out of competition for acylating agent), though the aggregation-precipitation event is usually too slow to prevent manifestation of the mixing problem. Since it is almost always possible to modify the acylating moiety of the needed carboxylic acid component at will, we see no reason why the combined strategy of low reactivity, high dilution, low temperature, and excess diamine cannot be generally employed for the synthesis of monoacylated diamines. Even in cases where the low volatility of diamine makes the separation of the desired monoamide product from unreacted diamine nontrivial, one can usually work out conditions employing selective extraction and/or chromatographic procedures.

An analogous strategy to that discussed above should be applicable to the selective monosulfonylation and mono*alkyl*ation of diamines.

Experimental Section

All reagents were used as obtained from commercial sources (ACS or AR grade), with the exception of phenylacetic anhydride[17] and *N*-(phenylacetoxy)succinimide ($PhCH_2COOSu$),[18] which were prepared as described. All diamines except 4-(dimethylamino)butylamine (Pfaltz & Bauer) were purchased from Aldrich Chemical Co., were of the highest quality obtainable (generally 99+% "Gold Label"), and were stored over NaOH pellets for 24 h before use. The *N*-monoacetyl derivatives of 1,3-propanediamine and 1,4-butanediamine were synthesized from the parent diamines by using Ac_2O in water containing NaOAc according to the published procedure.[15] *N*-Acetylethylenediamine and 4-nitrophenyl acetate were from Aldrich. Reactions were qualitatively monitored by TLC on silica gel plates using MeOH-EtOAc-NH_4OH (50:50:1) as eluant, with visualization by UV or ninhydrin. In this system, monoacyl product, diacyl product, and unreacted diamine had R_f's of about 0.4-0.5, 0.8-0.9, and 0, respectively. NMR spectra were recorded on Varian EM-360 and XL-200 instruments in Me_2SO-d_6. The reaction conditions for the kinetic experiments are given in Table II. Second-order plots constructed for representative kinetic runs, in order to ensure the accuracy of the rate constant calculated from measured $t_{1/2}$ values, were found to be linear to >75% reaction. It was found necessary to make up fresh CH_2Cl_2 solutions of the diamines prior to each kinetic run, in order to obtain reproducible rates.

"Standard" Acylation Procedure. RCOCl (2 mmol) diluted in 5 mL of CH_2Cl_2 was added dropwise over 30 min to a vigorously stirred solution of 1,2-ethanediamine or 1,4-butanediamine (10 mmol) in 15 mL of CH_2Cl_2 at -78 °C (dry ice, 2-propanol). Upon completion of the addition, the reaction mixture was allowed to come to room temperature with stirring overnight and extracted with two 30-mL portions of 5% aqueous HCl. TLC indicated that this extraction procedure removed all unreacted diamine and monoacyl product and that no hydrolysis occurred in the case of RCOCl. The organic layer was taken to dryness, an accurately weighed amount (20-30 mg) of hexamethylbenzene (HMB) and Me_2SO-d_6 were added, and the ^1H NMR spectrum was recorded. The yield of diacyl product was calculated from the relative integration of sample peaks and the HMB singlet. In some cases, the acidic aqueous layer was basified with NH_4OH and thoroughly extracted with CH_2Cl_2, and the organic layer was evaporated and analyzed by ^1H NMR as above in order to calculate the yield of monoacyl product.

For reactions involving $(RCO)_2O$ rather than RCOCl, the organic layer left after extraction with 5% aqueous HCl was extracted with saturated aqueous $NaHCO_3$ (to remove RCOOH) before processing as above.

"High-Dilution" Acylation Procedure. This was the same as above, except that the acylating agent in 100 mL of CH_2Cl_2 (20 times the volume used above) was added to the diamine in 300 mL of CH_2Cl_2 with vigorous stirring over 30 min.

Acknowledgment. This work was supported by grants from the National Institutes of Health (NS 18714) and the American Heart Association with partial contribution from the American Heart Association, Northeast Ohio Affiliate. We thank Dr. P. K. Arora for technical assistance.

(16) Barrett, A. G. M.; Lana, J. C. A.; Tograie, S. *J. Chem. Soc., Chem. Commun.* **1980**, 300.
(17) Heilbron, I. M.; Hey, D. H.; Lythgoe, B. *J. Chem. Soc.* **1936**, 295.
(18) Kricheldorf, H. R. *Chem. Ber.* **1973**, *106*, 3765.

Efficient Method for the Reductive Cleavage of Acetals and Ketals with $Zn(BH_4)_2/Me_3SiCl$

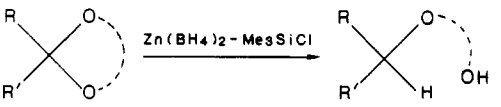
Hiyoshizo Kotsuki,* Yasuyuki Ushio, Naka Yoshimura, and Masamitsu Ochi

Department of Chemistry, Faculty of Science, Kochi University, Akebono-cho 2-5-1, Kochi 780, Japan

Received September 10, 1986

The reductive cleavage of acetals and ketals to ethers is a synthetically useful method in asymmetric synthesis[1] and protective chemistry.[2] Until recently, a number of methods have been developed for this transformation involving various reagents such as $LiAlH_4$-Lewis acids,[3] Me_3SiH-Me_3SiOTf,[4] Et_3SiH-acids,[5] diisobutylaluminum hydride,[6] B_2H_6,[7] BH_2Cl,[8] $NaBH_3CN$-HCl,[9] $NaBH_4$-CF_3COOH,[10] Li/NH_3,[11] and H_2 over catalysts.[12]

In a continuation of our study to develop the reducing ability of $Zn(BH_4)_2$,[13] we have found that the use of this reagent with Me_3SiCl is very effective in the reductive cleavage of a wide variety of acetals and ketals under mild conditions. Thus, the treatment of acetals or ketals with 0.5 equiv of $Zn(BH_4)_2$ in the presence of 1.2 equiv of Me_3SiCl leads to the formation of the ethers in excellent to good yields (Table I).



(1) Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 4581. Ishihara, K.; Mori, A.; Arai, I.; Yamamoto, H. *Ibid.* **1986**, *27*, 983. Mori, A.; Ishihara, K.; Yamamoto, H. *Ibid.* **1986**, *27*, 987.
(2) Fügedi, P.; Lipták, A. *J. Chem. Soc., Chem. Commun.* **1980**, 1234. Johansson, R.; Samuelsson, B. *Ibid.* **1984**, 201. Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593. Takano, S.; Akiyama, M.; Ogasawara, K. *Chem. Pharm. Bull.* **1984**, *32*, 791 and references cited therein.
(3) (a) Eliel, E. L.; Badding, V. G.; Rerick, M. N. *J. Am. Chem. Soc.* **1962**, *84*, 2371. (b) Abdun-Nur, A. R.; Issidorides, C. H. *J. Org. Chem.* **1962**, *27*, 67. (c) Ishikawa, H.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2059. (d) Bonner, T. G.; Lewis, D.; Rutter, K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1807.
(4) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1979**, 4679.
(5) Loim, L. M.; Parnes, Z. N.; Vasil'eva, S. P.; Kursanov, D. N. *Zh. Org. Khim.* **1972**, *8*, 896; *Chem. Abstr.* **1972**, *77*, 125841w. Doyle, M. P.; DeBruyn, D. J.; Kooistra, D. A. *J. Am. Chem. Soc.* **1972**, *94*, 3659. Olah, G. A.; Yamato, T.; Iyer, P. S.; Surya Prakash, G. K. *J. Org. Chem.* **1986**, *51*, 2826.
(6) Zakharkin, L. I.; Khorlina, I. M. *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* **1959**, 2255; *Chem. Abstr.* **1960**, *54*, 10837h. Schill, G.; Doerjer, G.; Longemann, E.; Vetter, W. *Chem. Ber.* **1980**, *113*, 3697.
(7) Fleming, B.; Bolker, H. I. *Can. J. Chem.* **1974**, *52*, 888.
(8) Borders, R. J.; Bryson, T. A. *Chem. Lett.* **1984**, 9.
(9) Horne, D. A.; Jordan, A. *Tetrahedron Lett.* **1978**, 1357.
(10) Nutaitis, C. F.; Gribble, G. W. *Org. Prep. Proc. Int.* **1985**, *17*, 11.
(11) Abdell, A. D.; Massy-Westropp, R. A. *Tetrahedron* **1985**, *41*, 2451.
(12) Covert, L. W.; Connor, R.; Adkins, H. *J. Am. Chem. Soc.* **1932**, *54*, 1651. Howard, W. L. Brown, Jr.; J. H. *J. Org. Chem.* **1961**, *26*, 1026. Fleming, B. I.; Bolker, H. I. *Can. J. Chem.* **1976**, *54*, 685.
(13) Kotsuki, H.; Yoshimura, N.; Ushio, Y.; Ohtsuka, T.; Ochi, M. *Chem. Lett.* **1986**, 1003. Kotsuki, H.; Ushio, Y.; Yoshimura, N.; Ochi, M. *Tetrahedron Lett.* **1986**, *27*, 4213.

0022-3263/87/1952-2594$01.50/0