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Synthesis of α-Amino-α′-diazomethyl Ketones via Ring Opening of Substituted Cyclopropanones with Alkyl Azides. A Facile Route to *N*-Substituted 3-Azetidinones

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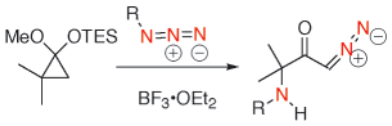
ABSTRACT



The reaction of alkyl azides with triethyl(1-methoxy-2,2-dimethyl-cyclopropoxy)silane affords a series of α-amino-α′-diazomethyl ketones in moderate yields (38–54%). The mechanism of this novel process is discussed. The diazomethyl ketones could also be cyclized to the corresponding *N*-substituted 3-azetidinones in good yield upon treatment with $Rh_2(OAc)_4$.

The chemistry of small-ring compounds continues to provide insight into basic chemical reactivity and new tools for synthesis. As part of a continuing program examining the fundamental nucleophilic reactivity of alkyl azides with ketones,[1] we investigated the Lewis acid-triggered reactions of several alkyl azides with cyclopropanone equivalents. In the corresponding reactions of standard and large ring sizes, these conditions generally lead to ring-expanded lactams in a process reminiscent of the Schmidt reaction. In this Letter, we describe the remarkable conversion of 2,2-dimethylcyclopropanone to a series of α-amino-α′-diazomethyl ketones. This process involves the ring opening of the cyclopropane between carbons 2 and 3 concurrent with the distribution of the azide nitrogen atoms to either side of the product ketone. The synthetic potential of these intermediates is briefly demonstrated by their efficient conversion to a series of 3-azetidinones.

Commonly, cyclopropanones are generated in situ from the more stable hemiketal or mixed ketal derivatives.[2] Since these species are in equilibrium with the carbonyl form under the Lewis acid conditions typically used in the Schmidt reaction of alkyl azides, triethyl(1-methoxy-2,2-dimethyl-cyclopropoxy)silane **1**[3] was treated with 2 equiv of benzyl azide and 1 equiv of BF_3•OEt_2 in CH_2Cl_2 (−78 °C → room temperature, overnight). Workup followed by chromatography provided two products. These conditions had been expected to lead to the standard Schmidt reaction product: in this case, a β-lactam. However, spectral data obtained from the major product were clearly inconsistent with 2-azetidinone formation. In particular, a lactam carbonyl could be ruled out by IR (two strong peaks at 1633 and 2099 cm^{-1} were observed) and ^{13}C NMR (201 ppm) analysis (the corresponding values for a β-lactam are ca. 1740 cm^{-1} and

(1) (a) Aubé, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965−8966. (b) Aubé, J.; Milligan, G. L.; Mossman, C. J. *J. Org. Chem.* **1992**, *57*, 1635−1637. (c) Aubé, J.; Rafferty, P. S.; Milligan, G. L. *Heterocycles* **1993**, *35*, 1141−1147. (d) Mossman, C. J.; Aubé, J. *Tetrahedron* **1995**, *52*, 3403−3408. (e) Milligan, G. L.; Mossman, C. J.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 10449−10459. (f) Gracias, V.; Frank, K. E.; Milligan, G. L.; Aubé, J. *Tetrahedron* **1997**, *53*, 16241−16252. (g) Forsee, J. E.; Smith, B. T.; Frank, K. E.; Aubé, J. *Synlett* **1998**, 1258−1260. (h) Schildknegt, K.; Agrios, K. A.; Aubé, J. *Tetrahedron Lett.* **1998**, *39*, 7687−7690.

(2) Salaun, J. *Chem. Rev.* **1983**, *83*, 619−632.

(3) Rousseau, G.; Slougui, N. *Tetrahedron Lett.* **1983**, *24*, 1251−1254.

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175 ppm, respectively). Furthermore, the mass spectrum indicated the retention of all three nitrogen atoms in the major product. In contrast, the minor product was readily identified as *N*-benzyl-2,2-dimethyl-3-azetidinone ($\nu_{C=O} = 1804$ cm^{-1}).

Intrigued, we surveyed a variety of alkyl azides in the reactions, systematically obtaining ca. 40−50% yields of the major product and occasionally noting low yields of the 3-azetidinone byproduct (Table 1). The identity of the major

Table 1. Yields of α-Amino-α-diazomethyl Ketones **2** and 2,2-Dimethyl-3-azetidinones **3** Obtained from Compound **1**

		yield (%)	
entry	R	**2**[a]	**3**[b]
a	phenyl	47 (4)	90
b	*p*-bromophenyl	41	87
c	*p*-carbomethoxyphenyl	46	77
d	2-naphthyl	38 (5)	95
e	9-anthracenyl	54	100
f	*n*-hexyl	44	72

[a] Yields of purified α-amino-α-diazomethyl ketones **2** (yields of byproducts **3** are noted in parentheses, where observed). [b] Yields of purified 2,2-dimethyl-3-azetidinones **3** as prepared by $Rh_2(OAc)_4$ treatment of precursors **2**.

product was finally secured through an X-ray crystallographic determination of the product obtained from **1** with *p*-carbomethoxybenzyl azide (**2c**, Figure 1). This finally

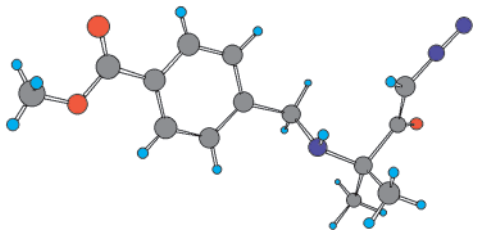
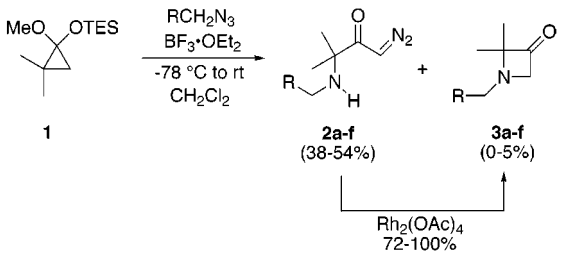


Figure 1. Ball-and-stick depiction of the X-ray determination of **2c**.

allowed us to formulate this process as depicted in Scheme 1. In addition, the occasional formation of 3-azetidinone

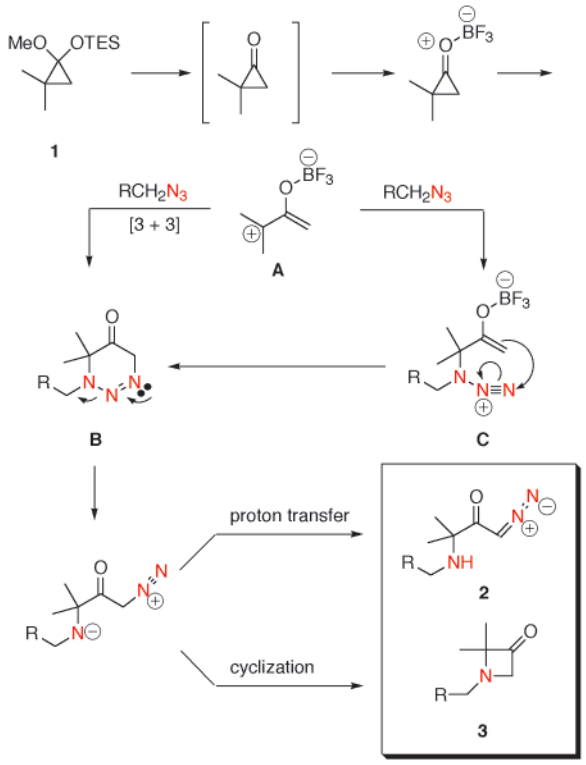
Scheme 1



suggested the possibility of generating these heterocycles from the main diazoketone products through metallocarbenoid formation.[4] As expected, treatment of diazoketones **2** with $Rh_2(OAc)_4$ afforded the azetidinones **3** in high yield as shown.

The mechanism for the reaction likely involves the known propensity of substituted cyclopropanones such as **1** to undergo cleavage of the 2,3-bond to afford 2-oxyallyl cation **A** (Scheme 2).[2,5] This intermediate could undergo a direct

Scheme 2



[3 + 3] cycloaddition with the alkyl azide to afford a 1,2,3-triazine-5-one intermediate (**B**). A stepwise process could afford the same adduct; these two pathways cannot be distinguished by our current observations. To our knowledge, the only other examples of formal [3 + 3] reactions of alkyl azides with allylic cations have been reported by Pearson.[6] In those examples, the reaction results in triazine formation followed by trapping or elimination of the resulting cation. Here, the cycloadduct subsequently undergoes ring opening

(4) (a) Baumann, H.; Duthaler, R. O. *Helv. Chim. Acta* **1988**, *71*, 1035−1041. (b) Podlech, J.; Seebach, D. *Helv. Chim. Acta* **1995**, *78*, 1238−1246. (c) Axenrod, T.; Watnick, C.; Yazdekhasti, H.; Dave, P. R. *J. Org. Chem.* **1995**, *60*, 1959−1964.

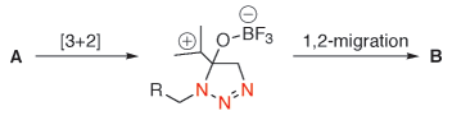
(5) (a) Turro, N. J.; Hammond, W. B. *J. Am. Chem. Soc.* **1967**, *89*, 1028−1029. (b) de Boer, T. J. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 321−322. (c) Bakker, B. H.; van Ramesdonk, H. J.; Steinberg, H.; de Boer, T. J. *Recl. Trav. Chim. Pays-Bas* **1975**, *94*, 64−69. (d) Cordes, M. H. J.; Berson, J. A. *J. Am. Chem. Soc.* **1996**, *118*, 6241−6251. (e) Hess, B. A., Jr.; Eckart, U.; Fabian, J. *J. Am. Chem. Soc.* **1998**, *120*, 12310−12315. (f) Chiba, T.; Saitoh, I.; Okimoto, M.; Tanase, T.; Yano, S. *J. Org. Chem.* **1999**, *64*, 2516−2519.

(6) Pearson, W. H.; Fang, W.-k.; Kampf, J. W. *J. Org. Chem.* **1994**, *59*, 2682−2684.

followed by proton transfer, leading to **2**. The small amounts of 3-azetidinones **3** isolated from some of these reactions could arise (1) from the direct cyclization reaction shown, (2) from the related acid-promoted decomposition of diazo compound **2**, or (3) by an alternative ring-closure pathway beginning with intermediate **C**.

Other mechanisms, including a [3 + 2] cycloaddition of the alkyl azide, followed by 1,2-migration of nitrogen to the adjacent carbocationic center, may also account for these results (Scheme 3). Further work will be done to distinguish between these various possibilities.

Scheme 3



Although known,[2,5] oxyallyl cations as obtained from cyclopropanones or their equivalents are rarely used in synthesis.[7] In addition, the mode of azide reactivity depicted herein is quite remarkable. It is especially interesting that the putative 1,2,3-triazine does not survive but instead splits the azide nitrogen atoms between an amine and a diazoketone. Diazoketones are highly useful synthetic intermediates and are normally synthesized by diazomethane addition to an acyl chloride or by diazo transfer technology.[8] The present reaction provides an alternative approach to these reactive intermediates in which the azido group, in effect, acts like an internal diazo transfer agent. In particular, α-amino-containing products **2** are useful for the formation of heterocycles such as **3** or other amino acid analogues.[9]

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Supporting Information Available: Characterization data for all new compounds and X-ray crystallographic analysis of compound **2c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) The related cyclopropenone ketals have proved to be of significant synthetic utility. For a few lead references, see: (a) Boger, D. L.; Brotherton-Pleiss. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI: Greenwich, 1990; Vol. 2, pp 147−219. (b) Tokuyama, H.; Isaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **1992**, *114*, 5523−5530. (c) Yu, Y.; Yamanaka, M.; Nakamura, E. *Org. Lett.* **1999**, *1*, 407−410.

(8) Regitz, M.; Maas, G. *Diazo Compounds: Properties and Synthesis*; Academic: Orlando, 1986.

(9) **General Experimental Procedures. 1-Diazo-3-methyl-3-phenylaminobutan-2-one (2a).** To a solution of benzyl azide (87 mg, 0.651 mmol) in 5 mL of CH_2Cl_2 at −78 °C was added triethyl(1-methoxy-2,2-dimethylcyclopropoxy)silane (75 mg, 0.326 mmol). The mixture was stirred for 10 min and $BF_3{\cdot}OEt_2$ (0.041 mL, 0.326 mmol) was added dropwise. The reaction was allowed to warm to room temperature and stirred for 20 h. The reaction was partitioned between saturated $NaHCO_3$ and CH_2Cl_2 and dried over anhydrous $MgSO_4$. Concentration followed by chromatography (20% EtOAc/hexanes) gave 67 mg of **2a** as a yellow oil (94%): $R_f = 0.06$ (20% ethyl acetate/hexanes); IR (neat) 3326, 2099, 1633 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.26 (m, 5H), 5.96 (br s, 1H), 3.66 (s, 2H), 1.60 (br s, 1H), 1.34 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 201.3, 140.7, 128.9, 128.4, 127.5, 62.6, 52.2, 48.6, 25.8; CIMS *m/z* (relative intensity) 218 (MH^+, 100), 190 (97); HRMS calcd for $C_{12}H_{16}N_3O$: 218.1293, found: 218.1268. **1-Benzyl-2,2-dimethyl-azetidin-3-one (3a).** Compound **2a** (30 mg, 0.138 mmol) in 2 mL of CH_2Cl_2 was added to a solution of $Rh_2(OAc)_4$ (3 mg, 0.007 mmol) in 2 mL of CH_2Cl_2 at 0 °C. The reaction was allowed to warm to room temperature and stirred for 20 h at which time 10 mL of water was added. The aqueous layer was partitioned between CH_2Cl_2 and brine and dried over anhydrous $MgSO_4$. Concentration followed by chromatography (20% ethyl acetate/hexanes) gave 23 mg of **3a** as a yellow oil (90%): $R_f = 0.14$ (20% ethyl acetate/hexanes); IR (neat) 2970, 1804 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25−7.39 (m, 5H), 4.03 (s, 2H), 3.84 (s, 2H), 1.30 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 209.1, 139.3, 128.8, 128.7, 127.5, 83.8, 71.0, 55.4, 20.3; CIMS *m/z* (relative intensity) 190 (MH^+, 76), 160(11), 148(23), 91 (100), 70 (81); HRMS calcd for $C_{12}H_{16}NO$ 190.1232, found 190.1221.