Acylative Dealkylation of *N-tert*-Butyl-3-substituted Azetidines: Facile Access to [1.1.0]Azabicyclobutane, 3-Hydroxyazetidinium Hydrochloride, and 3-Azetidinones

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A novel acylative dealkylation of *N-tert*-butylazetidines and its application to the facile high-yield syntheses of [1.1.0]azabicyclobutane, 3-hydroxyazetidinium hydrochloride, and 3-azetidinones is described.

Introduction

Since the first report of the synthesis and chemistry of azabicyclobutane in 1969,[1] the potential of this theoretically interesting small strained bicyclic heterocyclic system incorporating a reactive C−N bond has remained largely unexplored. The lack of exploitation of this highly reactive system is directly linked to the poor yields for the preparation of azabicyclobutane. This difficulty notwithstanding, the versatility of additions across the central C−N σ bond of the azabicyclobutane system has been elegantly demonstrated recently by Marchand et al.[2] Ready availability of azabicyclobutane is sure to fuel research activity in this area. In our work in the area of 3-substituted azetidines, an interesting development has led to a facile high-yield synthesis of azabicyclobutane, in addition to other important azetidines.

Results and Discussion

Treatment of *N-tert*-butyl-3-chloroazetidine, **1**,[3] with acetic anhydride at 115 °C in the presence of a catalytic amount of boron trifluoride etherate gave *N*-acetyl-3-chloroazetidine, **2**, in 82% yield. On the basis of the reported quantitative conversion of 3-phenyl-3-haloazetidines to 3-phenylazabicyclobutane,[4] hydrolysis of the amide group under basic conditions was attempted. Indeed, treatment of **2** with KOH in D_2O in an NMR tube showed facile quantitative conversion to azabicyclobutane, as depicted in Figure 1.

In a separate experiment, **2** was heated with aqueous alkali in a distillation apparatus under water aspirator vacuum. Azabicyclobutane distilled out along with water. Extraction with organic solvent followed by treatment with ethyl chloroformate gave the adduct **4** in 50% overall yield.If it is assumed that the reaction of azabicyclobutane with ethyl chloroformate is quantitative, then this result represents a minimum yield, since azabicyclobutane is appreciably water soluble and therefore cannot be completely extracted. This method provides a way for obtaining organic solutions of azabicyclobutane in a reasonable yield for further reactions. Additionally, the C−H coupling constant of the tertiary carbon in azabicyclobutane was determined to be 206 Hz, consistent with that for the carbon analog.[5]

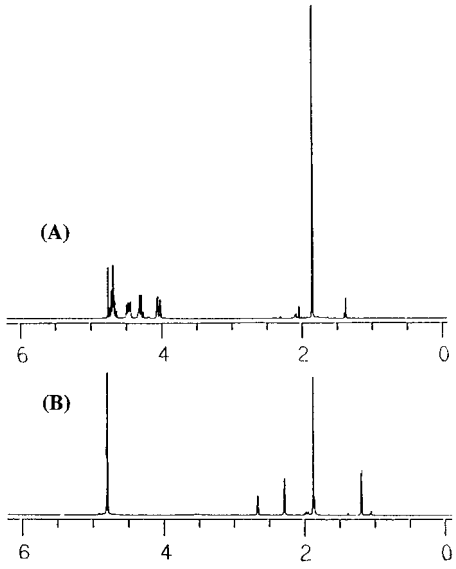
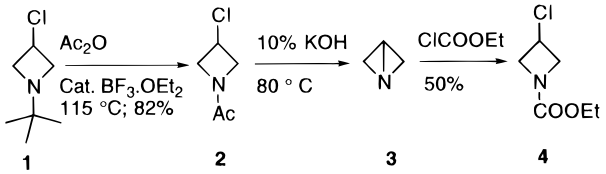


Figure 1. (A) ^{1}H NMR (D_2O) of **2**. (B) KOH added to sample A and heated at 80 °C for 3 h, showing complete conversion to **3** and KOAc.

Scheme 1



Similarly, when *N-tert*-butyl-3-hydroxyazetidine, **5**,[6] was treated with acetic anhydride in the presence of a catalytic amount of boron trifluoride etherate for 6 h, *N*-acetyl-3-acetoxyazetidine, **6**, was obtained in 95% yield and could be isolated simply by vacuum distillation. The spectral characteristics of the product match those reported earlier.[7] Compound **6** was treated with 5% aqueous HCl under reflux to give 3-hydroxyazetidine hydrochloride, **7**, in quantitative yield.[8] Compound **7** has found application in the synthesis of Charamin[9] and can be functionalized at the 1- and 3-positions.

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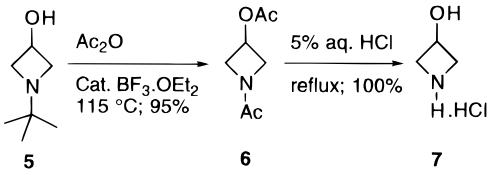
Scheme 2



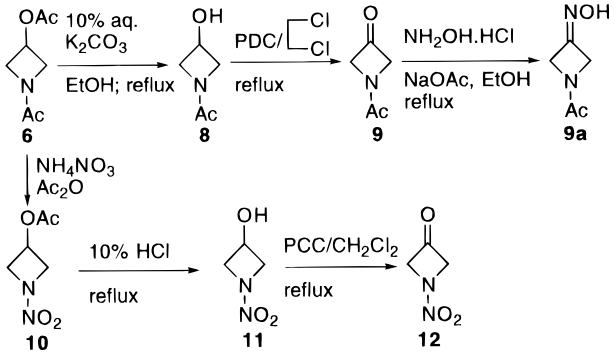
This acylative dealkylation is especially interesting in light of the fact that 3-acetoxy-*N*-*tert*-butylazetidine reportedly undergoes ring opening upon acetolysis.[3] Additionally, various 2- and 3-substituted *N*-alkylazetidines suffer ring opening on treatment with acetic anhydride.[10] One other example of dealkylation of 3,3-dinitro-*N*-*tert*-butylazetidine with chloroformate has been reported.[11] However, no study of the generalization of this reaction has been reported.

The acylative dealkylation offers easy access to a number of other 3-substituted azetidines (vide infra). The 3-substituted azetidine unit is present in a wide range of compounds having importance as drugs and pharmaceuticals,[12] natural products,[13] plant growth regulatory agents,[14] and potential new fuels and energetic materials.[2a,15]

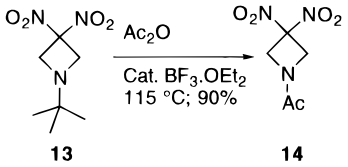
To date, the best method of synthesizing the 3-substituted azetidine ring structure remains the reaction of bulky amines with epichlorohydrin based on Gaertner's work.[3] A major limitation of this method is that the reaction is successful only with highly hindered amines like *tert*-butylamine and benzhydrylamine. The yields fall precipitously with smaller amines, and the reaction fails with amides and sulfonamides.[16] For this reason, several researchers have employed benzhydrylamine to achieve ring cyclization, followed by hydrogenolytic removal of the *N*-blocking group to synthesize *N*-unsubstituted azetidines, which can then be functionalized.[7,17] The Lewis acid-catalyzed acylative dealkylation of the *N*-*tert*-butyl group on azetidines offers several advantages. Cost and atom economy principles favor the *tert*-butyl group over the benzhydryl group. The reaction of the *tert*-butyl group with epichlorohydrin proceeds faster and in better yield than that of benzhydryl amine. This would also be advantageous in special cases, where hydrogenolysis may not be feasible because of the presence of other groups, e.g., nitro. Utilization of **6** in the synthesis of various important azetidines is reported.

Compound **6** was selectively hydrolyzed by aqueous K_2CO_3 as reported[7] to give the 3-hydroxy derivative, **8**, which was oxidized with pyridinium dichromate in refluxing dichloroethane to give hitherto unknown *N*-acetyl-3-azetidinone, **9**. Compound **9** offers the potential for further functionalization of the azetidine ring system. It has been identified as a suitable precursor to polyoximic acid, an amino acid constituent of polyoxin A.[18] Treatment of **9** with hydroxylamine led to the smooth formation of its derived oxime, **9a**.

Scheme 3



Scheme 4



Additionally, the acetyl group in **6** is quite labile and is easily nitrolized with concd nitric acid to *N*-nitro-3-acetoxyazetidine, **10**. Compound **10** was hydrolyzed to *N*-nitro-3-azetidinol, **11**, which was oxidized with PCC to give *N*-nitro-3-azetidinone, **12**, whose spectral data match that reported for this compound.[2c] **3**-Azetidinones are important intermediates for further functionalization of the azetidine ring. However, not many 3-azetidinones are known because of the difficulties inherent in obtaining the corresponding 3-azetidinols or appropriate diazoketones that can be cyclized.[19]

The acylative dealkylation appears to be quite general. *N*-*tert*-Butyl-3,3-dinitroazetidine, **13**,[15a] reacted with acetic anhydride under Lewis acid catalysis to give *N*-acetyl-3,3-dinitroazetidine, **14**, in 90% yield. The structure of the product was determined by the NMR spectral characteristics and additionally confirmed by X-ray crystallography.[20]

In conclusion, a novel, simple and efficient method for the acylative dealkylation of *N*-*tert*-butylazetidines has been developed. As a result, such key intermediates as azabicyclobutane, 3-hydroxyazetidine hydrochloride, and 3-azetidinones are now readily accessible.

Experimental Section

All yields are unoptimized. Melting points are uncorrected. Elemental microanalysis was performed by Galbraith Laboratories, Inc., Knoxville, TN. *N*-*tert*-Butyl-3-chloroazetidine, **1**,[3] *N*-*tert*-butylazetidinol, **5**,[6] and *N*-*tert*-butyl-3,3-dinitroazetidine, **13**,[15a] were prepared by literature precedents. The spectral data for **3**,[1] **6**,[7] **7**,[8] **8**,[7] and **12**[2c] were identical to that reported in the literature.

***N*-Acetyl-3-chloroazetidine, 2.** To a solution of *N*-*tert*-butyl-3-chloroazetidine, (10 g, 67.7 mmol) in acetic anhydride (30 mL) was added boron trifluoride etherate (1mL). The

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resulting solution was heated at 115 °C for 4 h. The reaction mixture was cooled to room temperature and vacuum distilled to give *N*-acetyl-3-chloroazetidine (7.4 g, 82%) as a viscous oil: bp 110−115 °C, 2.5 mm; ^{1}H NMR ($CDCl_3$) δ1.6 (s, 3H), 4.1−4.6 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.8, 44.2, 58.4, 60.6, 170.6; HRMS (FAB) *m/z* 134.0373 [$(M + H)^+$, calcd for C_5H_9NOCl 134.0373].

Azabicyclobutane, 3,[1] and 3-Chloro-*N*-carbethoxyazetidine, 4. To a solution of aqueous KOH (10%, 50 mL) heated at 80 °C in a distillation apparatus was added **2** (1.4 g, 10 mmol) in one portion. Water aspirator vacuum was applied and the distillate collected for 1 h. The aqueous distillate was extracted with $CDCl_3$ (3 × 10 mL). The organic extracts were combined and dried over $MgSO_4$. ^{1}H and ^{13}C NMR spectra of this solution were identical to that reported for azabicyclobutane. In order to determine the yield, excess ethyl chloroformate was added to the solution. An immediate exothermic reaction occurred. The mixture was stirred for 1 additional h and then concentrated in vacuo to give 3-chloro-*N*-carbethoxyazetidine, **4** (0.87 g, 50%): ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3H), 4.0−4.6 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 14.5, 45.0, 59.6, 61.2, 156.2.

***N*-Acetyl-3-acetoxyazetidine, 6.**[7] To ice-cooled acetic anhydride (190 mL) in a round-bottom flask equipped with a drying tube was added in portions *N-tert*-butyl-3-azetidinol (50 g, 387 mmol). Boron trifluoride etherate (5 mL) was injected dropwise. A refluxing condenser was attached and the reaction mixture was heated at 115 °C overnight. The reaction mixture was then fractionally distilled under vacuum to obtain **6** as a colorless oil (58 g, 95%): bp 120−25 °C (∼2 mm) (lit.[7] bp 90 °C/0.05 mm); ^{1}H NMR ($CDCl_3$) δ 1.9 (s, 3H), 2.1 (s, 3H), 3.9−4.5 (m, 4H), 5.2 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 19.2, 20.9, 54.9, 57.7, 63.0, 170.5, 170.7.

3-Hydroxyazetidine Hydrochloride, 7.[8] To **2** (7 g, 44.6 mmol) was added 5% aqueous HCl (100 mL), and the resulting solution was heated under reflux for 4 h. The cooled reaction mixture was concentrated on a rotary evaporator connected to a vacuum pump. Toluene (25 mL) was added to the residue and again concentrated to yield 3-hydroxyazetidine hydrochloride (4.9 g, 100%) as a colorless solid. A small sample was recrystallized from methanol/acetone to give **7** as colorless needles: mp 90−91 °C (lit.[8] mp 91−92 °C).

***N*-Acetyl-3-hydroxyazetidine, 8.**[7] To **6** (10 g, 63.7 mmol) were added 100% aqueous potassium carbonate (100 mL), and methanol (100 mL) and the mixture was heated under reflux for 1 h. The cooled reaction mixture was concentrated in vacuo, and the residue was extracted with methylene chloride (3 × 50 mL). The combined organics were dried over magnesium sulfate and concentrated under reduced pressure to give **8** as a viscous oil that solidified in the freezer overnight (7 g, 95%): ^{1}H NMR ($CDCl_3$) δ1.9(s, 3H), 3.8−4.3 (m, 4H), 4.6 (m, 1H); ^{13}C NMR ($CDCl_3$) δ18.6, 57.4, 59.8, 59.9, 170.8.

***N*-Acetyl-3-azetidinone, 9.** To a solution of **8** (2 g, 17.4 mmol) in 1,2-dichloroethane was added pyridinium dichromate (9 g, 23.4 mmol) under dry atmosphere. The resulting suspension was heated under reflux overnight. The cooled reaction mixture was passed through a short column of Florisil, and the residue was washed through with acetone. The combined organics were concentrated under reduced pressure, and the residue was chromatographed on silica gel, eluting with 40% acetone in hexanes. The relevant fractions were combined and concentrated in vacuo to give pure **9** as a colorless oil (1.2 gm, 61%): ^{1}H NMR ($CDCl_3$) δ 2.1 (s, 3H), 4.8 (bs, 2H), 4.9 (bs, 2H); ^{13}C NMR ($CDCl_3$) δ 20.8, 70.4, 71.4, 170.8, 194.8; HRMS (FAB) *m/z* 114.0554 [$(M + H)^+$, calcd for $C_5H_8NO_2$ 114.0555].

***N*-Acetyl-3-oximidoazetidine, 9a.** To a solution of **9** (1 g, 8.8 mmol) in absolute ethanol (20 mL) was added hydroxylamine hydrochloride (0.7 g, 10 mmol) and sodium acetate trihydrate (2.4 g, 17.6 mmol), and the resulting suspension was heated under reflux for 3 h. The reaction mixture was then concentrated under reduced pressure. Ice-cold water (1 mL) was added, and the mixture was filtered to provide **9a** as a colorless solid (0.65 gm, 57%). Recrystallization from acetone afforded **9a** as a colorless micrcocrystalline solid: mp 220−21 °C dec; ^{1}H NMR (CD_3COCD_3) δ 1.9 (s, 3H), 4.5 (m, 2H), 4.8 (m, 2H); ^{13}C NMR (CD_3COCD_3) δ 20.28, 56.95, 57.09, 59.39, 59.44, 146.16, 146.19, 170.82, 170.91; HRMS (FAB) *m/z* 129.0666 [$(M + H)^+$, calcd for $C_5H_9N_2O_2$ 129.0664]. Anal. Calcd for $C_5H_8N_2O_2$: C, 46.87; H, 6.29; N, 21.86. Found: C, 46.68; H, 6.81; N, 21.36.

***N*-Nitro-3-acetoxyazetidine, 10.** To a mixture of *N*-acetyl-3-acetoxyazetidine (12 g, 76 mmol) in acetic anhydride (30 mL) was added ammonium nitrate (8 g, 100 mmol). The resulting suspension was slowly heated in an oil bath at 75 °C. CAUTION: Higher temperatures lead to a vigorous exotherm. The mixture was heated overnight. The cooled mixture was then vacuum distilled to give pure 10 (11 g, 90%) boiling at 95−100 °C at 2 mm pressure. The compound solidifies in the condenser. Recrystallization from acetone/hexanes afforded needles: mp 61−63 °C; ^{1}H NMR ($CDCl_3$) δ 2.1 (s, 3H), 4.3−4.75 (m, 4H), 5.1 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.9, 60.6, 63.8, 170.6; HRMS (FAB) *m/z* 161.0554 [$(M + H)^+$, calcd for $C_5H_9N_2O_4$ 161.0562]. Anal. Calcd for $C_5H_8N_2O_4$: C, 37.50; H, 5.04; N, 17.49. Found: C, 37.61, H, 5.40, N, 17.15.

***N*-Nitro-3-azetidinol, 11.** To *N*-nitro-3-acetoxyazetidine (10 g, 62.5 mmol) was added aqueous HCl (5%, 200 mL). The resulting solution was heated under reflux for 2 h. The cooled mixture was then concentrated under reduced pressure to give *N*-nitro-3-azetidinol (6.5 g, 100%) as a colorless waxy solid: ^{1}H NMR ($CDCl_3$) δ 3.8 (s, 1H), 4.2 (m, 2H), 4.5 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 58.7, 66.8; HRMS (FAB) *m/z* 119.0460 [$(M + H)^+$, calcd for $C_3H_7N_2O_3$ 119.0457].

***N*-Nitro-3-azetidinone, 12.**[2c] To a suspension of PCC (1.5 g, 7 mmol) and sodium acetate trihydrate (0.5 g, 3.7 mmol) in methylene chloride (10 mL) was added *N*-nitro-3-azetidinol (0.5 g, 4.2 mmol). The resulting mixture was heated under reflux for 2 h. The reaction mixture was cooled, and ether (20 mL) was added. The supernatant liquid was passed through a short pad of Florisil. The residue was washed with two portions of ether (10 mL). The combined organics were concentrated, and the residue was chromatographed on silica gel, eluting with 40% acetone/hexanes to obtain **12** as a colorless solid, with spectral characteristics identical to those reported (0.25 g, 50%): mp 60−61 °C (lit.[2c] mp 61−62 °C); ^{1}H NMR ($CDCl_3$) δ 5.2 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 77.3, 190.6.

***N*-Acetyl-3,3-dinitroazetidine, 14.** To *N-tert*-butyl-3,3-dinitroazetidine, **13** (31 g, 147.7 mmol), was carefully added acetic anhydride (60 mL) followed by boron trifluoride etherate (2 mL) via syringe. The mixture was heated at 115 °C overnight under nitrogen atmosphere. Excess acetic anhydride was removed by vacuum distillation, and the residue was poured into ice−water. A dark colored solid separated, which was purified by passing through a short column of silica gel eluting with 20% acetone in hexanes. The eluent was concentrated, and the residue was recrystallized from methylene chloride/hexanes to give pure **14** (25 g, 90%): mp 111−112 °C; ^{1}H NMR ($CDCl_3$) δ 2.0 (s, 3H), 4.8 (bs, 2H), 5.0 (bs, 2H); ^{13}C NMR ($CDCl_3$) δ 19.5, 57.4, 59.0, 105.7, 170.9; HRMS (FAB) *m/z* 190.0462 [$(M + H)^+$, calcd for $C_5H_8N_3O_5$ 190.0464]. Anal. Calcd for $C_5H_7N_3O_5$: C, 31.75; H, 3.73; N, 22.22. Found: C, 31.90; H, 3.88; N, 21.81.

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Supporting Information Available: ^{13}C NMR spectra of compounds **2**, **4**, **6**, **9**, **9a**, **10**, **11**, and **14** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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