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Intramolecular Schmidt Reactions of Alkyl Azides with Ketals and Enol Ethers

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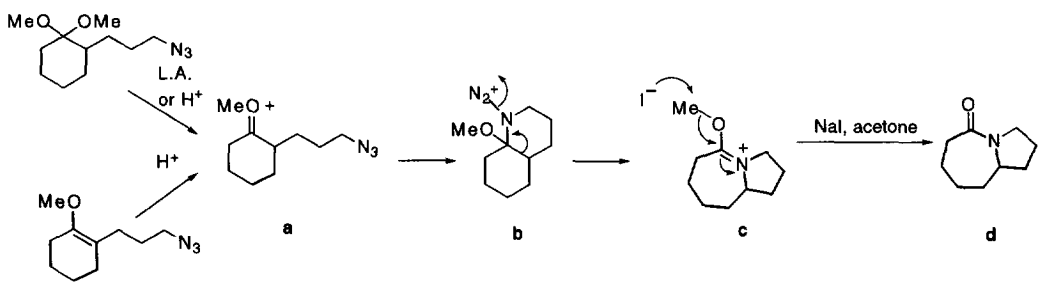
Abstract: The ketals or enol ethers of 1,5-azidoketones were converted into lactams using a two-stage process. Treatment of the ketals and enol ethers with acid (trifluoroacetic acid, triflic acid, or trimethylsilyl triflate) afforded an oxonium ion which reacted with the tethered azide to give a 1,1-azido-alkoxy intermediate. Bond reorganization led to an iminium ether that was reacted with sodium iodide in acetone to expose the amide products. Seven intramolecular examples proceeding in yields of 68 to ≥95% are reported using dimethyl or diethyl ketals. Attempts using 1,3-dioxolanes and an intermolecular example are also described.

The Schmidt rearrangement is used widely for converting acyclic and cyclic ketones into *N*-unsubstituted amides and lactams, respectively.[1] Early attempts to extend the general scope of the Schmidt reaction to include alkyl azides (resulting in *N*-substituted amides) failed,[2] although some low-yielding exceptions have been reported.[3] More recently, Schmidt reactions of alkyl azides with ketones[4] have been realized using intramolecularity, strong Lewis acids, or both. In addition, Schmidt reactions of alkyl azides with cations derived from alkenes or alcohols have proved facile in both intra- and intermolecular examples.[5]

In this paper, we describe the extension of this chemistry to ketals and enol ethers. Since enol ethers and especially ketals are commonly used as protecting groups for ketones, the direct reaction of these moieties in the intramolecular Schmidt route might result in the streamlining of some synthetic sequences. In addition, we were interested to see whether improvements in yields or scope (relative to the direct reactions with ketones) might be possible using this strategy. Ketone equivalents have been utilized in a variety of synthetic strategies, e.g. Lewis acid-mediated reactions of acetals with a variety of nucleophiles.[6] Specifically relevant are syntheses of *N*-substituted lactams from activated ketals using *N*-(*p*-nitrobenzenesulfonoxy)alkylamine[7] and alternative Schmidt-type reactions of enol ethers.[8]

Scheme 1

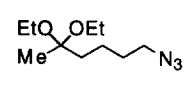
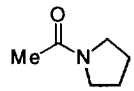
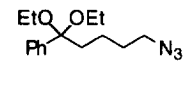
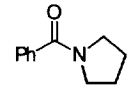
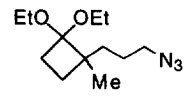
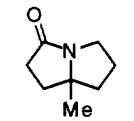
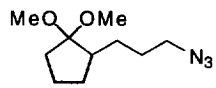
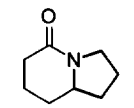
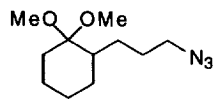
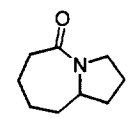


Although the reactions of ketones with alkyl azides afford lactams directly, dimethyl ketals or enol ethers would be expected to react via carbocation **a** and then intermediate **b**. Bond migration in **b** would result in iminium ether **c**; among several possibilities, revealing the target lactam by nucleophilic attack by I^- in acetone had precedent in the work of Hoffman.[7]

A brief survey of the utilization of ketals in the intramolecular Schmidt reaction was undertaken. Dimethyl or diethyl ketals were prepared in the usual way (ROH, $(RO)_3CH$, *p*-TsOH) from the corresponding 2-(3'-azidopropyl) ketones. These ketones (i.e., those with 4 carbons between the azide and ketone) were previously found to be optimal substrates in the intramolecular Schmidt reaction.[4a,e]

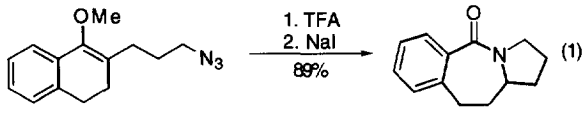
Ketal activation was accomplished with trifluoroacetic acid (TFA) or trimethylsilyl triflate (TMSOTf) in CH_2Cl_2 (Table 1). In either case, gas evolution was observed and the reaction allowed to proceed overnight. At this time, the solvent was removed in vacuo and the crude residue treated with a solution of NaI in acetone. An aqueous bicarbonate workup delivered the target lactams in good to excellent yields. For comparison, the yields of the reactions beginning with the starting ketone using TFA promotion are given in parentheses.

Table 1. Reactions of Alkyl Azides with Ketals

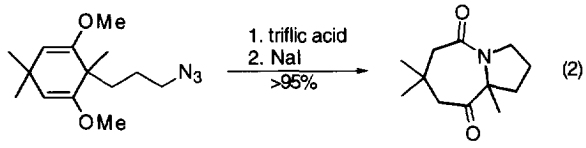
entry	starting material	product	acid	yield (%)[a]
1	 **1**	 **2**	TMSOTf	81 (75)
2	 **3**	 **4**	TFA	79 (77)
3	 **5**	 **6**	TFA	68 (66)
4	 **7**	 **8**	TMSOTf	94 (83)
5	 **9**	 **10**	TFA	72 (85)

[a]Yields from the corresponding ketones using TFA are enclosed in parentheses.

Two reactions using methyl enol ethers were carried out as shown in eq 1 and 2. In these cases, simple protonation generates the necessary oxonium ion (**a** in Scheme 1) and therefore protic acids (triflic acid or TFA) were used. Lactams were obtained in excellent yields, although it was not possible to prevent hydrolysis of the non-reacting enol ether in **13** (eq 2). It is conceivable that the acidic conditions promote hydrolysis to ketones that then undergo ring expansion. However, this seems unlikely in light of the fact that no lactam products were observed (TLC) prior to the iodide dealkylation step.



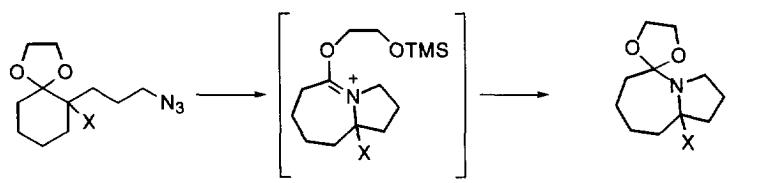
11 **12**



13 **14**

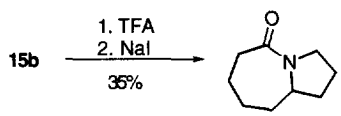
We wished to examine the effect of using a cyclic ketal (Scheme 2). In this case, TMSOTf treatment of **15a** directly gave amide acetal **16a** in 94% yield without using a dealkylation step. The reaction presumably proceeds via the iminium ether shown, followed by intramolecular attack of the appended TMS ether onto the carbocationic center. The phenylthio substituent, unexpectedly, plays an important role here: in its absence, the reaction failed. However, treatment of the 1,3-dioxolane derived from 2-(3'-azidopropyl)-cyclohexanone **15b** with TFA followed by NaI gave **10** in 35% yield. This low yield (cf. entry 5, Table 1) may be due to the relative ease of dealkylation of ketals derived from less sterically demanding alcohols.

Scheme 2



15a, X = SPh
15b, X = H

16a, X = SPh, 94% yield
16b, X = H, not formed



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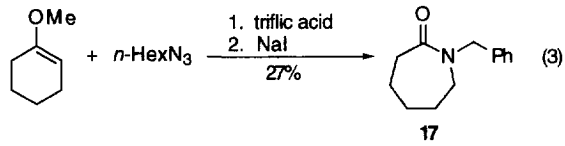
We had hoped that the use of ketals or enol ethers would improve the facility of intermolecular reactions with alkyl azides as well.[4] Unfortunately, the only glimmer of success came with the example shown in eq 3; still, even this modest yield surpassed those obtained from the corresponding reactions of cyclohexanone with *n*-hexyl azide under similar conditions (ca. 0%).



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Summary. Overall, these protocols complement previously described ketone azide reactions and extend the synthetic utility of intramolecular Schmidt chemistry. A comparison of the results obtained herein with our previously reported reactions of alkyl azides with ketones indicates that little additional value is obtained by using ketals or enol ethers in terms of yields or generality of substrate. Still, the ability to directly utilize ketals in the intramolecular Schmidt reaction is likely to streamline its application to total synthesis.

Experimental Section

General experimental procedures and syntheses of the starting ketones are available in reference 4e.

General Procedure for Ketal or Enol Ether Formation. 2-(3'-Azidopropyl)-1,1-dimethoxycyclohexane (9). A solution of 2-(3'-azidopropyl)-1-cyclohexanone (0.252 g, 1.39 mmol), trimethyl orthoformate (0.521 g, 4.91 mmol), methanol (0.170 g, 5.18 mmol), and *p*-toluenesulfonic acid (0.03 g, 0.1 mmol) was stirred at 70 °C for 3 h. The solution was concentrated and then partitioned between Et_2O (50 mL) and saturated $NaHCO_3$ (5 mL). The organic layer was washed with saturated NaCl and dried over anhydrous $NaSO_4$. Flash chromatography (5% EtOAc/hex) afforded the title compound as a clear oil (0.260 g, 82%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.31-1.83 (m, 13H), 3.14 (s, 3H), 3.16 (s, 3H), 3.26 (m, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 19.8, 22.4, 23.7, 24.9, 27.3, 27.8, 38.9, 47.0, 47.3, 51.6, 101.8; IR (neat) 2920, 2080 cm^{-1}; MS (CI) *m/e* 184, 168. Anal. Calcd for $C_{11}H_{21}N_3O_2$: C, 58.12; H, 9.31; N, 18.48, found: C, 58.05; H, 9.00; N, 18.80.

6-Azido-2,2-diethoxyhexane (1). Prepared as described for **9**, except using EtOH and (EtOH)3CH (3.49 g, 76%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (t, *J* = 7.1 Hz, 6H), 1.29 (s, 3H), 1.43 (m, 2H), 1.56-1.67 (m, 4H), 3.29 (t, *J* = 6.8 Hz, 2H), 3.45 (m, 4H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 15.4, 21.5, 22.0, 29.0, 37.0, 51.3, 55.5, 101.2; IR (neat) 2960, 2090, 1100 cm^{-1}. Anal. Calcd for $C_{10}H_{21}N_3O_2$: C, 55.78; H, 9.75; N, 19.50; found: C, 55.55; H, 10.00; N, 19.42.

5-Azido-1,1-dimethoxy-1-Phenylpentane (3). Prepared as described for **9** (0.510 g, 82%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (m, 2H), 1.44 (quintet, *J* = 7.2 Hz, 2H), 1.86-1.91 (m, 2H), 3.14 (s, 6H), 3.13 (partially obscured t, *J* = 4.5 Hz, 2H), 7.24-7.36 (m, 3H), 7.41-7.45 (m, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 20.6, 28.6, 36.6, 48.5, 51.0, 103.3, 126.8, 127.8, 127.9, 140.5; IR (neat) 2960, 2875, 1620, 1420 cm^{-1}; MS m/e 218 (M - CH_3O); Anal. Calcd for $C_{13}H_{19}N_3O_2$: C, 62.62; H, 7.62; N, 16.85; found: C, 62.82; H, 7.91; N, 17.01.

2-(3'-Azidopropyl)-1,1-diethoxy-2-methylcyclobutane (5). Prepared as described for **9** (0.151 g, 72%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.12 (s, 3H), 1.15-1.78 (m, 12H), 1.95-2.12 (m, 2H), 3.26-3.47 (m, 6H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 15.2, 15.3, 20.4, 24.4, 25.5, 27.4, 33.0, 48.4, 52.2, 57.0, 57.4, 103.8; IR (neat) 2970, 2920, 2870, 2090 cm^{-1}; MS (CI) *m/e* 196, 168. Anal. Calcd for $C_{12}H_{23}N_3O_2$: C, 59.72, H; 9.60; N, 17.41; found: C, 59.82; H, 9.75; N,17.60.

2-(3'-Azidopropyl)-1,1-dimethoxycyclopentane (7). Prepared as described for **9** (0.86 g, 72%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.12-1.93 (m, 11H), 3.17 (s, 3H), 3.22 (s, 3H), 3.27 (m, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 20.7, 27.4, 27.8, 29.7, 33.4, 43.9, 48.1, 49.7, 51.5, 111.4; IR (neat) 2950, 2090 cm^{-1}. Anal. Calcd for $C_{10}H_{19}N_3O_2$: C, 56.25; H, 8.97; N, 19.68; found: C, 56.10; H, 9.18; N, 19.29.

2-(3'-Azidopropyl)-1,2-dihydro-1-methoxy-naphthalene (11). Prepared as described for **9** (0.525 g, 99%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73 (quintet, J = 7.0 Hz, 2H), 2.24 (t, J = 7.6 Hz, 2H), 2.38 (t, J = 7.6 Hz, 2H), 2.73 (t, J = 7.9 Hz, 2H), 3.28 (t, J =7.0 Hz, 2H), 3.61 (s, 3H), 7.10-7.22 (m, 3H), 7.31 (d, J = 7.3 Hz, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 26.5, 27.0, 27.1, 27.9, 51.1, 59.6, 121.3, 123.7, 126.3, 126.6, 127.2, 131.4, 136.5, 149.0; IR (neat) 2930, 2090, 1295 cm^{-1}; MS (EI) *m/e* 241 (M^+ + H), 202. Anal. Calcd for $C_{14}H_{17}N_3O$: C; 69.13; H; 6.99; N; 17.28, found: C; 69.14; H; 7.00; N, 17.30.

2-(3'-Azidopropyl)-1,3-dimethoxy-2,5,5-trimethyl-1,3-cyclohexadiene (13). Prepared as described for **9** (0.084 g, 93%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 6H), 1.22 (s, 3H), 1.23-1.35 (m, 2H), 1.58-1.64 (m, 2H), 3.16 (t, J = 7.1 Hz, 2H), 3.50 (s, 6H), 4.51 (s, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 24.8, 25.5, 31.7, 33.1, 33.3, 42.6, 51.6, 51.7, 54.3 (2 signals), 103.6, 154.3; IR (neat) 2940, 2080, 1680 cm^{-1}. Anal. Calcd for $C_{14}H_{23}N_3O_2$: C, 63.37; H, 8.74; N, 15.84; found: C, 63.17; H, 8.76; N, 16.11.

6-(3'-Azidopropyl)-6-phenylthio-1,4-dioxa[4.5]decane (15a). To 2-(3'-azidopropyl)-2-phenylthio-1-cyclohexanone (0.510 g, 1.70 mmol) in 13 mL of benzene and 2.0 mL of ethylene glycol was added *p*-TsOH (0.031 g, 0.173 mmol). The two-phase solution was stirred at reflux using a condenser equipped with a Dean-Stark trap for 3 h. Workup (Et_2O/$NaHCO_3$) followed by chromatography (2.5% EtOAc/hex) gave the title compound (0.295 g, 51%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20-1.45 (m, 1H), 1.52-2.08 (m, 11H), 3.06-3.11 (m, 2H), 3.99-4.14 (m, 4H), 7.27-7.31 (m, 3H), 7.58-7.61 (m, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 21.2, 23.0, 23.8, 30.5, 31.8, 34.0, 51.8, 60.8, 64.9, 65.4, 112.1, 128.3, 132.1, 137.0; IR (neat) 2930, 2080, cm^{-1}; MS (EI) *m/e* 333 (M^+), 306, 262. Anal. Calcd for $C_{17}H_{23}N_3O_2S$: C, 61.23; H, 6.95; N, 12.60; found: C, 61.58; H, 7.20; N, 12.78.

6-(3'-Azidopropyl)-1,4-dioxa[4.5]decane (15b). Prepared as described for **15a** (1.03 g, 99%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34-1.80 (m, 13H), 3.22-3.27 (m, 2H), 3.90-3.99 (m, 4H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 23.7, 24.4, 23.7, 27.0, 29.1, 34.5, 44.2, 51.8, 64.5, 64.7, 110.5; IR (neat) 2980, 2940, 2860, 2090 cm^{-1}; MS (EI) *m/e* 225 (M^+), 183; Anal. Calcd for $C_{11}H_{19}N_3O_2$: C, 58.64; H, 8.50; N, 18.65; found: C, 58.54; H, 8.90; N, 19.00.

General Procedure for Intramolecular Schmidt reactions. 1-Benzoylpyrrolidine (4). To 5-azido-1,1-dimethoxy-1-phenylpentane **3** (0.230 g, 0.92 mmol) in 1.0 mL of CH_2Cl_2, cooled to 5 °C, was added 1.0 mL of trifluoroacetic acid, resulting in a vigorous evolution of gas. The solution was stirred for 16 h at ambient temperature, the solvent then removed in vacuo, and replaced with a solution of sodium iodide (0.276 g, 1.85 mmol) in 2 mL of anhydrous acetone. After stirring at 70 °C for 4 h, the reaction mixture was partitioned between EtOAc and $NaHCO_3$. The organic layer was separated and washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give an oil. Flash chromatography (EtOAc) afforded **4**[4e] as a yellow oil (0.137 g, 79%).

Synthesis of 2 and 8. Known[4e] compounds **2** and **8** were prepared as described for **4**, substituting 1.25 equiv. of TMSOTf for TFA: **1** (0.749 g)→**2** (0.320 g, 81%), **7** (0.190 g)→**8** (0.116 g, 94%).

Synthesis of Lactams 6, 10, 12, and 14. The following known[4e] compounds were prepared as described for **4**: **5** (0.131 g)→**6** (0.051 g, 68%), **9** (0.380 g)→**10** (0.185 g, 72%), **11** (0.190 g)→**12** (0.139 g, 89%), **13** (0.084 g)→**14** (0.049 g, ≥95%).

Hexahydro-4-(phenylthio)-pyrrolo[1,2-a]azepine-9-one ethylene glycol ketal (16a). To ketal **15a** (0.087 g, 0.26 mmol) in 1 mL of CH_2Cl_2, cooled to 5 °C, was added TMSOTf (0.17 g, 0.765 mmol) dropwise, resulting in a vigorous evolution of gas. The solution was stirred at 5 °C for 20 min and ambient temperature for 20 min. Workup and chromatography as described for **4** gave a clear oil (0.075 g, 94%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (m, 1H), 1.58-1.93 (m, 7H), 2.20 (m, 1H), 2.40 (m, 1H), 2.55-2.70 (m, 2H), 3.24 (m, 1H), 3.37 (td, J = 3.9, 13.0 Hz, 1H), 3.98-4.18 (m, 4H), 7.26-7.31 (m, 3H), 7.58 (m, 2H);

^{13}C NMR (75.6 MHz, $CDCl_3$) δ 23.6, 25.7, 29.9, 38.7, 39.5, 49.2, 50.4, 57.5, 62.7, 65.4, 115.9, 128.1, 128.2, 133.1, 137.5; IR (neat) 3810, 1460, 1440 cm^{-1}; MS (EI) *m/e* 305 (M^+), 196; HRMS calcd for $C_{17}H_{24}NO_2S$: 306.1528, found: 306.1531.

Hexahydro-1-hexyl-2*H*-azepin-2-one (17). To 1-methoxy-1-cyclohexene[9] (0.30 g, 2.67 mmol) and 1-azidohexane[4b] (0.679 g, 5.35 mmol) in 5 mL of CH_2Cl_2, cooled to 5 °C, was added triflic acid (0.601 g, 4.0 mmol) dropwise, resulting in a slow evolution of gas. The solution was stirred at ambient temperature for 16 h. Removal of the solvent in vacuo was followed by addition of 2 mL of anhydrous acetone and sodium iodide (0.801 g, 5.35 mmol). Workup (EtOAc/$NaHCO_3$) followed by chromatography (50% EtOAc/hex) gave **18**[4b] (0.145 g, 27%).

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References and Notes

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