

[3 + 2] and [3 + 3] Cycloadditions of Azides with Allylic Carbocations

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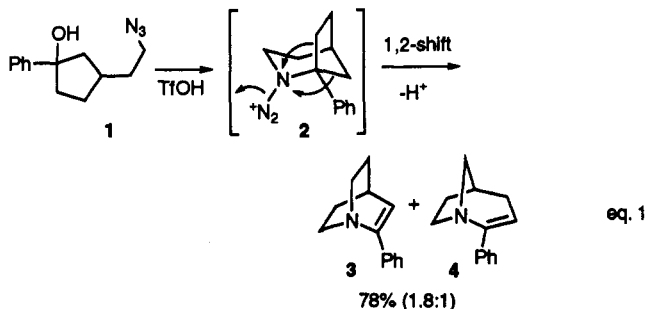
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Summary: Azides undergo unprecedented low-temperature [3 + 2] or [3 + 3] cycloadditions with allylic carbocations, producing triazolines or dihydrotriazines.

We wish to describe the novel finding that azides may react with allylic cations at low temperature to afford either [3 + 2] or [3 + 3] cycloadducts.

We have recently reported the intramolecular Schmidt reaction of azides with carbocations, a process that can afford bridged or fused 1-azabicyclic structures.²⁻⁴ For example, cyclization of **1** with triflic acid affords a mixture of the quinuclidine **3** and a regioisomer **4**, each a result of rearrangement of the aminodiazonium ion **2** (eq 1).³ In



an attempt to apply this reaction to the synthesis of the quinuclidine **8**, a model for a synthesis of the alkaloid cinchonamine, we treated the hydroxy azide **5** with SnCl_4 at -78°C (Scheme 1). Rather than the expected quinuclidine **8**, the crystalline triazolone **10** was isolated in excellent yield as a mixture of two diastereomers (see Table 1 and Scheme 1). The formation of **10** can be interpreted as either a low-temperature 1,3-dipolar cycloaddition of an azide with the allylic cation segment of the indolic cation **6** to produce the benzylic cation **9** or as a stepwise proceeding through the aminodiazonium ion **7** which reacts at C-2 of the indole to give **9** (Scheme 1). The dipolar cycloaddition of azides at such a low temperature is unprecedented and may reflect the highly electron-deficient nature of the dipolarophile.⁵ It is not possible to distinguish between the concerted and stepwise routes at this point. If the reaction is stepwise, the divergence in reactivity of **1** vs **5** may be explained by the greater nucleophilicity of indole ring toward the aminodiazonium ion, thus effectively competing with a Schmidt reaction.

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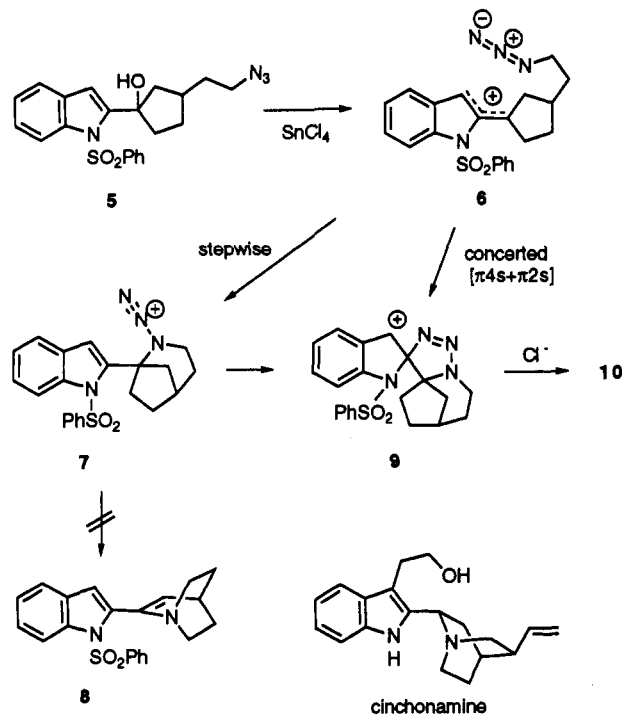
(1) Author to whom correspondence regarding the X-ray crystallographic determinations should be directed.

(2) Pearson, W. H.; Schkeryantz, J. M. *Tetrahedron Lett.* **1992**, *33*, 5291-5294.

(3) Pearson, W. H.; Walavalkar, R.; Schkeryantz, J. M.; Fang, W.; Blickensdorf, J. D. *J. Am. Chem. Soc.* **1993**, *115*, 10183-10194.

(4) For intra- and intermolecular Schmidt reactions of azides with carbonyl compounds, see: (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*, 1635-1637. (d) Le Dréau, M.-A.; Desmaële, D.; Dumas, F.; d'Angelo, J. *J. Org. Chem.* **1993**, *58*, 2933-2935.

(5) Lwowski, W. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 1; pp 559-651.

Scheme 1. Mechanism of Formation of **10** from **5**

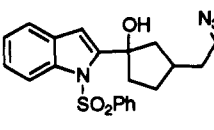
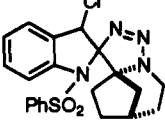
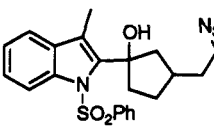
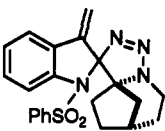
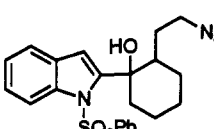
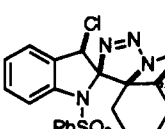
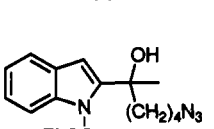
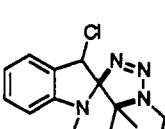
If the reaction is concerted, the greater contribution of the allylic cation resonance contributor **6** in the indole system (versus in the benzylic system derived from **1**) would explain the cycloaddition process versus the Schmidt reaction.

In an attempt to avoid triazolone formation and favor the Schmidt reaction by introducing a sterically encumbering group, the 3-methylindole derivative **11** was cyclized. Again, a triazolone was formed (i.e., **12**) in addition to some elimination of the original tertiary alcohol. This compound was formed as a mixture of two diastereomers at the spiroindoline stereocenter, and its structure was verified by X-ray crystallography.⁶ Elimination of the cation analogous to **9** had occurred rather than capture by chloride ion. Related azides **13** and **15** also produced the [3 + 2] adducts **14** (a single stereoisomer) and **16** (two diastereomers) in good yield. The structure **14** was verified by X-ray crystallography.

We then examined the cyclization of indoles **17**, **19**, **21**, and **22**, all lacking the electron-withdrawing sulfone group at N-1 (Table 2). Switching from SnCl_4 to $\text{BF}_3\cdot\text{OEt}_2$ produced the best yields. Rather than Schmidt reaction products or [3 + 2] cyclization products, a [3 + 3] cyclization ensued, producing the 1,6-dihydrotriazines **18**, **20**, and **23** in modest to good yield. These reactions are likely to proceed through a cations such as **24** and **25**

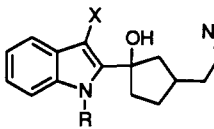
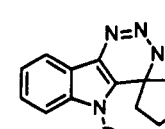
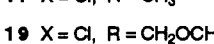
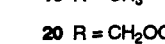
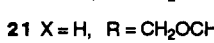
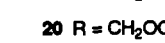
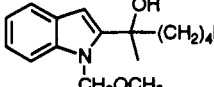
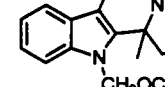
(6) The X-ray determination was carried out on the mixture of diastereomers of **12**. The author has deposited atomic coordinates for **12** and **14** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

Table 1. [3 + 2] Cyclizations of Azides with Carbocations

azide	condns ^a	yield (%)	product (ratio)
	A	75-95	 10 (1.4:1)
	A	31% ^b	 12 (1.3:1)
	A	78%	 14
	B	73%	 16 (3:1)

^a A: 1.5 equiv of SnCl₄, -78 °C, CH₂Cl₂, 1 h, then aqueous NaOH. B: 1.5 equiv of SnCl₄, -78 °C, CH₂Cl₂, 3 h, then aqueous NaOH.
^b Plus 24% elimination.

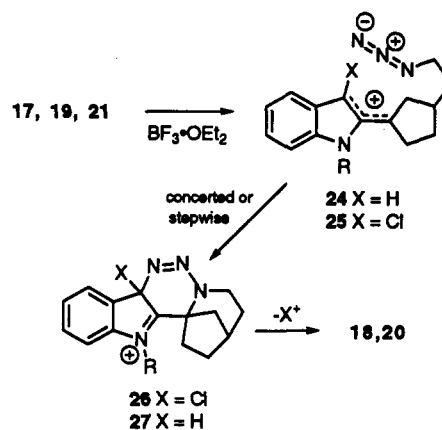
Table 2. [3 + 3] Cyclizations of azides with carbocations

azide	condns ^a	yield ^b (%)	product
	A	44%	 18 R = CH ₃
	B	40% ^c	 20 R = CH ₂ OCH ₃
	B	85%	 20 R = CH ₂ OCH ₃
	B	27%	 23

^a A: BF₃·OEt₂, -78 °C, then NaBH₄. B: BF₃·OEt₂, -78 °C, then NaHCO₃. ^b Isolated, chromatographed yields. ^c Plus 37% elimination.

(Scheme 2). The cyclizations of 17 and 19 are of special interest, since the chlorine substituent is lost as "Cl⁺" during the cyclization. We had placed the 3-chloro substituent on the indole in an attempt to disfavor cyclization of the aminodiazonium ion and thus allow the Schmidt reaction to become competitive. Note that a much higher yield of 21 was obtained from 19, where the C-3 chlorine is replaced with a hydrogen. It is presumably easier to remove a proton from the penultimate intermediate 27 than it is to remove a chloronium ion from 26. The formation of an electrophilic chlorinating agent is also avoided, which may be partially responsible for the increased yield.

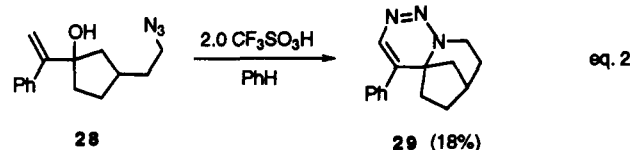
Scheme 2. Formation of [3 + 3] Cyclization Products



The [3 + 3] cyclization of an azide with an allylic cation is unprecedented, although Schultz reported a related [3 + 3] cycloaddition of an azide with a photochemically generated oxallyl zwitterion intermediate.^{7,8} The reactions in Table 2 may proceed through a symmetry-allowed [π4s + π2s] cycloaddition or may be the result of a stepwise reaction, proceeding through an aminodiazonium ion analogous to 7 in Scheme 1 except that electrophilic substitution at C-3 of the indole occurs. The closest analogies to the concerted pathway are Schultz's work^{7,8} and the cycloaddition of allylic cations with dienes.⁹ Symmetry-forbidden (presumably stepwise) [3 + 3] cyclizations between two different 1,3-dipoles have also been reported, although examples with azides do not exist.^{10,11} Indolymethyl cations and benzylic cations have also been shown to participate in stepwise [3 + 2] cyclizations with alkenes to produce cyclopenta[b]indoles¹² and dihydroindenes,¹³ respectively.

An explanation of the difference between the examples in Table 1 and Table 2 may lie in the greater stabilization of the cation resulting from [3 + 3] "cycloaddition" (e.g., 26 and 27, Scheme 2) when a more electron-releasing substituent is present at the center carbon of the allylic cation (i.e., *N*-alkyl vs *N*-sulfonyl).

Preliminary results show that indolylalkyl cations are not the only examples of these remarkable low-temperature cyclizations. Equation 2 illustrates the use of an allylic cation in a [3 + 3] cycloaddition, producing the dihydrotriazine 29.



In conclusion, two new reactions of azides have been discovered, both proceeding at low temperature by

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(8) Schultz, A. G.; Macielag, M.; Plummer, M. *J. Org. Chem.* 1988, 53, 391-395.

(9) Hosomi, A.; Tominaga, Y. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 5; pp 593-615.

(10) Crabb, J. N.; Storr, R. C. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 2; pp 543-595.

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(12) Harrison, C.-A.; Leineweber, R.; Moody, C. J.; Williams, J. M. J. *Tetrahedron Lett.* 1993, 34, 8527-8530.

(13) Angle, S. R.; Arnaiz, D. O. *J. Org. Chem.* 1992, 57, 5937-5947.

what may be considered concerted symmetry-allowed [$\pi 4s + \pi 2s$] processes. The generality of these reactions and their use in heterocyclic synthesis are currently under investigation and will be reported in due course.

Acknowledgment. We thank the National Institutes of Health (GM-35572) for funding this research.

Supplementary Material Available: Experimental procedures for the preparation of all new compounds, copies of NMR spectra for compounds without elemental analysis, and ORTEP drawings for compounds 12 and 14 (60 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.