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3-ARYLPYRROLIDINES via AZOMETHINE YLIDE 1,3-DIPOLAR CYCLOADDITION TO STYRENES

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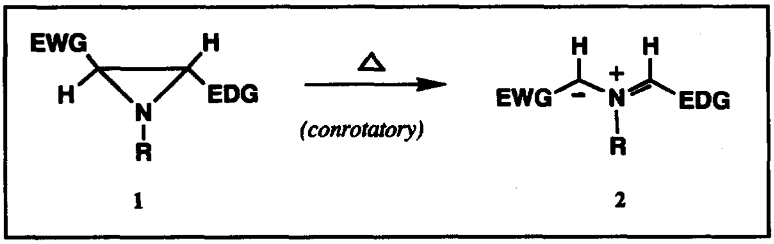
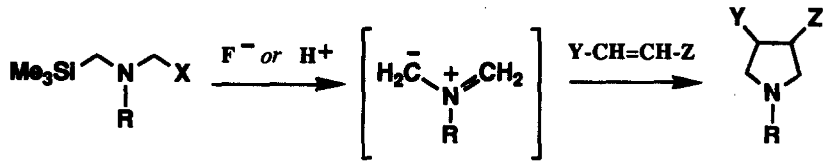
***Abstract:** Monosubstituted olefins conjugated to an aromatic or heteroaromatic ring undergo 1,3-dipolar cycloaddition with the azomethine ylide derived from N-benzyl-N-(methoxymethyl)trimethylsilylamine to give 3-aryl- and 3-heteroarylpyrrolidines in good to excellent yield.*

The 1,3-dipolar cycloaddition of an azomethine ylide with an olefin represents one of the most convergent approaches for the construction of the pyrrolidine ring.[1,2] In spite of its simplicity, the synthetic potential of this methodology has often been restricted by the unavailability of suitable methods for the generation of nonstabilized azomethine ylides. The thermally-induced ring opening of aziridines to give azomethine ylides works well only in the presence of substituents capable of stabilizing the dipole centers (eq. 1).[3] This requirement necessarily precludes the synthesis of 2- or 2,5-unsubstituted pyrrolidines.



[1]

In the past few years, however, several innovative methods for the generation of a variety of nonstabilized azomethine ylides have appeared.[4] Among them, those involving desilylation of appropriately substituted N-(silylmethyl)amine derivatives have proven particularly useful owing to the ready availability of the starting materials and the mild conditions required for the generation of the ylide.[5] As predicted by the principles of Frontier Molecular Orbital (FMO) theory,[6] these nonstabilized ylides readily react with electron-deficient alkenes providing access to a wide array of 3- and 3,4-substituted pyrrolidines (eq. 2). Typical examples of dipolarophiles include α,β-unsaturated esters, ketones, nitriles and amides.



3a, X = CN
3b, X = OMe

4

5

[2]

As part of a medicinal chemistry program investigating the design and synthesis of novel quinolone antibacterials, we required a short and efficient procedure for the preparation of pyrrolidines bearing an aromatic or heteroaromatic substituent at the C-3 position. A conceptually simple way to access this molecular framework would involve the reaction of the parent azomethine ylide with a styrene derivative. However, to date there have been no reports on the successful cycloaddition of the nonstabilized azomethine ylide 4 (R = CH_2Ph), generated by the desilylation procedure, with an aryl substituted alkene. The lack of success experienced in several *inter-* as well as *intramolecular* attempts apparently agrees with molecular orbital calculations, which predict that olefins lacking either electron-withdrawing or electron-donating substituents should be the least reactive dipolarophiles in the reaction.[7,8]

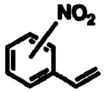
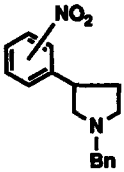
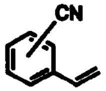
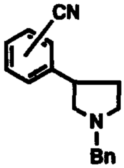
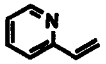
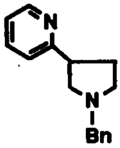
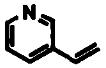
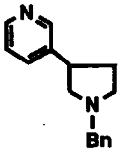
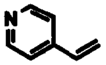
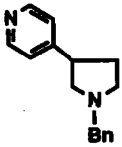
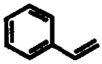
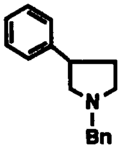
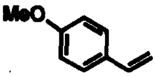
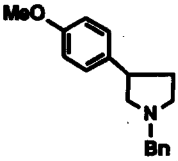
Pursuant to our synthetic objective, we chose to investigate the effect that different substituents on the phenyl ring of a styrene system would have upon the cycloaddition. *A priori*, a properly positioned electron-withdrawing group on the phenyl ring would be expected to lower the LUMO energy of the olefinic double bond and, therefore, narrow the gap between this frontier orbital and the HOMO of the transient ylide. Whether the magnitude of this narrowing would be sufficient to promote cycloaddition remained in question. We report here the successful execution of this strategy and its extension to include heteroaryl substituted ethylenes.

The aryl or heteroaryl substituted olefins utilized in this study are summarized in Table I. 3-Vinylpyridine, 2- and 4-nitrostyrene, and 3- and 4-cyanostyrene were prepared from 3-pyridinecarboxaldehyde and the corresponding nitro- or cyano-substituted benzaldehydes *via* a Wittig reaction with triphenylphosphonium methylide. 3-Nitrostyrene, as well as 2- and 4-vinylpyridine were purchased from a commercial source,[9] whereas 2-cyanostyrene was obtained by a palladium-catalyzed cross coupling of 2-bromobenzonitrile with tributylvinyltin.[10]

The cycloaddition reactions were performed using a modification of the procedure reported by Achiwa.[5b] Accordingly, a solution of dipolarophile in CH_2Cl_2 was treated with a catalytic amount (0.1-0.5 eq.) of trifluoroacetic acid, followed by the dropwise addition (*ca.* 15-30 min) of the ylide precursor 3b (R = CH_2Ph) (1.2-1.5 eq.). Thin-layer chromatography immediately upon completion of the addition revealed total consumption of 3b.

The cycloaddition reactions proceeded smoothly to give the corresponding pyrrolidines in good to excellent yields (Table I).[11] It is noteworthy that the yields of cycloadducts obtained for all three regioisomers within a series of equally functionalized dipolarophiles were comparable. Indeed, due to their resonance stabilization, the *ortho* and *para* substituted styrene derivatives were expected to react more readily with the azomethine ylide than the corresponding *meta* isomer. A similar consideration could be applied to the three

TABLE I

Entry	*Dipolarophile*	*Product*	*Yield (%)*
1			*ortho-* 76
2			*meta-* 85
3			*para-* 71
4			*ortho-* 58
5			*meta-* 76
6			*para-* 76
7			79
8			36
9			68
10			20
11			20

regioisomeric pyridines, particularly if protonation of the heterocyclic nitrogen occurs under the reaction conditions employed. Although the lower yield of cycloadduct obtained with 3-vinylpyridine (entry 8) would seem to support this hypothesis, the results obtained with the substituted styrenes indicate that inductive effects play a very significant role in stabilizing the transition state of the cycloaddition.

As a final test to determine the influence of the aromatic substituent upon the reactivity of the olefinic double bond, we performed the cycloaddition with styrene itself and isolated 3-phenylpyrrolidine in *ca.* 20% yield (entry 10). This reaction constitutes the first example of an *intermolecular* trapping of the nonstabilized azomethine ylide **4**, generated by the desilylation procedure, with a relatively unactivated activated olefin such as styrene. Moreover, the presence of an electron-donating substituent on the phenyl ring, as in 4-vinylanisole, did not totally prevent the formation of the corresponding cycloadduct (entry 11). However, other olefins bearing electron-donating substituents, such as ethyl vinyl ether and vinylene carbonate, failed to give any appreciable amount of cycloadducts.

In summary, the present strategy provides a convergent synthesis of 3-aryl or heteroarylpyrrolidines in a very convenient one-pot procedure and broadens the scope of the 1,3-dipolar cycloaddition of nonstabilized azomethine ylides with relatively unactivated olefins.

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