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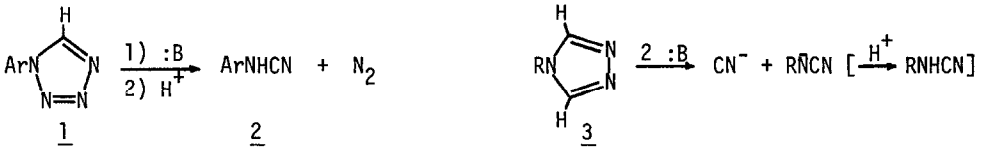
N-CYANAMIDOPYRROLES AND N-CYANAMIDOIMINES FROM 4-AMINO-1,2,4-TRIAZOLE

R. A. Olofson* and Joseph P. Pepe
Chemistry Department, The Pennsylvania State University
University Park, Pennsylvania 16802

Summary. Novel, useful, and unstable cyanamides including the title compounds have been made cleanly from readily available 1-substituted-1,2,4-triazoles by titration with n-BuLi.

Previously known monosubstituted cyanamides (RNHCN) are limited to simple alkyl and aryl derivatives and these usually self-polymerize (e.g., to isomelamines) and otherwise decompose so readily that they have been used only rarely as reactants in preparative chemistry.[1] To minimize decomposition in such applications, the cyanamides generally have not been isolated but instead used immediately in the medium required for their formation, a restriction which places a premium on routes to RNHCN which proceed in near quantitative yield under mild conditions and in which the byproducts don't interfere in the next step of a desired preparative sequence. By this measure, published RNHCN syntheses[1] are inadequate, though the base-induced cleavage of aryltetrazoles (1) to 2 and N_2 might be suitable if a practical solvent-base were found.[2]

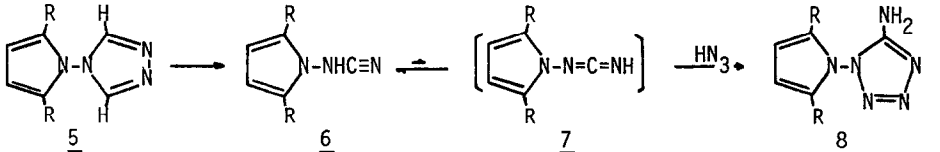


1 2 3

In this communication, we describe a new synthesis of RNHCN from the triazoles (3) which is formally related to the scission, 1 → 2. However, the precursors (3) are readily available in greater structural variety[3] than 1 thus permitting the generation of previously inaccessible cyanamides. The new scheme is illustrated by the conversion of 3 (R=Ph) in THF at 0° to PhNHCN in ca. quantitative yield by treatment with 2 eq. n-BuLi in hexanes (then neutralization with H^+).

More significant examples of the new methodology involve the pyrrolotriazoles (5) which are easily made by condensation of 4-amino-1,2,4-triazole (4, Aldrich) with acetonylacetone (→5a[4]) or the succinaldehyde equivalent, 2,5-dimethoxytetrahydrofuran (→5b,[5] mp 137-137.5°, 68% yield).

a: R = Me
b: R = H



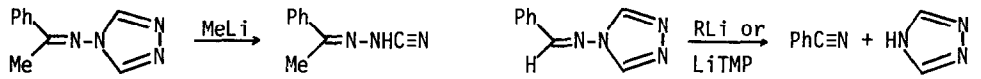
5 6 7 8

Treatment of 5 with n-BuLi (then H^+) yielded the first known N-cyanamidopyrroles (6) as unstable oils with strong IR cyanamide absorptions at 4.45μ. In other experiments ca. 2 eq. ethereal HN_3 and 2 drops conc. H_2SO_4[6] were added directly to the reaction mixtures obtained by cleaving 5 with n-BuLi in THF. The next day the aminotetrazoles (8) were isolated as white solids (8a:[5] 61% recrystallized yield, mp 156.5-157° dec; 8b:[5] 64% yield, mp 150° dec, IR 2.90 and 2.98μ).

The transformations, 5→8, provide an effective demonstration of the value of the present RNHCN synthesis as part of a preparative sequence in which very unstable cyanamides are generated cleanly and then used without the necessity of prior isolation. This reaction sequence, which was predicted apriori, also supplies an efficient and facile route to an interesting class of target compounds. Many 1-substituted-5-aminotetrazoles and their derivatives have important pharmaceutical activities: e.g., 1-phenyl-5-aminotetrazole (fenamole) is an early generation non-steroidal antiinflammatory and muscle relaxant devoid of analgetic properties.[7] Tetrazoles such as 8 in which both the 1- and 5-positions are attached to nitrogen substituents have never been made before and could not be considered as potentially available by published methodology.

The conversion of cyanamides to 5-aminotetrazoles by treatment with HN_3 has been reported previously[8] and is rationalized by postulating that in solution 6 is in rapid equilibrium with a trace of its carbodiimide tautomer (7). The substituted C=N bond of the latter then participates as a selectively activated dipolarophile in a 1,3-dipolar cycloaddition to the HN_3, thus generating 8. The high selectivity for the substituted C=N bond in 7 is in accord with earlier work.[8]

In attempts to further expand the scope of the new cyanamide synthesis, the iminotriazoles[9] (9 and 11) also were titrated with ethereal MeLi. After neutralization, the former cleanly yielded 10, the first known iminocyanamide, as a very unstable yellow oil (IR 4.52μ). However, 11 fragmented instead to benzonitrile and triazole.[10]



9 10 11

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References and Footnotes

1) Review: P. A. S. Smith, The Chemistry of Open-Chain Nitrogen Compounds, Vol. I, Benjamin, N.Y., 1965, p. 251; also see: R. A. Olofson and K. D. Lotts, following communication.
2) Hot aqueous NaOH and pyridine at reflux are recommended: R. Stollé and F. Henke-Stark, J. Prakt. Chem., 124, 261 (1930); R. Huisgen, Angew. Chem., 72, 359 (1960).
3) For example, by condensation of amines or amine derivatives with sym-diformylhydrazine.
4) C. Bülow, Chem. Ber., 39, 4106 (1906).
5) New compound: satisfactory combustion analyses were obtained for all air stable new compounds; IR, NMR, and mass spectra are also in accord with all proposed structures.
6) When H^+ was left out, 8 wasn't as easily purified; cycloaddition of HN_3 to RNC to give tetrazoles is acid-catalyzed: D. M. Zimmerman and R. A. Olofson, Tetrahedron Lett., 5081 (1969).
7) Other 1-aryl-5-aminotetrazoles and derivatives have similar activity: W. E. Coyne in Medicinal Chemistry, ed. A. Burger, Wiley-Interscience, N.Y., 1970, Ch. 37, p. 966. Some are also coccidiostatic: P. Kulsa and L. H. Peterson, Ger. Pat., 2334821 (CA, 80, 108535u (1974)).
8) See ref. 6 and: W. L. Garbrecht and R. M. Herbst, J. Org. Chem., 18, 1014 (1953). Though searched for, no aminotetrazole with a substituent on the 5-amino group was found.
9) C. Bülow, Chem. Ber., 42, 2715 (1909); S. Ruhemann and R. Merrimen, J. Chem. Soc., 1768 (1905).
10) For precedents see: H. G. O. Becker and H. H. Timpe, Z. Chem., 4, 304 (1964); H. G. O. Becker, H. Hübner, H. J. Timpe, and M. Wahren, Tetrahedron, 24, 1031 (1968).

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