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Lewis Acid Catalyzed 1,3-Dipolar Cycloadditon Reactions of Stabilized Azomethine Ylides

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Diethylzinc was tested for the first time as the Lewis acid in 1,3-dipolar cycloaddition reactions of azomethine ylides to synthesize pyrrolidine derivatives. A new, easily applicable and highly selective method was developed for the synthesis of highly substituted pyrrolidines. By the application of this method, the synthesis of three new pyrrolidine derivatives was achieved.

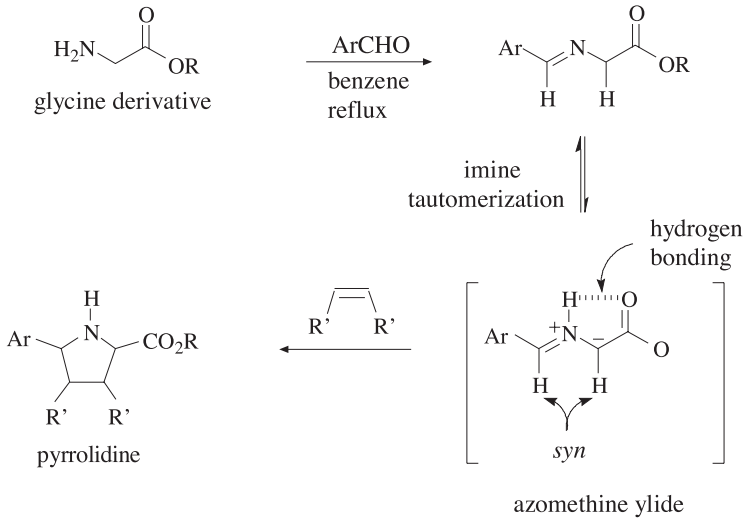
Introduction

The synthesis of pyrrolidine derivatives is an important subject in organic chemistry because they are found in the structure of most natural compounds and drugs.[1] They are also as important as chiral ligands.[2] Due to these facts, research related to the synthesis of pyrrolidine derivatives continues actively. One of the most commonly used methods for the synthesis of pyrrolidine derivatives is the 1,3-dipolar cycloaddition reactions of azomethine ylides with dipolarophiles.[3] For the generation of azomethine ylides, different methods are known but only some of them have general applicability. Among these methods, the imine toutomerization method discovered by Grigg[4], Joucla[5], and Tsuge[6] is one of the most commonly used. Recent research in this area has involved Lewis acid catalyzed reactions. So far, Ag(I), Li(I), Mg(II), Co(II), Mn(II), Ti(IV), Zn(II, only as $ZnBr_2$) and Tl(I) metal ions have been tried in 1,3-dipolar cycloaddition reactions of azomethine ylides as the Lewis acids.[7c,3a,8] In the presence of these Lewis acids as the catalyzers, pyrrolidine derivatives were synthesized in about 70-90% yields depending on the Lewis acid used. When Lewis acids catalyze the reactions, it is believed that the interaction between the azomethine ylide and the dipolarophile is $LUMO_{dipole}$ + $HOMO_{dipolarophile}$, just the reverse of the normal $HOMO_{dipole}$ + $LUMO_{dipolarophile}$.[9] In carrying out these types of reactions, there are four issues to be considered: 1-Geometry of the azomethine ylide. 2-Diastereofacial selectivity. 3-*Endo/exo* selectivity. 4-Regioselectivity with unsymmetrical dipolarophiles.

The present article describes in full the details of diethylzinc catalyzed 1,3-dipolar cycloaddition reactions of azomethine ylides with electron deficient dipolarophiles for the synthesis of pyrrolidine derivatives. Diethylzinc is used for the first time in these types of reactions.

Results and Discussion

As mentioned in the introduction, one general approach to create azomethine ylides is the condensation of glycine derivative with an aldehyde (especially the aromatic ones), which gives stable imines. Tautomerization of imines results in the formation of intermediate azomethine ylides that can be trapped with dipolarophiles.

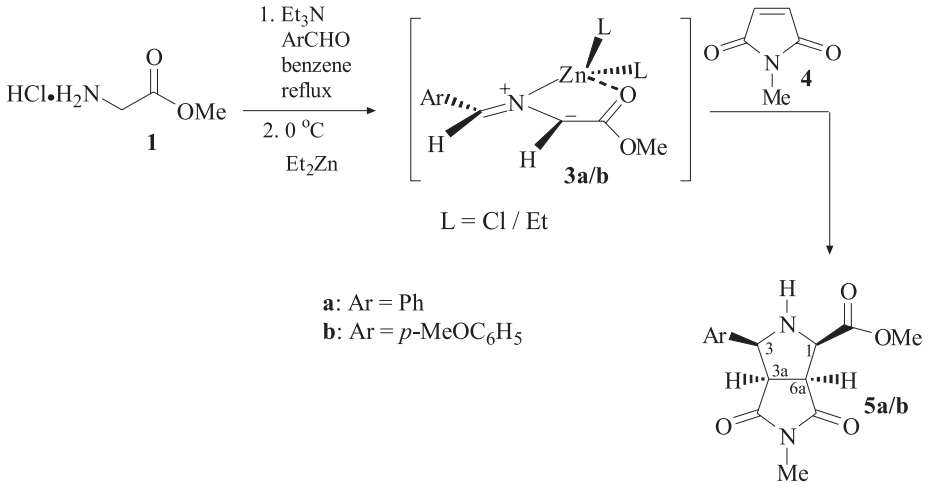


Scheme 1

As explained by Tsuge,[7a] the most stable geometry of the intermediate azomethine ylide has the *syn* arrangement of hydrogens (Scheme 1), and thus the steric repulsion between the groups is minimum. Hydrogen bonding is also effective in the stability of this ylide geometry.

1,3-Dipolar cycloaddition reactions of azomethine ylides were easily achieved by condensing benzaldehyde/anisaldehyde with glycine methyl ester under reflux by using a Dean-Stark apparatus. This process results in the formation of corresponding imines that tautomerize to give intermediate azomethine ylides. The ylides were reacted with different dipolarophiles via 1,3-dipolar cycloaddition reactions in the presence of diethylzinc at room temperature under argon atmosphere (Table 1). When N-methylmaleimide (**4**) was used as the dipolarophile, cycloadducts **5a** and **5b** (Scheme 2) were obtained as the only products in 70% and 63% yields respectively (Table 1, entries 1 and 2).

The stereochemistry of these cycloadducts was easily determined by spectroscopic analysis. Both ^{1}H-NMR and ^{13}C-NMR spectra matched well with the same compound in the literature,[7c] so we were sure that compound **5a** had the stereochemistry shown in Scheme 2. New compound (**5b**) had ^{1}H-NMR and ^{13}C-NMR spectra[10] very similar to those of compound **5a**, so its structure was also assigned as in (Scheme 2).



Scheme 2

The stereochemistry of these cycloadducts conforms to an *endo* transition state where the dipolarophile approaches the ylide in such a way that the substituents (R - groups) are on the opposite side of the metal (Zn) coordinated to nitrogen and carbonyl oxygen (Figure 1). The cycloadduct corresponding to *exo*-TS was not isolated. This can be explained by the secondary orbital interaction between the phenyl group and carbonyl of the N-methylmaleimide (**4**). This interaction is possible only by the *endo*-TS.

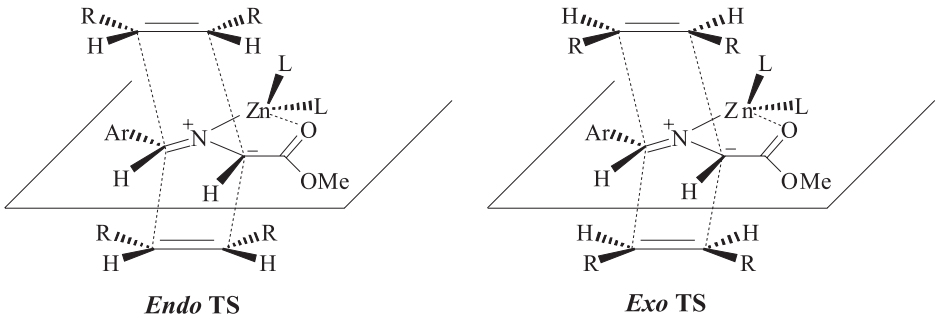


Figure 1. Possible transition states for the addition of azomethine ylide to the dipolarophiles.

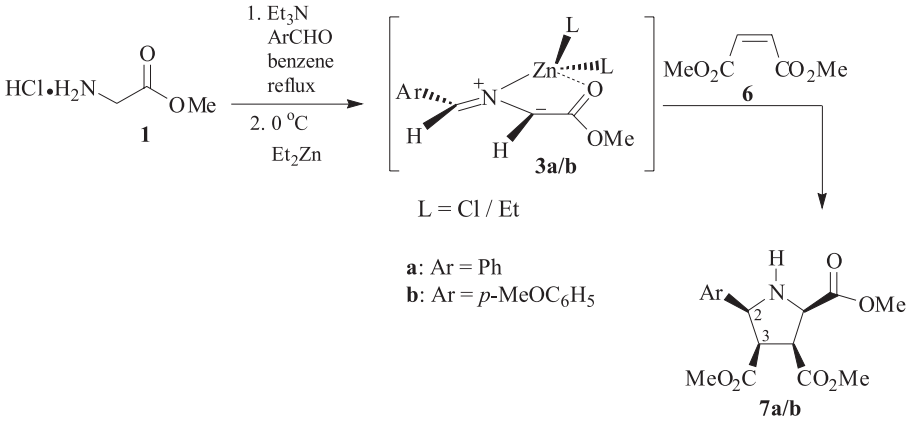
The coordination of azomethine ylide to Zn was confirmed by our control experiment, which gave no cycloadduct under the same reaction conditions but in the absence of diethylzinc. In order to achieve cycloadducts in these types of reactions without using Lewis acids, it was necessary to carry out the reaction at a higher temperature (e.g., boiling in toluene).

Although we used Et_2Zn as the Lewis acid, we believe that the ligands on the Zn are Cl and Et during the transition state, because, during the imine formation step, Et_3NHCl salts that react with Et_2Zn and convert it into EtZnCl are also formed. Our second control experiment also supported this hypothesis. In this experiment, imine was isolated from Et_3NHCl salts and the reaction was carried out under the same conditions as with Et_2Zn. This reaction was very slow and the yields of the cycloadducts were very low. This result showed that the reaction was catalyzed by a more active zinc reagent, most likely by EtZnCl.

Table 1. Diethylzinc Catalyzed 1,3-Dipolar Cycloaddition Reactions of Azomethine Ylides **3a** & **3b** to Dipolarophiles **4, 6, 8,** and **11**.

entry	azomethine ylide	dipolarophile	cycloadduct(s)	yield (%)
1	**3a**	**4**	**5a**	70
2	**3b**	**4**	**5b**	63
3	**3a**	**6**	**7a**	65
4	**3b**	**6**	**7b**	62
5	**3a**	**8**	**9a/10a**	68
6	**3b**	**8**	**9b/10b**	65
7	**3a**	**11**	**12a**	63
8	**3b**	**11**	**12b**	58

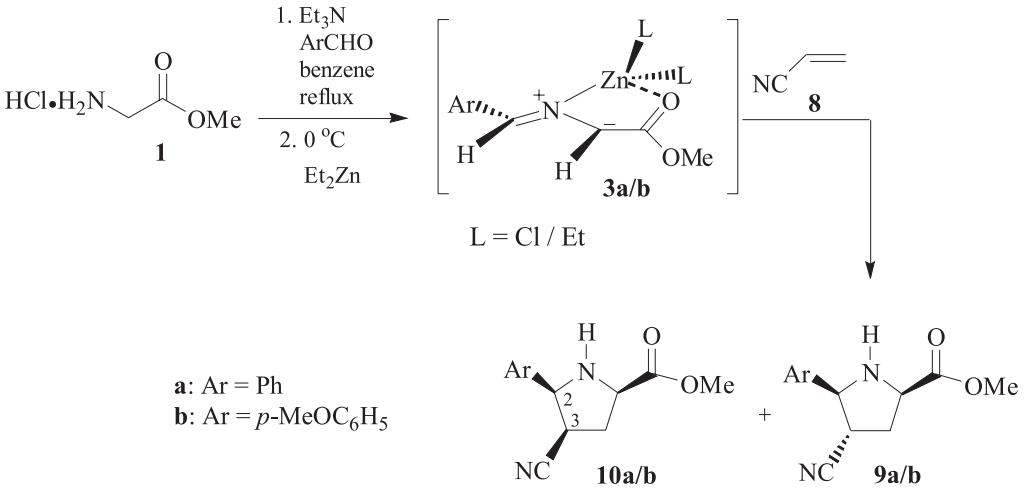
The second symmetrical dipolarophile **6** produced compounds **7a** and **7b** (Scheme 3) in about 65% and 62% yields respectively (Table 1, entries 3 and 4). Both compounds were also obtained by the *endo*-TS. Characterization of these compounds (**7a** and **7b**) were easily carried out by comparing their ^{1}H-NMR and ^{13}C-NMR spectra with those in the literature.[7c,7d]



Scheme 3

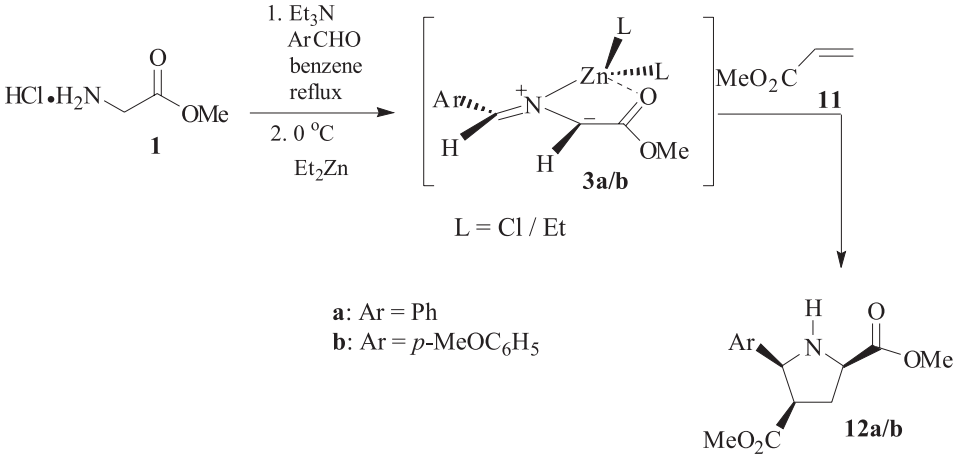
Repetition of the dipolar cycloaddition reaction with the unsymmetrical dipolarophile **8** resulted in a clean formation of two cycloaddition products **9** and **10** (Scheme 4) in high regioselectivity but poor *endo-exo* selectivity in a total yield of 68% (Ar = Ph) and 65% (Ar = *p*-MeOC$_6$H$_5$) and a ratio of ~1.6/1 in both cases (Table 1, entries 5 and 6). ^{1}H-NMR and ^{13}C-NMR spectra of the cycloadducts **9a** and **10a** were the same as those reported for the same compounds in the literature,[7c] so we assigned the structures of these compounds as in Scheme 4. For the structures of the new compounds **9b** and **10b**, once again, they had ^{1}H-NMR and ^{13}C-NMR spectra[10] very similar to those of compounds **9a** and **10a**, so it was reasonable to assume that these compounds also had the structures shown in Scheme 4.

Methyl acrylate was tested as the second unsymmetrical dipolarophile and it formed the corresponding cycloadducts **12a** and **12b** (Scheme 5) as a single stereo- and regioisomer in 63% and 58% yields respectively (Table 1, entries 7 and 8).



Scheme 4

Characterization of both compounds (**12a& 12b**) was achieved easily by just comparing their spectroscopic data (^{1}H-NMR and ^{13}C-NMR spectra), which matched well with that in the literature.[7c,8] Therefore, we assigned the structures as in Scheme 5. This reaction also showed high *endo* and regioselectivity. This can be explained by the transition state shown in Figure 2, where both the ylide and the dipolarophile coordinate to the metal (Zn).



Scheme 5

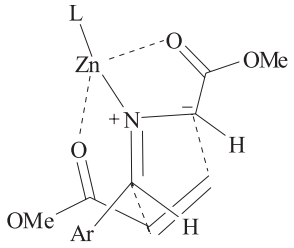


Figure 2. Transition state for the cycloaddition of azomethine ylide to methyl acrylate

It is more likely that such a transition state does not exist in the case of acrylonitrile (**8**), because it gives a very poor *endo* selectivity. The high regioselectivity of this dipolarophile, on the other hand, could result from the HOMO and LUMO coefficients. The terminus of the dipole bearing a larger LUMO coefficient combines with the terminus of the dipolarophile bearing a larger HOMO coefficient, and therefore the sites carrying smaller coefficients combine with each other.

In conclusion, we demonstrated that diethylzinc, which becomes EtZnCl in the reaction medium, can be used as the Lewis acid in the catalysis of 1,3-dipolar cycloaddition reactions of azomethine ylides obtained via imine tautomerization with electron deficient dipolarophiles. These cycloaddition reactions produced the corresponding pyrrolidine derivatives in high stereo- and regioselectivities in reasonable yields under milder reaction conditions.

Representative experimental procedure: Benzaldehyde/anisaldehyde (1eq) was refluxed with glycine methyl ester hydrochloride (1eq, usually experiments were carried out on a 200 mg scale) and triethylamine (1eq) for 1h in a Dean-Stark apparatus in benzene (con. 0.4M) to form the imines (Schiff bases) under argon atmosphere. At the end of this period, the reaction flask was cooled to 0°C, diethylzinc (1eq, 1.6 M Et_2Zn in hexanes) and dipolarophile (2eq) (N-methylmaleimide, dimethylmaleate, methyl acrylate, or acrylonitrile) were added to the same reaction flask. The resulting mixture was stirred for 30 min at 0°C and then for 3 hours at rt. Then it was hydrolyzed with sat. NH_4Cl soln. and extracted with CH_2Cl_2 (3x20 mL for the 200 mg of the starting material). The combined organic layer was dried over $MgSO_4$, and concentrated and purified by flash column chromatography on silica gel (CH_2Cl_2/ EtOAc; 2/1, used as the eluent). ^{1}H-NMR and ^{13}C-NMR spectra were recorded at Brucker Spectrospin Avance DPX-400 Ultrashield instrument and reported in ppm on the δ scale relative to residual $CDCl_3$ (δ 7.25 and 77.00).

Acknowledgment

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10. **5b:** ^{1}H-NMR (CCl_4-$CDCl_3$) δ 7.17 (d, J = 8.6 Hz, 2H, Ph), 6.79 (d, J = 8.6 Hz, 2H, Ph), 4.37 (d, 1H, J = 8.6 Hz, H-6), 3.95 (d, 1H, J = 6.8 Hz, H-4), 3.81 (s, 3H, 4-COOMe), 3.73 (s, 3H, OMe), 3.46 (t, 1H, J = 7.2 Hz, H-3a), 3.30 (t, 1H, J = 8.1 Hz, H-6a), 2.80 (s, 3H, N-Me), 2.12 (br, 1H, N-H). ^{13}C-NMR (CCl_4-$CDCl_3$) δ 176.2, 175.0, 170.4, 159.9, 128.2, 128.5 (2xC), 114.2 (2xC), 64.11, 61.98, 55.47, 52.63, 49.88, 48.64, 46.15. IR (KBr pallet): 3333, 2956, 1748, 1701, 1613, 1513, 1438, 1381, 1281, 1249, 1211, 1115, 1094, 820 cm^{-1}.

    9b: ^{1}H-NMR (CCl_4-$CDCl_3$) δ= 7.32 (d, J=8.6 Hz, 2H, Ph), 6.84 (d, J= 8.7 Hz, 2H, Ph), 4.28 (d, J= 6.3 Hz, 1H, H-2), 3.86 (dd, J= 8.7 & J= 6.5 Hz, 1H, H-5), 3.77 (s, 3H, COOMe), 3.74 (s, 3H, OMe), 3.03 (dt, J= 6.5 & J= 6.4 Hz, 1H, H-3), 2.54-2.39 (m, 2H, 2xH-4). ^{13}C-NMR (CCl_4-$CDCl_3$) δ= 173.1, 160.2, 129.9, 128.6 (2xC), 119.3, 114.5 (2xC), 64.9, 58.9, 55.5, 52.9, 36.5, 34.7. IR (neat): 3348, 2956, 2244, 1736, 1612, 1514, 1444, 1244, 1114, 1031, 831 cm^{-1}.

    10b: ^{1}H-NMR (CCl_4-$CDCl_3$) δ 7.33 (d, J = 8.6 Hz, 2H, Ph), 6.82 (d, J = 8.6 Hz, 2H, Ph), 4.22 (d, J = 9.2 Hz, 1H, H-2), 3.96 (dd, J = 8.9 & J= 4.9 Hz, 1H, H-5), 3.74 (s, 3H, COOMe), 3.73 (s, 3H, OMe), 2.67 (dt, J = 9.3 & J = 8.7 Hz, 1H, H-3), 2.52-2.38, (m, 2H, 2xH-4). ^{13}C-NMR (CCl_4-$CDCl_3$) δ 173.9, 160.3, 130.9, 128.1(2xC), 119.8, 114.7 (2xC), 67.4, 58.8, 55.5, 52.8, 36.9, 34.7. IR (KBr pallet): 3332, 2949, 2241, 1742, 1613, 1513, 1441, 1297, 1244, 1199, 1131, 1031, 841, 823 cm^{-1}.