ORGANIC LETTERS

2001
Vol. 3, No. 25
4091−4094

An Intramolecular [2 + 3] Cycloaddition Route to Fused 5-Heterosubstituted Tetrazoles

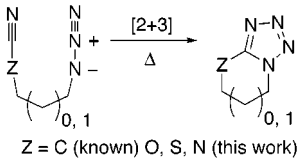
Zachary P. Demko and K. Barry Sharpless*

Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, BCC-315 10550 North Torrey Pines Road, La Jolla, California 92037

sharples@scripps.edu

Received October 3, 2001

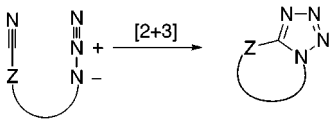
ABSTRACT



Fused 5-heterotetrazole ring systems are synthesized in high yield via intramolecular [2 + 3] cycloadditions of organic azides and heteroatom-substituted nitriles. Cyanates, thiocyanates, and cyanamides are all competent dipolarophiles for this reaction. A variety of scaffolds are tolerated when the new enclosed ring is five- or six-membered.

Tetrazoles are an increasingly popular functionality,[1] often used as metabolically stable surrogates for a carboxylic acid group,[2] as precursors to a variety of nitrogen-containing heterocycles,[3] and as convenient lipophilic spacers in pharmaceuticals.[4] A facile, modular route to substituted tetrazoles would be very useful; however, to date only a few highly activated nitriles are known to undergo this cycloaddition in an *inter*molecular fashion with organic azides.[5] Of course, when azide and nitrile moieties are in the same molecule, rates of cycloaddition can be greatly enhanced; several groups have reported the efficient synthesis of polycyclic fused tetrazoles via *intra*molecular [2 + 3] cycloaddition for cases where the nitrile is bound to a carbon (Scheme 1, Z = C).[6]

Scheme 1



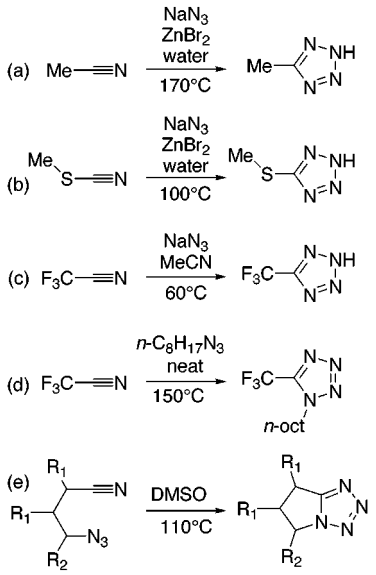
Metal azides are much more activated toward [2 + 3] cycloaddition with nitriles; indeed, a common route to 5-functionalized 1*H*-tetrazoles is via the intermolecular addition of metal azides to nitriles, thiocyanates, cyanates, and cyanamides.[7] We and others have shown that nitriles attached to heteroatoms react with sodium azide to form the corresponding 1*H*-tetrazoles at lower temperatures than carbon-bound nitriles (relative rates of reaction of various nitriles and azides are illustrated in Scheme 2).

Given these precedents, we were not surprised to find that nitriles attached to heteroatoms are also highly competent

(1) Butler, R. N. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergammon: Oxford, U.K., 1996; Vol. 4.
(2) Singh, H.; Chawla, A. S.; Kapoor, V. K.; Paul, D.; Malhotra, R. K. *Prog. Med. Chem.* **1980**, *17*, 151−183.
(3) Moderhack, D. *J. Prakt. Chem.* **1998**, *340*, 687−709.
(4) A simple search of the MDDR database (6/01) provided 173 1-alkylated and 151 2-alkylated 5-*C*-tetrazoles and 147 1- alkylated and 33 2-alkylated 5-heterotetrazoles.
(5) (a) Carpenter, W. R. *J. Org. Chem.* **1962**, *27*, 2085−2088. (b) Quast, H.; Bieber, L. *Tetrahedron Lett.* **1976**, *18*, 1485−1486. (c) Krayushin, M. M.; Beskopylnyi, A. M., Zlotin, S. G.; Lukyanov, O. A., Zhulin, V. M., *Izv. Akad. Nauk. SSSR Ser. Khim.* **1980**, *11*, 2668. (d) Katner, A. S. U.S. Patent 3,962,272, 1974.

10.1021/ol010220x CCC: $20.00
Published on Web 11/17/2001

Scheme 2[a]

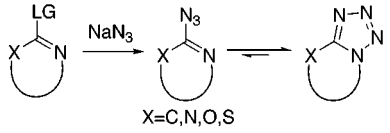


[a] (a) Reference 7d; (b) reference 7d; (c) reference 7b; (d) reference 5a; (e) reference 6e. R_1 = acetonide, R_2 = −CH(OH)CH_2OH.

partners for *intra*molecular cycloaddition reactions with organic azides. To the best of our knowledge, this report describes the first examples of the synthesis of 1,5-fused tetrazoles via an intramolecular [2 + 3] cycloaddition wherein the pendant nitrile component is attached to a heteroatom (Scheme 1, Z = O, S, N).

The resulting fused tetrazolo ring systems are known, and the most common route to these compounds is via the imidoyl azide, which spontaneously cyclizes to the tetrazole. Imidoyl azides are typically formed by nucleophilic attack of azide anion on an imidoyl chloride,[8] a related species (see Scheme 3),[9] or by nitrosation of an imidoyl hydrazine.[10] A

Scheme 3

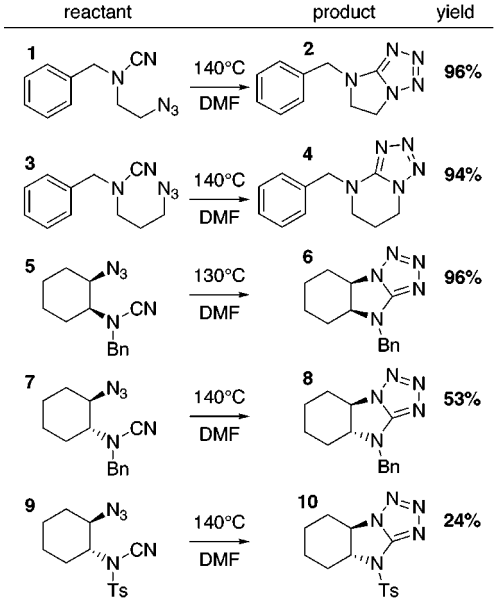


less common route begins with the 5-heterosubstituted 1*H*-tetrazole from which the fused bicyclic ring system is subsequently formed.[11]

The range of the azidonitrile species (Scheme 1) which participate in these intramolecular [2 + 3] cycloadditions is quite broad. The tetrazoles formed can be fused to five- or six-membered ring systems which can be either saturated or unsaturated, and the heteroatom, (Scheme 1, Z), can be nitrogen, oxygen, or sulfur. The [2 + 3] reaction itself is highly reliable; therefore where the reported yields are moderate, product decomposition is the suspected cause. Also noteworthy is the better synthetic access to the precursors than for the analogues with all-carbon tethers—two carbon−carbon σ-bonds are replaced by two carbon−heteroatom σ-bonds, with the latter generally being easier to make[12] (see Supporting Information for details).

Simple heating of the azido cyanamides in solution at 130−140 °C usually provides pure tetrazole. Azido-*N*,*N*-disubstituted cyanamides (R_2NCN) of various geometries (cf. **1**, **3**, **5**) are excellent substrates (>90% yields, Table 1).

Table 1. Intramolecular Cycloadditions of Azidocyanamides



However, their N−H analogues (cf. **27** and **29**) yield predominantly side products, involving the "apparent" displacement of cyanamide (Scheme 4). Strain introduced by *trans*-ring fusion between the scaffold and the enclosed ring can affect reaction times and yields, for example, the rate of formation of **6** is approximately 15 times that of **8** at 130 °C; in addition, the higher temperature necessary in the formation of **8** significantly increases the amount of decom-

(6) (a) *The Chemistry of the Cyano Group*; Rappaport, Z., Ed.; Interscience Publishers: London, England, 1970; p 351. (b) Smith, P. A. S.; Clegg, J. M.; Hall, J. H. *J. Org. Chem.* **1958**, *23*, 524−529. (c) Fusco, R.; Garanti, L.; Zecchi, G. *J. Org. Chem.* **1975**, *40*(13), 1906−1909. (d) Garanti, L.; Zecchi, G. *J. Org. Chem.* **1980**, *45*, 4767−4769. (e) Davis, B.; Brandstetter, T.; Smith, C.; Hackett, L.; Winchester, B. G.; Fleet, G. *Tetrahedron Lett.* **1995**, *36*(41), 7507−7510. (f) Porter, T. C.; Smalley, R. K.; Teguiche, M.; Purwono, B. *Synthesis* **1997**, *7*, 773−777.

(7) (a) Finnegan, W. G.; Henry, R. A.; Lofquist, R. *J. Am. Chem. Soc.* **1958**, *80*, 3908−3911. (b) Norris, W. *J. Org. Chem.* **1962**, *27*, 3248−3251. (c) Wittenberger, S. J. *Org. Prep. and Proceed. Int'l.* **1994**, *26(5)*, 499−531. (d) Demko, Z.; Sharpless, K. B. *J. Org. Chem.* **2001**, *66*, 7945−7950.

(8) Some recent examples: (a) Kadaba, P. K. *J. Org. Chem.* **1976**, *41*, 1073. (b) Bencteux, E.; Houssin, R.; Henichart, J. P. *J. Heteroat. Chem.* **1997**, *34*(4), 1375−1378.

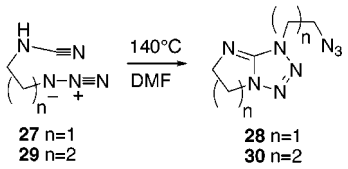
(9) Krantz, A.; Hoppe, B. *Tetrahedron Lett.* **1975**, *9*, 695−698.

(10) (a) Dornow, A.; Menzel, H.; Marx, P. *Chem. Ber.* **1964**, *97*, 2185. (b) Goodman, M. M.; Atwood, L. J.; Carlin, R.; Hunter, W.; Paudler, W. W. *J. Org. Chem.* **1976**, *41*(17), 2860−2864.

(11) Willer, R. L. *J. Org. Chem.* **1988**, *53*, 5371−5374.

(12) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Intl. Ed.* **2001**, *40*(11), 2004−2021.

Scheme 4



position. Electron-withdrawing substituents on nitrogen, while increasing the rate of reaction by activating the nitrile, significantly decrease the thermal stability of the product (see **10**, vide supra).

When the "nitrile" enters as a thiocyanate (see Table 2, R−SCN), the reaction temperatures necessary for nucleophilic displacement by the thiocyanate anion are in the same range as the temperatures required for cyclization (ca. 110 °C vs ca. 130 °C), so the two steps can often be performed in tandem with little or no effect on the overall yield. We have found that formation of the [5,5] and [6,5] ring systems is quite favorable under these conditions, while the [7,5] ring systems are not accessible under the same conditions (see **14**, **16**, **18**). The lower overall yield of **20** is attributable to the increased difficulty of the thiocyanate anion S_N2 displacement step for **19** vs **13**.

Table 2. Intramolecular Cycloaddition of Azidothiocyanates

reactant		product	yield
11	100°C, DMF	**12**	91%
13	NaSCN, DMF, 130°C	**14**	96%
15	NaSCN, DMF, 140°C	**16**	93%
17	NaSCN, DMF, 140°C	**18**	0%
19	NaSCN, DMF, 120°C	**20**	70%

When using cyanates as the dipolarophile (R−OCN), their relative instability toward various undesired acid−base-catalyzed processes limits the value of the present strategy for the synthesis of 5-oxotetrazoles. For example, we have been unable to achieve intramolecular tetrazole formation from in situ generated alkyl cyanates, themselves extremely unstable.[13] For example, when 2-azidoethanol and 3-azidopropanol were treated with bromocyanogen, only decomposition products were observed. However, for several reasons, including a more facile cycloaddition step, 2-azido- and 2-azidomethylphenols provide good substrates for this transformation (see Table 3). *N*-Aryl cyanamides proved to be an intermediate case (see **26**) proceeding at 60 °C.

Table 3. Intramolecular Cycloaddition of More Activated Azidonitriles

reactant		product	yield
21	BrCN, Et_3N, DCM, RT	**22**	92%
23	BrCN, Me_3N, H_2O, RT	**24**	80%
25	BrCN, THF, 60°C	**26**	71%

One important factor limiting the stability of fused tetrazole products is the substituent attached to the 5-position, with its well-known effects on the ring−chain equilibrium between the open chain, azido form and the closed, tetrazolo form (see Scheme 3).[14] In the case of 5-aryloxytetrazoles, where oxygen acts as a strong σ-withdrawing group, the equilibrium has been shown to lie predominately to the side of the open chain, azido form.[15] While there is no direct evidence that this isomer contributes directly to the instability of the tetrazole (presumably initiated by loss of N_2), there is a strong correlation. Although a potential source of instability, these azido tautomers offer a synthetic benefit when they are captured as triazoles via cycloaddition with acetylenes.[16]

In summary, we have shown that heteroatom-substituted nitriles (cyanates, thiocyanates, and cyanamides) readily participate in a [2 + 3] cycloaddition reaction with pendant azides, yielding various five- and six-membered heterocyclic systems fused to a tetrazole ring.

Acknowledgment. We thank the National Institute of General Medical Sciences, National Institutes of Health (GM-28384), the National Science Foundation (CHE-9985553), the Skaggs Predoctoral Fellowship (Z.P.D.), and the W. M. Keck Foundation for financial support.

(13) (a) Jenseni, K. A.; Holm, A. *Acta Chem. Scand.* **1964**, *18*(3), 826−828. (b) Jenseni, K. A.; Due, M.; Holm, A. *Acta Chem. Scand.* **1965**, *19*(2), 438−442. For synthesis of this class of compounds via an alternate method, see reference 9.

(14) (a) Butler, R. N. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boutton, A. J., Eds.; Academic Press: New York, 1977; Vol. 21. (b) Lwowski, W. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; J. Wiley and Sons: New York, 1984; p 559.

(15) Dabbagh, H. A.; Lwowski, W. *J. Org. Chem.* **2000**, *65*, 7284−7290.

(16) An example using dimethyl acetylenedicarboxylate as the dipolarophile is given in: Sasaki, T.; Kanematsu, K.; Murata, M. *J. Org. Chem.* **1971**, *36*, 446−449.

Supporting Information Available: Detailed experimental procedures and spectral data for all compounds, including those not explicitly described in the text but required in the synthesis of the starting materials. This material is available free of charge via the Internet at http://pubs.acs.org.

OL010220X