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Synthesis of ferrocene substituted pyrrolidine derivatives via Et_2Zn catalyzed 1,3-dipolar cycloaddition reactions of azomethine ylides

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Abstract

Synthesis of ferrocene substituted pyrrolidine derivatives via diethylzinc catalyzed 1,3-dipolar cycloadditions of azomethine ylides is described. Azomethine ylides were generated from glycine methyl ester and ferrocenecarboxaldehyde by the 'imine tautomerization' method and trapped with dipolarophiles to give the corresponding cycloadducts in reasonable yields and high regio- and stereoselectivity.

Keywords: Ferrocene; Pyrrolidine; Diethylzinc catalysis; 1,3-Dipolar cycloadditions

1. Introduction

1,3-Dipolar cycloaddition reactions of azomethine ylides [1] are one of the commonly used methods in the synthesis of pyrrolidine derivatives [2]. An efficient and useful method in generating azomethine ylides is the imine tautomerization discovered by Grigg, Joucla, and Tsuge separately [3]. Due to the stabilizing effect of the aromatic and ester groups, this method works well with the ylides obtained from aromatic aldehydes and 2-amino esters. The yield, regio- and stereoselectivity of the products in these reactions can be affected by using different Lewis acids [1d,4]. The use of Lewis acids lower the energy difference between the HOMO and LUMO of the dipole and dipolarophile so that the reaction works at low temperatures, otherwise the reaction has to be carried out at relatively high temperatures.

We have recently investigated for the first time the effect of Et_2Zn, as the Lewis acid, on 1,3-dipolar cycloaddition reactions of azomethine ylides [5]. We have found that pyrrolidine derivatives could be synthesized under milder reaction conditions in good yields and high regio- and stereoselectivity. Ferrocene substituted organic molecules hold great potential due to their biological activity [6], increasing application in asymmetric catalysis [7] and material science [8]. Therefore, we were interested in synthesizing ferrocene substituted pyrrolidine derivatives by employing our method. Described herein are the details of the Et_2Zn catalyzed 1,3-dipolar cycloaddition reactions of azomethine ylide **2** with electron deficient dipolarophiles: *N*-methylmaleimide, dimethyl maleate, methyl acrylate, and acrylonitrile.

2. Results and discussion

Condensation of ferrocenecarboxaldehyde with glycine methyl ester (**1**) produced the corresponding imine, which tautomerized to give the intermediate azomethine ylide **2**. This ylide was trapped with electron deficient dipolarophiles in the presence of Et_2Zn (Scheme 1, Table 1). When methyl acrylate (**3**) was used as the dipolarophile, only cycloadduct **4** was obtained in high regio- and stereoselectivity (Table 1, entry 1). The regiochemistry and 2,3-*cis* configuration of the cycloadduct **4** were easily deduced from the characteristic upfield shift of the 3-CO_2Me ^{1}H-NMR signal due to the shielding effect of *cis*-2-ferrocenyl group [1k]. The regiochemistry was further confirmed by the splitting patterns of H5 and H2 protons, which appeared as a triplet and a doublet, respectively. Formation of this compound can be explained by *endo* addition of dipo-

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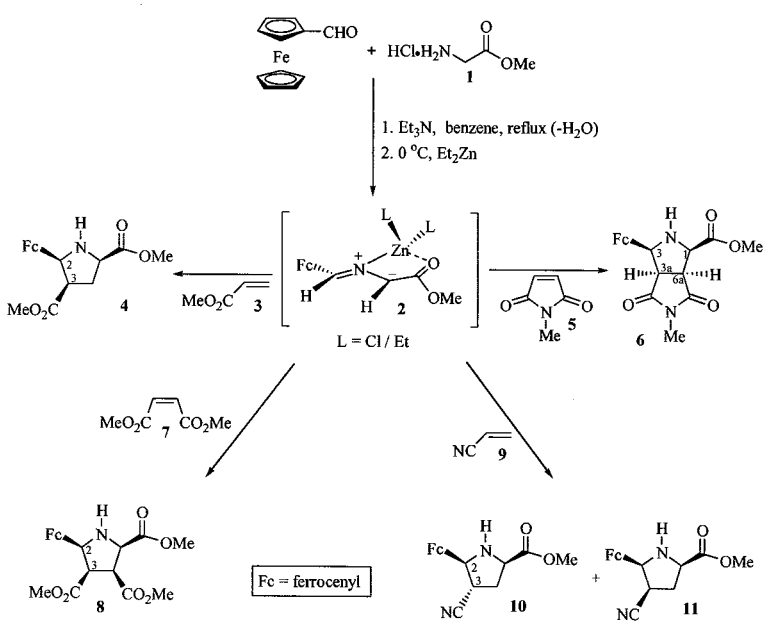

Scheme 1.

larophile to *syn* ylide **2**. Tsuge observed a similar result in a reaction carried out with benzaldehyde and methyl acrylate in the presence of LiBr [1d]. It is also known that *N*-metallated azomethine ylides, obtained by imine tautomerization, show high *endo* selectivity with carbonyl bearing dipolarophiles [1b].

The analogous 1,3-dipolar cycloaddition reaction of ylide **2** to *N*-methylmaleimide (**5**) afforded cycloadduct **6** in good yield and high *endo* selectivity (Table 1, entry 2). The structure of the cycloadduct **6** was assigned by comparing the vicinal coupling constants ($J_{1,6a} = 6.8$ Hz and $J_{3,3a} = 8.6$ Hz) with those of the similar compounds having phenyl or other aromatic groups in place of the ferrocenyl group. The same coupling constants ($J_{1,6a}$ and $J_{3,3a}$) are either zero or closer to zero when the corresponding protons (H1–H6a and H3–H3a) are *trans* to each other [1k]. Repetition of the 1,3-dipolar cycloaddition reaction with dimethyl maleate (**7**) gave cycloadduct **8** as a single product (Table 1, entry 3). The structure of cycloadduct **8** was determined by the upfield shift of the 3-CO_2Me ^{1}H-NMR signal by *cis*-2-ferrocenyl group as in the cycloadduct **4**. This assignment was further confirmed by NOE experiment, wherein irradiation of H3 resulted in enhancement of H4 and H2 signals. Finally, when acrylonitrile (**9**) was used as the dipolarophile, cycloadducts **10** and **11** were isolated (Table 1, entry 4). The structures of these isomers were also assigned by ^{1}H-NMR spectra, where H2 appeared as a triplet and H5 as a doublet in both isomers. High regioselectivity of this reaction can be attributed to the secondary orbital interactions between the ferrocenyl and the nitrile groups. Low *endo–exo* selectivity, however, is the result of weak coordination of the nitrile group to the metal in the transition state. This result also mirrors Tsuge's observations with the same dipolarophile used in similar reactions.

In summary, we have synthesized ferrocene substituted pyrrolidine derivatives for the first time in reasonable yields and high regio- and stereoselectivity by using 1,3-dipolar cycloaddition reactions of azomethine ylides obtained by the imine tautomerization method. We have also shown that Et_2Zn catalyzes 1,3-dipolar cycloaddition reactions of azomethine ylides to give the cycloadducts in high *endo* selectivity, which are in line with the literature observations in similar reactions. It should also be noted that the use of THF as the co-solvent increases the yields of the products to a considerable amount.

Table 1
The reaction of azomethine ylide **2** with dipolarophiles **3**, **5**, **7**, and **9**

Entry	Azomethine ylide	Dipolarophile	Product	Yield (%)
1	**2**	**3**	**4**	65
2	**2**	**5**	**6**	70
3	**2**	**7**	**8**	70 [a]
4	**2**	**9**	**10**+**11**	68 [b]

[a] When no THF was used as the co-solvent, formation of another isomer in minor amounts was seen in the ^{1}H-NMR spectrum of the crude reaction mixture.

[b] Products were isolated in 3:2 ratio respectively.

3. Experimental

3.1. Representative experimental procedure

Ferrocenecarboxaldehyde (340 mg, 1.59 mmol) was refluxed with glycine methyl ester hydrochloride (200 mg, 1.59 mmol) and Et_3N (0.24 ml, 1.75 mmol) for 1 h in a Dean–Stark apparatus in C_6H_6 (con. 0.4 M) to form the imines (Schiff bases) under Ar atmosphere. At the end of this period, the reaction flask was cooled to 0 °C, diethylzinc (1.00 ml of 1.6 M Et_2Zn in hexanes, 1.59 mmol), THF (0.50 ml) and dipolarophile (*N*-methylmaleimide, dimethylmaleate, methyl acrylate, or acrylonitrile, 3.18 mmol) were added to the reaction flask. The resulting mixture was stirred for 30 min at 0 °C and then for 5 h at room temperature. Then it was hydrolyzed with sat. NH_4Cl solution and extracted with CH_2Cl_2 (3×20 ml). The combined organic layer was dried over $MgSO_4$, concentrated, and purified by flash column chromatography on silica gel (Merck 60 0.040–0.060 nm). ^{1}H-NMR and ^{13}C-NMR spectra were obtained in CCl_4–$CDCl_3$ (2:3) solvent system, recorded in a Brucker Spectrospin Avance DPX-400 Ultrashield instrument and reported in ppm on the δ scale relative to residual $CHCl_3$ (δ 7.24 and 77.00). IR spectra were recorded on a Perkin–Elmer 1600 series FTIR spectrometer and reported in reciprocal centimeters (cm^{-1}). Mass data obtained by Micromass UK Platform-II instrument were reported for M^+ and high mass fragments derived from M^+ in electron impact (EI) mode. R_f values were determined in hexanes–EtOAc (1:1) solvent system. Melting points (m.p.) are uncorrected and were recorded on a Reichter 7905 apparatus.

4 ($R_f = 0.17$): ^{1}H-NMR: δ 4.28 (d, 1H, $J = 7.8$ Hz, H-2), 4.20 (s, 6H, ferrocene), 4.10 (s, 1H, ferrocene), 4.06 (s, 1H, ferrocene), 4.04 (s, 1H, ferrocene), 3.84 (t, 1H, $J = 8.3$ Hz, H-5), 3.82 (s, 3H, 5-COOMe), 3.35 (s, 3H, 3-COOMe), 3.18 (dt, 1H, $J = 7.9$ and 8.1 Hz, H-3), 2.77 (brs, 1H, N–H), 2.23 (t, 2H, $J = 7.63$ Hz, H-4). ^{13}C-NMR: δ 174.9, 172.0, 88.4, 69.0 ($5 \times$ C), 68.8, 68.5, 68.2, 65.8, 61.3, 59.7, 52.6, 51.6, 50.4, 32.5. IR (neat, cm^{-1}): 3349.6, 2951.2, 1733.2, 1435.1, 1225.6, 819.4, 505.9, 484.2. MS: 371 (M^+, 100), 253 (36), 224 (90), 186 (22), 130 (20), 121 (63), 103 (12), 59 (15), 55 (16).

6 ($R_f = 0.20$, m.p. = 182–184 °C): ^{1}H-NMR (CCl_4–$CDCl_3$): δ 4.26 (d, 1H, $J = 8.6$ Hz, H-3), 4.24 (s, 1H, ferrocene), 4.20 (s, 1H, ferrocene), 4.13 (s, 6H, ferrocene), 4.00 (d, 1H, $J = 6.8$ Hz, H-1), 3.88 (s, 3H, COOMe), 3.48 (t, $J = 7.2$ Hz, H-6a), 3.20 (t, $J = 8.1$ Hz, H-3a), 2.80 (s, 3H, N-Me). ^{13}C-NMR: δ 175.5, 174.3, 170.0, 84.4, 68.7 ($5 \times$ C), 68.3, 67.9, 65.2, 61.4, 60.7, 52.1, 49.6, 49.5, 24.8. IR (KBr pellet, cm^{-1}): 3456.6, 2956.9, 1745.3, 1697.0, 1436.1, 1285.9, 1224.9, 1203.8, 1090.8, 976.1, 844.0, 729.1, 495.1. MS: 396 (M^+, 100), 253 (17), 225 (45), 130 (48), 121 (66), 77 (23), 55 (37), 43 (55), 32 (88).

8 ($R_f = 0.17$, m.p. = 111–113 °C): ^{1}H-NMR: δ 4.29 (s, 1H, ferrocene), 4.22 (d, 1H, $J = 7.2$ Hz, H-2), 4.20 (s, 5H, ferrocene), 4.08 (m, 4H, H-5 + ferrocene), 3.80 (s, 3H, 5-COOMe), 3.68 (s, 3H, 4-COOMe), 3.55 (t, 1H, $J = 8.0$ Hz, H-4), 3.31 (s, 3H, 3-COOMe), 3.19 (t, 1H, $J = 7.2$ Hz, H-3). ^{13}C-NMR: δ 171.9, 171.2, 170.7, 84.6, 69.2 ($5 \times$ C), 68.9, 68.2, 68.1, 65.8, 62.2, 62.0, 52.7, 52.2, 52.1, 51.6, 51.2. IR (KBr pellet, cm^{-1}): 3347.4, 2946.9, 1733.2, 1437.5, 1256.0, 1235.0, 1202.9, 1168.0, 819.4, 513.2, 487.0. MS: 429 (M^+, 100), 253 (26), 225 (55), 130 (20), 121 (61), 77 (21), 59 (92), 55(25), 48 (66), 35 (87), 32 (86), 29 (32).

10 ($R_f = 0.23$): ^{1}H-NMR: δ 4.34 (s, 1H, ferrocene), 4.24 (s, 1H, ferrocene), 4.23 (s, 6H, ferrocene), 4.21 (s, 1H, ferrocene), 4.14 (d, 1H, $J = 6.5$ Hz, H-2), 3.86 (t, 1H, $J = 7.7$ Hz, H-5), 3.84 (s, 3H, COOMe), 3.13 (dt, 1H, $J = 7.0$ and 7.0 Hz, H-3), 2.48 (dt, 1H, $J = 12.9$ and 7.4 Hz, H-4), 2.30 (dt, 1H, $J = 12.9$ and 7.4 Hz H-4). ^{13}C-NMR: δ 173.9, 118.9, 86.9, 69.2 ($5 \times$ C), 69.0, 68.9, 68.8, 66.3, 61.1, 59.1, 53.0, 36.2, 34.7. IR (neat, cm^{-1}): 3345.4, 2952.1, 2922.3, 2240.5, 1736.4, 1435.7, 1217.9, 1105.2, 820.6, 486.1. MS: 338 (M^+, 100), 253 (25), 225 (72), 121 (64), 77 (17), 56 (25), 49 (24), 32 (67).

11 ($R_f = 0.52$, m.p. = 64–67 °C): ^{1}H-NMR: δ 4.25 (s, 1H, ferrocene), 4.19 (s, 1H, ferrocene), 4.15 (s, 5H, ferrocene), 4.12 (s, 2H, ferrocene), 3.97 (d, 1H, $J = 8.6$ Hz, H-2), 3.92 (dd, 1H, $J = 5.5$ and 8.4 Hz, H-5), 3.73 (s, 3H, COOMe), 2.62 (dt, 1H, $J = 8.9$ and 8.8 Hz, H-3), 2.48 (m, 2H, $2 \times$ H-4). ^{13}C-NMR: δ 172.8, 118.7, 86.4, 67.6 ($5 \times$ C), 67.3, 67.2, 67.1, 66.0, 64.4, 61.9, 57.8, 51.4, 34.6. IR (neat, cm^{-1}): 3289.1, 2925.4, 2236.0, 1730.7, 1424.9, 1358.8, 1214.3, 1122.8, 1103.2, 819.4, 773.0, 503.1, 486.6. MS: 338 (M^+, 100), 252 (30), 225 (75), 121 (59), 77(15), 49 (18), 32 (57).

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