Synthesis of Functionalized *N*-Alkyl Heterocycles from Ketones by a Sequential Ring Expansion/Nucleophilic Addition Process

Vijaya Gracias, Gregory L. Milligan, and Jeffrey Aubé*

Department of Medicinal Chemistry, University of Kansas, Lawrence, Kansas 66045-2506

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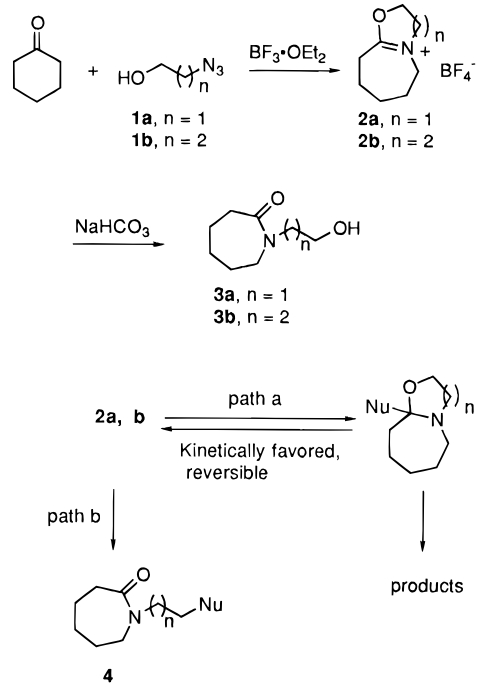
The utility of the Schmidt reaction[1] in heterocyclic chemistry has been expanded by the discovery of variants that use alkyl azides as nucleophiles.[2] The intermolecular reaction of alkyl azides with ketones was initially limited by the types of ketones and azides that would react in high yield.[2b] This ceiling was largely lifted by the realization that 1,2- or 1,3-hydroxy azides were superior to simple alkyl azides as Schmidt reaction partners.[2i] In these reactions, initial hemiketal formation rendered the azide addition step intramolecular (Scheme 1). The primary reaction products were iminium ethers **2a** or **2b** that could be transformed into *N*-hydroxyalkyl lactams by the addition of hydroxide ion.

This report details how the scope of this sequence can be extended by exploiting the ambident electrophilicity[3] of iminium ethers like **2a** and **2b**. *N*-Alkyloxazolinium salts, usually prepared by alkylation of lactams, imides, or oxazolines, can be reacted with heteroatom or carbon nucleophiles[4] via the two pathways indicated in Scheme 1; a related pathway operates in the cationic polymerization[5] of oxazolines. Kinetic attack occurs at the formally positive carbon giving a neutral intermediate

Scheme 1



(path a) that can render product but that may also revert to the relatively stable **2**. Thus, the reversible addition of nucleophiles at this center may ultimately result in attack at the distal end of the N−O tether, as shown in path b.

Of course, one of these pathways was already demonstrated in the aqueous base workup leading to lactam products **3**, with HO^- as the nucleophile.[2i] Iminium ethers **2a** and **2b** were prepared from cyclohexanone as previously reported and treated with a variety of nucleophilic reagents. Most heteroatom-based nucleophiles gave functionalized *N*-alkyl lactams by reacting through path b (Table 1). In this way, azides, alcohols, ethers, sulfides, and halides could be directly obtained from the activated lactams formed in the Schmidt reaction. In addition, carbon−carbon bonds were formed in good yields by the addition of nitrile or the anion of bis(phenylsulfonyl)methane.

The regiochemistry of carbon nucleophilic addition depended on the nature of the anion-stabilizing groups.[6] Thus, in contrast to the result in entry 5 (Table 1), $NaCH(CN)_2$ reacted only via path a followed by elimination, yielding **5** (Scheme 2). As previously reported,[6c] the anion of dimethyl malonate gave reaction by path b but afforded O-alkylation material. Reductions also utilized path a to lead directly to the fully reduced tertiary amines. Besides the sodium borohydride reaction shown, catalytic hydrogenation conditions also afforded **6** in 87% yield. These mild conditions stand in contrast to the usual reductions of lactams with lithium aluminum hydride or borane reagents. In these reactions, the iminium ethers were reacted without isolation; see, for example, the direct formation of **7** from 2-methoxycyclohexanone in 64% overall yield. In general, the reactions given in Table 1 could also be carried out on iminium ethers

* To whom correspondence should be addressed: Tel: (913) 864-4496. Fax: (913) 864-5326. E-mail: jaube@rx.pharm.ukans.edu.

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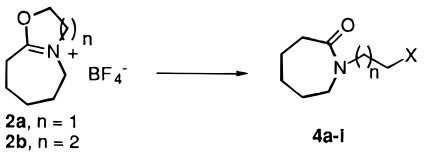
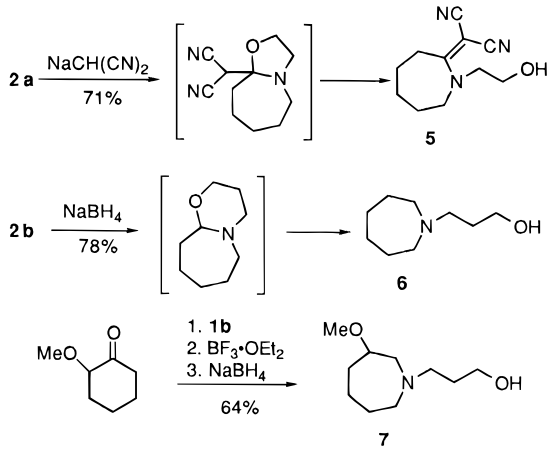
Table 1. Nucleophilic Addition Reactions to 2a,b



entry	iminium ether	nucleophile	X	product	yield (%)
1	**2a**	NaOH	−OH	**3a**	98[a]
2	**2b**			**3b**	90[a]
3	**2a**	NaCN	−CN	**4a**	82
4	**2a**	$NaCH(CO_2Me)_2$	$-OCOCH_2COOMe$	**4b**	34
5	**2a**	$NaCH(SO_2Ph)_2$	$-CH(SO_2Ph)_2$	**4c**	54
6	**2a**	NaN_3	$-N_3$	**4d**	85
7	**2b**	NH_2NMe_2	$-NHNMe_2$	**4e**	88
8	**2a**	NaOPh	−OPh	**4f**	74
9	**2a**	NaSPh	−SPh	**4g**	95
10	**2a**	$(n\text{-}Bu)_4N^+Ph_3SiF_2^-$ [b]	−F	**4h**	64
11	**2a**	$(n\text{-}Bu)_4N^+I^-$	−I	**4i**	55

[a] See reference 2i for full description of reaction conditions and spectral data. [b] Reference 8.

Scheme 2



generated in situ from a ketone and an azido alcohol, but higher overall yields were obtained when the intermediate salt was isolated.

In conclusion, the continuing evolution of the classical Schmidt reaction to include direct routes to N-substituted lactams[7] has been continued by the present work. The extension of these ideas to other classes of nucleophiles is a matter of continuing concern to this laboratory.

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Supporting Information Available: Experimental details and characterization data for compounds **4a**,**b**,**d**−**i** and **5**−**7**, including copies of ^1H and ^{13}C NMR spectra for compounds (27 pages).

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(7) The reaction of **2b** with the anion of bis(phenylsulfonyl)methane is representative. Bis(phenylsulfonyl)methane (657 mg, 2.22 mmol) in THF (20 mL) was added to NaH (60% in mineral oil, 93 mg, 2.23 mmol) in THF (10 mL) at 0 °C, and the reaction mixture was stirred for 15 min. A solution of **2b** in DMF (2 mL) was introduced (the synthetic procedure for **2b** can be found in the supporting information for ref 2i). The reaction mixture was allowed to warm to room temperature over 1 h and was stirred at room temperature for an additional 17 h. The reaction was quenched by pouring it into water (5 mL) and extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with brine (5 mL), dried (anhyd Na_2SO_4), and concentrated to afford a white solid. Chromatography (65% EtOAc/hexane) gave 593 mg (54%) of **4c** as a white crystalline solid: R_f 0.43 (65% EtOAc/Hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 1.60−1.75 (m, 6H), 2.42 (m, 4H), 3.18 (m, 2H), 3.58 (t, J = 5.5 Hz, 2H), 5.17 (t, J = 4.9 Hz, 1H), 7.51−7.97 (m, 10H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 22.9, 24.5, 27.8, 29.7, 36.9, 46.7, 49.5, 79.7, 128.9, 129.3, 134.2, 138.0, 177.1; IR (KBr) 2900, 1620 cm^{-1}; MS (EI) m/e 436 ($M^+ + 1$), 294, 153, 140, 126; HRMS calcd for $C_{21}H_{25}NO_5S$ + H 436.1252, found 436.1270. Anal. Calcd for $C_{21}H_{25}NO_5S$: C, 57.91; H, 5.79; N, 3.22. Found: C, 57.50; H, 5.66; N, 3.10.

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