Notes

Convenient Acylative Dealkylation of Tertiary Amines

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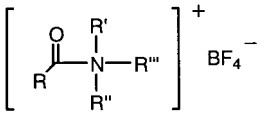
Protecting groups in the form of *N*-alkyl or *N*-aryl substituents hold a key position in heterocyclic chemistry in that selected groups on nitrogen frequently make possible the synthesis of ring compounds, which are otherwise inaccessible. Bulky N-protecting groups often provide control over the reaction pathway and heterocycle formation through Mannich condensations[1] and Gaertner cyclizations,[2] to cite two examples. The versatility of this protocol in an overall synthetic strategy depends in no small measure on the subsequent N-dealkylation of the protecting group employed to direct the cyclization. Catalytic hydrogenolysis of benzyl groups using H_2/Pd−C is an efficient, although slow, deprotection method for benzylamines.[3] A variety of carbonochloridate (chloroformates) reagents developed to improve the ease, selectivity, and yields of the amines resulting from N-dealkylations have been the focus of many reports in the recent literature. The advantages and drawbacks that these reagents offer have been reviewed.[4] Recently, it has been shown that a convenient and efficient replacement of the *N*-*tert*-butyl group by an *N*-acyl function is readily achieved in the reaction of *N*-*tert*-butyl-3-substituted azetidines with acetic anhydride in the presence of boron trifluoride diethyl etherate.[5] To extend the scope and usefulness of this acylative dealkylation reaction, we have undertaken an examination of the range of compounds and facility with which protecting N-alkyl groups can be removed. The resulting amides would be amenable to simple acid or base-catalyzed hydrolysis to provide secondary amines. In this paper, we detail the results of this investigation.

The reaction of a number of readily available tertiary amines (Table 1) of various ring sizes and different *N*-alkyl groups with acylating agents under Lewis acid catalysis was investigated.

Among the compounds studied, *N*-benzhydryl-3-azetidinol was transformed into the corresponding *N*-acyl-3-azetidinol acetate[5] (entry 1). Pyrrolidines containing *N*-isopropyl and *N*-benzyl groups were easily converted to *N*-acetylpyrrolidine[6] (entries 2 and 3), whereas *N*-ethylpiperidine and 1,4-diazabicyclo[2.2.2]octane failed to react under these conditions (entries 5 and 7) and *N*-methylpyrrolidine gave a complex reaction product in which no *N*-acylpyrrolidine could readily be identified (entry 4). Deprotective removal of the isopropyl groups from 1,4-diazacyclohexane occurred quite easily to give the 1,4-diacetyl-1,4-diazacyclohexane[7] derivative (entry 6). In the case of 1,3-di-*tert*-butyl-5-bromo-5-nitro-1,3-diazacyclohexane, different products were obtained depending on the reaction conditions used. At room temperature, only one of the *tert*-butyl groups was replaced (entry 8). However, heating at 100 °C resulted in the replacement of both *tert*-butyl groups in good yield (entry 9). Similarly, treatment of 1,5-di-*tert*-butyl-3-acetoxy-7-methylidine-1,5-diazacyclooctane and the corresponding 3-benzoyloxy compound with acetic anhydride resulted in the formation of the corresponding diacetyl derivative in good yield (entries 10 and 11).

The success of the methodology was also demonstrated in an analogous dealkylative trifluoroacetylation reaction. The reaction of 1-*tert*-butyl-3-azetidinol with trifluoroacetic anhydride and boron trifluoride diethyl etherate gave 1-trifluoroacetylazetidinyl-3-trifluoroacetate (entry 12). The use of an acyl chloride in these dealkylation reactions was also demonstrated by treating 1-*tert*-butyl-3,3-dinitroazetidine with oxalyl chloride to obtain bis(3,3-dinitroazetidinyl)oxamide (entry 13).

The formation of the observed products can be explained by postulating a reaction pathway that proceeds from the initial formation of an *N*-acyltrialkylammonium salt similar to **1**, which was isolated by Paukstelis and co-workers.[8]



1

This intermediate complex then undergoes an SN_1-like cleavage[9] of a C−N bond with selective loss of the alkyl

(1) Cichra, D. A.; Adolph, H. G. *J. Org. Chem.* **1982**, *47*, 2474.
(2) Gaertner, V. R. J. *J. Org. Chem.* **1970**, *35*, 3952.
(3) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley-Interscience: New York, 1991. Kocienski, P. J. *Protecting Groups*; Thieme, New York, 1994.
(4) Cooley, J. H.; Evain, E. J. *Synthesis* **1989**, 1.
(5) Dave, P. R. *J. Org. Chem.* **1996**, *61*, 5453.
(6) Ochiai, E.; Tsuda, K. *Ber.* **1934**, *67*, 1017.
(7) Reppe, W. *Ann.* **1955**, *596*, 38.
(8) Paukstelis, J. V.; Kim, M.-G. *J. Org. Chem.* **1974**, *39*, 1503.
(9) Mariella, R. P.; Brown, K. H. *Can. J. Chem.* **1971**, *49*, 3348.

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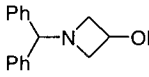
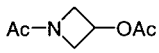
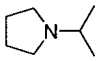
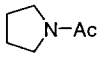
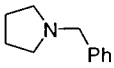
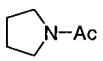
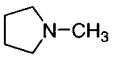
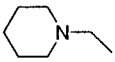
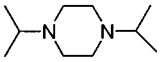
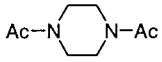
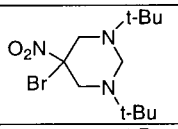
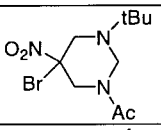
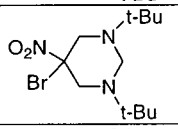
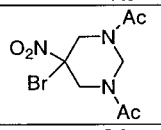
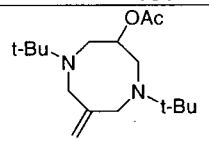
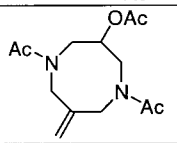
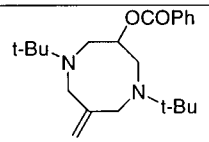
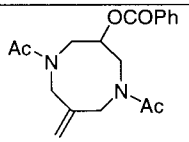
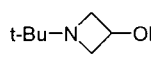
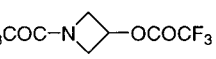
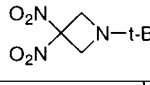
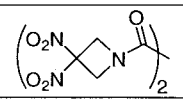
Table 1. Dealkylation of Tertiary Amines

Entry	Substrate (a)	Product (b)	Time (h)	Temp. (°C)	Yield (%)
1			96	120	41
2			14	120	76
3			38	120	58
4		Decomposition			
5		No Reaction			
6			14	120	71
7		No Reaction			
8			24	RT	81
9			3.5	100	73
10			72	Reflux	29
11			48	Reflux	19
12[a]			12	Reflux	72
13[b]			12	Reflux	68

[a]Trifluoroacetic anhydride used. [b]Reaction with oxalyl chloride in 1,1,2-trichloroethane.

group that is progenitor to the most stable carbocation to give the desired *N*-acylamine. In the limited number of examples that we have examined, our findings are consistent with this hypothesis. It is found that simple primary alkyl groups are not displaced from nitrogen, but that secondary, tertiary, and benzyl groups are. On this basis, it is reasonable to rationalize the preservation of the ring structures in those *N*-alkyl reactants that undergo dealkylation as due the failure to expel an unstable primary carbocation from complex **1**.

In summary, we have demonstrated that the treatment of tertiary amines with acetic anhydrides and acyl chloride containing catalytic amounts of boron trifluoride diethyl etherate provides a practical means of nitrogen dealkylation to afford *N*-acylamines. The process should have wide applicability as an alternate to chloroformate displacements as an amine deprotection method. The method is mild and can tolerate functionalities such as nitro, hydroxyl, and double bonds that would not survive hydrogenolysis.

Experimental Section

Solvents were purified and dried prior to use. Reagents were used as obtained from the commercial supplier. *N*-Benzhydryl-3-azetidinol was prepared according to a literature precedent.[10] The preparation of 1,3-di-*tert*-butyl-5-bromo-5-nitro-1,3-diazacyclohexane is described in the previous paper in this issue.[11] Preparation of the 1,5-diazacyclooctane substrates used in entries 10 and 11 will be described elsewhere. Melting points

(10) Chatterjee, S. S.; Triggle, D. J. *Chem. Commun.* **1968**, 93.

(uncorrected) were determined on a Hoover Thomas capillary melting point apparatus. High-resolution mass spectra were recorded on a JEOL JMS-HX110A using FAB ionization and peak matching techniques. Flash column chromatography was performed with Merck 9385 silica gel as the stationary phase. TLC was performed with Merck silica gel 60 F_{254} (0.2 mm) precoated plates. ^{1}H NMR spectra and ^{13}C NMR spectra were measured on a 300 MHz spectrometer in $CDCl_3$ with TMS as an internal standard.

General Procedure for Dealkylation Reactions. To a solution of the alkylamine (2 mmol) in acetic anhydride (10 mL) was added boron trifluoride diethyl etherate (10 drops) with stirring. The reaction mixture was immersed in an oil bath at the indicated temperature for the time indicated in Table 1. The reaction mixture was cooled, and the excess acetic anhydride was removed by fractional distillation at reduced pressure (10 mmHg). The residue was purified by vacuum distillation, crystallization, or extractive workup followed by crystallization or chromatography to give the respective *N*-acetyl compounds. The known compounds 1-acetyl-3-acetoxyazetidine,[5] 1-acetylpyrrolidine[6] and 1,4-diacetyl-1,4-diazacyclohexane[7] were identified by comparison of their physical properties and spectral data with reported literature values. Characterization data for the new compounds are given below.

Additionally, the molecular structures of 1-acetyl-3-*tert*-butyl-5-bromo-5-nitro-1,3-diazacyclohexane (entry 8), 1,3-diacetyl-5-bromo-5-nitro-1,3-diazacyclohexane (entry 9), 1,5-diacetyl-3-acetoxy-7-methylidene-1,5-diazacyclooctane (entry 10), and bis(3,3-dinitroazetidinyl)oxamide (entry 13) were further confirmed via single-crystal X-ray crystallography. Atomic coordinates for these structures have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

1-Acetyl-3-*tert*-butyl-5-bromo-5-nitro-1,3-diazacyclohexane (Entry 8). The product was recrystallized from ethanol−water, mp 152−154 °C dec. The NMR spectra of this material show an equilibrium mixture of a major and minor isomer in a ratio of 2.5:1.

^{1}H NMR (minor isomer, $CDCl_3$): δ 1.12 (s, 9H), 2.09 (s, 3H), 2.98 (d, J = 12.82 Hz, 1H), 3.31 (d, J = 13.65 Hz, 1H), 3.72 (d, J = 10.99 Hz, 1H), 4.17−4.23 (m, 1H), 4.66−4.71 (m, 1H), 5.55−5.61 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 21.0, 26.4, 49.9, 54.6, 62.2, 84.9, 167.9.

^{1}H NMR (major isomer, $CDCl_3$): δ 1.12 (s, 9H), 2.25 (s, 3H), 2.92 (d, J = 12.81 Hz, 1H), 3.18 (d, J = 10.98 Hz, 1H), 3.65 (d, J = 14.65 Hz, 1H), 4.23−4.28 (m, 1H), 4.88−4.94 (m, 1H), 5.53−5.56 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 20.8, 26.4, 49.9, 54.2, 57.1, 57.4, 84.6, 168.5. HRMS (FAB): calcd for $C_{10}H_{19}BrN_3O_3$ (MH^+) 308.0610, found *m*/*z* 308.0607.

1,3-Diacetyl-5-bromo-5-nitro-1,3-diazacyclohexane (Entry 9). Recrystallization from ethyl acetate/hexanes gave pure 1,3-diacetyl-5-bromo-5-nitro-1,3-diazacyclohexane as a colorless solid. Mp: 116−118 °C. ^{1}H NMR ($CDCl_3$): δ 2.23 (s, 2H), 2.25 (s, 3H), 3.99 (d, J = 14.65 Hz, 1H), 4.13 (d, J = 14.65 Hz, 1H), 4.69 (d, J = 13.27 Hz, 1H), 4.77 (d, J = 14.65 Hz, 1H), 5.15 (d, J = 14.19 Hz, 1H), 5.61 (d, J = 13.28 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 20.3, 20.9, 50.2, 54.9, 55.1, 83.6, 168.4, 168.9. HRMS (FAB): calcd for $C_8H_{13}BrN_3O_4$ (MH^+) 294.0089, found *m*/*z* 294.0081.

1,5-Diacetyl-3-acetoxy-7-methylidene-1,5-diazacyclooctane (Entry 10). Recrystallization from ethyl acetate/hexanes (1:3) gave colorless crystals. Mp: 100.8−101.2 °C. ^{1}H NMR ($CDCl_3$): δ 2.01 (s, 3H), 2.05 (s, 3H), 2.15 (s, 3H), 3.02 (dd, J_{AB} = 13.3 Hz, J = 10.1 Hz, 1H), 3.10 (dd, J_{AB}=14.7 Hz, J = 10.1 Hz, 1H), 3.49 (d, J_{AB} = 14.7 Hz, 1H), 3.75 (dd, J_{AB} = 14.7 Hz, J = 3.7 Hz, 1H), 3.76 (d, J_{AB} = 13.7 Hz, 1H), 3.89(dd, J_{AB} = 13.3 Hz, J = 4.5 Hz, 1H), 4.22(d, J_{AB} = 13.7 Hz, 1H), 4.88 (d, J_{AB} = 14.7 Hz, 1H), 5.26 (m, 1H), 5.28 (s, 1H), 5.32 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 20.8, 21.0, 21.8, 47.1, 49.4, 51.7, 55.7, 66.4, 122.0, 141.3, 169.7, 170.8, 171.5. HRMS (FAB): calcd for $C_{13}H_{20}N_2O_4$ (MH^+) 269.1501, found *m*/*z* 269.1490. Anal. Calcd for $C_{13}H_{20}N_2O_4$: C, 58.19; H, 7.51; N, 10.44. Found: C, 57.89; H, 7.44; N, 10.35.

1,5-Diacetyl-3-(*O*-benzoyl)-7-methylidene-1,5-diazacyclooctane (Entry 11). The product was obtained as a straw yellow oil that crystallized on standing. Mp: 105 °C. ^{1}H NMR ($CDCl_3$): δ 2.12 (s, 3H), 2.14 (s, 3H), 3.19−3.33 (m, 2H), 3.58 (AB, J_{AB} = 13.74 Hz, 1H), 3.86 (AB, J_{AB} = 13.74 Hz, 1H), 3.95 (ABq, J_{AB} = 13.73 Hz, 1H), 4.11 (ABq, J_{AB} = 13.73 Hz, 1H), 4.32 (AB, J_{AB} = 13.74 Hz, 1H), 4.96 (AB, J_{AB} = 13.74 Hz, 1H), 5.37 (s, 1H), 5.41 (s, 1H), 5.54−5.63 (m, 1H), 7.44 (t, 2H), 7.58 (t, 1H), 8.00 (d, 2H). ^{13}C NMR ($CDCl_3$): δ 21.1, 21.8, 47.4, 49.6, 51.8, 55.8, 67.0, 122.2, 128.5, 129.7, 133.4, 141.3, 165.5, 170.9, 171.5.

***N*-Trifluoroacetyl-3-trifluoroacetoxyazetidine (Entry 12).** The product was obtained by distillation as a pale yellow oil. Bp: 90−100 °C (2 mm Hg). IR (film): 2360 (s), 2341 (m), 1693 (vs), 1247 (s), 1204 (s), 1154 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 4.22−4.35 (m, 1H), 4.45−4.65 (m, 2H), 4.78−4.89 (m, 1H), 5.52 (m, 1H). HRMS (EI): calcd for $C_8H_5F_6NO_3$ (M^+) 265.0173, found *m*/*z* 265.0164.

Bis(3,3-dinitroazetidinyl)oxamide (Entry 13). The product was recrystallized from acetonitrile. Mp: 267 °C dec. ^{1}H NMR (acetone-d_6): δ 5.05 (s, 4H), 5.52 (s, 4H). ^{13}C NMR (acetone-d_6): δ 58.0, 62.9, 105.0, 158.6. Anal. Calcd for $C_8H_8N_6O_{10}$: C, 27.60; H, 2.32; N, 24.14. Found: C, 27.56, H, 2.40; N, 23.90.

Acknowledgment. We thank Drs. Richard S. Miller and Judah Goldwasser of the Office of Naval Research and Dr. Rao Surapaneni of ARDEC for financial support of this work. We acknowledge the Nebraska Center for Mass Spectroscopy for mass spectral analysis.

Supporting Information Available: Copies of the ^{1}H and ^{13}C NMR spectra of entries 8, 9, 10, and 11 and ^{1}H of entry 12 and tables of X-ray data and ORTEP views for entries **10** and **13**. This material is free of charge via the Internet at http://pubs.acs.org.

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(11) Axenrod, T.; Sun, J.; Das, K. K.; Dave, P. R.; Forohar, F.; Kaselj, M.; Trivedi, N. J.; Gilardi, R. D.; Flippen-Anderson, J. L. *J. Org. Chem.* **2000**, *65*, 1200.