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SYNTHESIS OF PYRROLIDINES USING AN α-CYANOAMINOSILANE AS AN AZOMETHINE YLIDE EQUIVALENT

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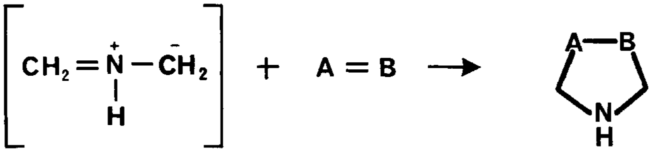
Abstract: The potential of α-cyanoaminosilane (3) to act as an azomethine ylide equivalent is illustrated by its treatment with silver fluoride in the presence of electron deficient olefins to give substituted pyrrolidines in high yield.

Azomethine ylides are reactive dipolar intermediates that have found extensive use in heterocyclic synthesis.[1,2] The parent azomethine ylide system 1 offers many synthetic attractions. It provides a functional group of sufficient flexibility that a diverse range of alkaloids would be approachable. Its absence as a synthetic method stems from the lack of suitable methods for its generation. Although ring opening of aziridines to azomethine ylides works well when the substituent groups are capable of stabilizing the dipole centers,[3-6] the ring cleavage fails completely when simple alkyl substituents are used. In circumventing the perceived problems of azomethine ylide 1, a mild method for its generation from readily available precursors is required. The propensity of silicon to transfer to a silylophile when bound to an electronegative carbon[7] raised the possibility of the desilylation of an intermediate such as 3.[8,9] With the hope that such a species would participate in a cycloaddition, α-cyanoaminosilane 3 was exposed to silver fluoride in the presence of an electron deficient trapping reagent. In all cases a single product emerged in good overall yield. Equation 1 summarizes the general features of the reaction. Hydrogenolysis of the benzyl group of 4 affords the unsubstituted NH-pyrrolidine ring.



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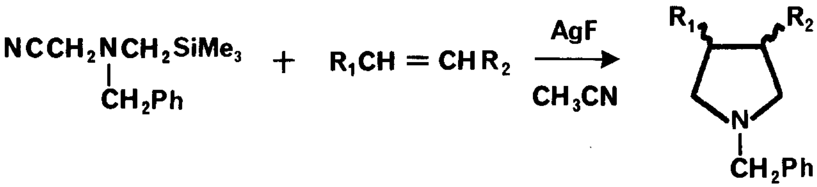
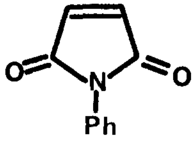
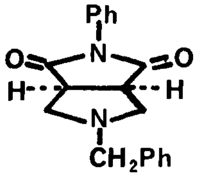
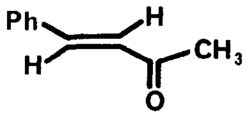
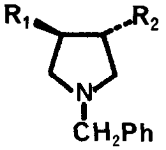
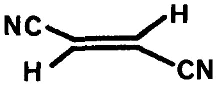
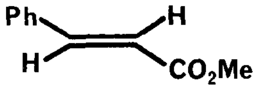
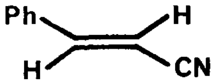
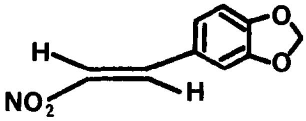
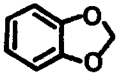
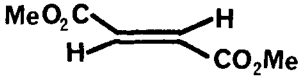
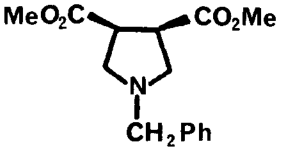


3 **4**

In spite of its simplicity and its obvious potential as an azomethine ylide equivalent, N-benzyl α-cyanoaminosilane **3** could not be found in the literature. This reagent was conveniently prepared in multigram quantities by treating benzyl amine with chloromethyltrimethylsilane followed by reaction of the resulting secondary amine with formaldehyde in the presence of potassium cyanide; NMR ($CDCl_3$,90 MHz) δ 0.10 (9H, *s*), 2.02 (2H, *s*), 3.23 (2H, *s*), 3.51 (2H, *s*) and 7.20 (5H, *s*). A solution of **3** (2.5 mmole) and the appropriate dipolarophile (2.5 mmole) in acetonitrile (5 ml) was allowed to react in the dark with a slight excess of silver fluoride (2.75 mmole). Stirring was continued at 25^{0}C over the course of 10 hr. The black precipitate that formed was filtered, the solvent was removed under reduced pressure and the residue was subjected to silica gel chromatography to provide cycloadduct **4**. Some of our results are shown in the Table.

As the Table indicates, the azomethine ylide derived from **3** can be trapped in good to high yields. The last two entries clearly indicate the stereospecific nature of the cycloaddition. The *trans*-fumarate cycloadduct showed NMR signals ($CDCl_3$,360 MHz) at δ 2.79 (*dd*, 2H, J=9.3 and 5.9 Hz), 2.91 (*t*, 2H, J=9.3 Hz), 3.45 (*dd*, 2H, J=9.3 and 5.9 Hz), 3.61 (*s*, 2H), 3.70 (*s*, 6H) and 7.25 (*s*, 5H). The *cis*-maleate cycloadduct exhibited a set of signals at 2.73 (*m*, 2H), 3.16 (*m*, 2H), 3.32 (*m*, 2H), 3.65 (*m*, 8H) and 7.3 (*m*, 5H). All attempts to obtain a cycloadduct from the reaction of **3** with nonactivated olefins (i.e. cyclohexene, 1-octene, etc.) failed. Our inability to isolate a 1,3-cycloadduct with these systems is perfectly consistent with the principles of frontier MO theory.[11] Azomethine ylides only react with electron deficient alkenes, since such a pair of addends possesses a narrow dipole HOMO-dipolarophile LUMO gap.[12]

	Dipolarophile	Cycloadduct	Isolated Yield
1.			84%
2.		 R_1 = Ph ; R_2 = CH_3CO	42%
3.		R_1 = R_2 = CN	69%
4.		R_1 = Ph ; R_2 = CO_2Me	45%
5.		R_1 = Ph; R_2 = CN	33%
6.		R_1 = NO_2; R_2 = 	51%
7.		R_1 = R_2 = CO_2Me	70%
8.			23%

In summary, this work demonstrates that α-cyanoaminosilane 3 is a convenient and useful synthon for the simplest of all azomethine ylides. Further applications of these cycloadditions to the synthesis of some members of the amaryllidaceae, dendrobium and mesembrine alkaloids will be reported in forthcoming publications.

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