Reactivity of 2-Methylene-1,3-dicarbonyl Compounds. 1,3-Dipolar Cycloaddition Reaction with Ethyl Diazoacetate

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The reaction of 2-methylene-1,3-dicarbonyl compounds (1) with ethyl diazoacetate gave 4,5-dihydro-1*H*-pyrazole derivatives (2), which were stable for several months at room temperature in good yields.

Key words 2-methylene-1,3-dicarbonyl compound; 1,3-dipolar addition; ethyl diazoacetate; 4,5-dihydro-1*H*-pyrazole derivative

1,3-Dipolar cycloadditions are a useful class of synthetic reactions for the construction of functionalized five-membered heterocycles.[1] Although cycloadditions using nitrile oxides,[2] azomethine ylides,[3] carbonyl ylides,[4] nitrones,[5] and nitroalkenes[6] as dipoles have been well studied, the use of diazoalkanes as dipoles has not been extensively examined. Because of the instability of the initial [3+2] adduct, synthetic applications of these dipoles have typically been limited to the preparation of the derived cyclopropanes or pyrazoles obtained by nitrogen extrusion or aromatization, respectively.[7] During the course of our studies on the reactivity of 2-methylene-1,3-dicarbonyl compounds **1**[8] we investigated the reaction with ethyl diazoacetate and obtained relatively stable pyrazoline derivatives (Chart 1).

2-Methylene-1,3-dicarbonyl compounds **1**[9] were reacted with ethyl diazoacetate in CH_2Cl_2 at room temperature to give 1,3-dipopar cycloadducts in good yields regardless of R (methyl, phenyl, alkoxy groups) (Table 1). In the ^{1}H-NMR spectrum of the adduct from **1a** (R=OMe), signals at 3.50 and 4.07 ppm show geminal coupling constant (18.3 Hz), and the latter shows long-range coupling (1.5 Hz) with NH which appeared at 7.42 ppm. In addition the frontier molecular orbital (FMO) theory[10] predicts the adduct should be **3**. From these facts the final product is thermodynamically more stable **2** (**2a** from **1a**) which is isomerized from **3**. The other possible regioisomers **4** and **5** must show different ^{1}H-NMR spectra.

We earlier succeeded in the enantioselective catalytic Diels–Alder reaction,[11] and next we examined the chiral Lewis acid catalyzed dipolar addition reactions. As **1b** gave almost the same result under the identical conditions shown in Table 1, except for the reaction temperature (entry 4), the chiral Lewis acid catalyzed reaction of **1b** was carried out by slowly adding ethyl diazoacetate using MgI_2 and bis(oxazoline) **6** as a chiral ligand (Table 2). However, the products (entries 1—3) show no specific optical rotation. This means the reactivity of **1b** is too reactive to introduce the chirality into the adduct.

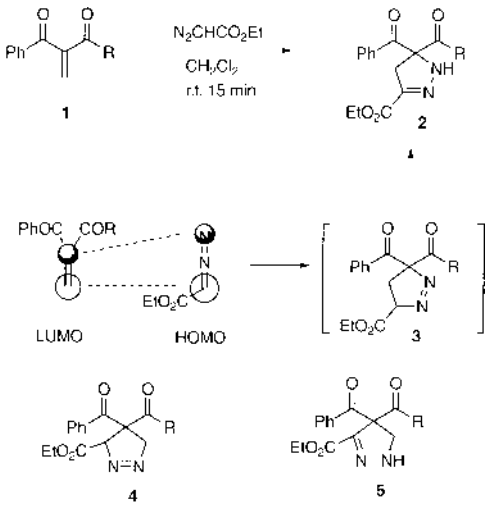

Chart 1

Experimental

NMR spectra were measured on a JEOL GX-270 spectrometer for samples in $CDCl_3$ solution at 270 MHz for ^{1}H and 67.89 MHz for ^{13}C, and chemical shifts are expressed in δ-units using tetramethylsilane or chloro-

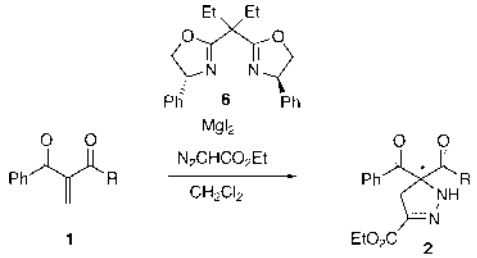

Chart 2

Table 1. Reaction of **1** with Ethyl Diazoacetate at Room Temperature

1	R	Yield(%) of **2**
a	OMe	93
b	OEt	95
c	Opr^i	98
d	Cyclopentyloxy	93
e	Cyclohexyloxy	97
f	OCH_2Ph	88
g	Me	98
h	Ph	93

Table 2. Reaction of **1** with Ethyl Diazoacetate in the Presence of Chiral Lewis Acid

Entry	MgI_2 (eq)	**6** (eq)	Temp. (°C)	Addition time (h) of N_2CHCO_2Et	Yield (%)
1	0.1	0.2	0	3	84
2	0.1	0.1	0	3	94
3	0.1	0.1	−90	6	78
4	None	None	−90	0.25	95

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form as an internal standard. IR spectra were recorded on a JASXCO FT/IR-410 spectrometer. High-resolution mass spectra (HR-MS) were obtained with a JEOL JMS-700 spectrometer. $MgSO_4$ was used to dry organic layers after extraction. Preparative thin layer chromatography (p-TLC) was performed with Merck Silica Gel 60 F_{254} (0.5 mm).

Reaction of 2-Methylene-1,3-dicarbonyl Compounds with Ethyl Diazoacetate General Procedure A solution of ethyl diazoacetate (0.6 mmol) in CH_2Cl_2 (3 ml) was added to a solution of 2-methylene-1,3-dicarbonyl compounds (0.5 mmol) in CH_2Cl_2 (4 ml) during a period of 15 min at room temperature. As soon as the addition was completed the solvent was evaporated off and the resulting residue was applied to p-TLC. The adducts were obtained in the yields shown in Table 1.

5-Benzoyl-4,5-dihydro-1*H*-pyrazole-3,5-dicarboxylic Acid 3-Ethyl Ester 5-Methyl Ester (**2a**): A yellow oil. IR (neat): 1738, 1691 cm^{-1}. ^{1}H-NMR δ: 1.33 (3H, t, J=7.1 Hz, CH_3), 3.50 (1H, d, J=18.3 Hz, 4-H), 3.75 (3H, s, CH_3), 4.07 (1H, dd, J=18.3, 1.5 Hz, 4-H), 4.29 (2H, q, J=7.1 Hz, OCH_2), 7.42 (1H, br s, NH), 7.49 (2H, t, J=7.5 Hz, ArH), 7.63 (1H, tt, J=7.5, 1.5 Hz, ArH), 7.88 (2H, dd, J=7.5, 1.5 Hz, ArH). ^{13}C-NMR δ: 13.8, 39.2, 53.4, 61.1, 78.2, 128.7, 128.8, 131.4, 134.0, 142.7, 161.1, 169.0, 191.6. HR-MS m/z: Calcd for $C_{15}H_{16}N_2O_5$: 304.1059. Found: 304.1066.

5-Benzoyl-4,5-dihydro-1*H*-pyrazole-3,5-dicarboxylic Acid Diethyl Ester (**2b**): A yellow oil. IR (neat): 1736, 1692 cm^{-1}. ^{1}H-NMR δ: 1.13 (3H, t, J=7.1 Hz, CH_3), 1.33 (3H, t, J=7.1 Hz, CH_3), 3.52 (1H, d, J=18.3 Hz, 4-H), 4.06 (1H, dd, J=18.3, 1.5 Hz, 4-H), 4.11 (2H, q, J=7.1 Hz, OCH_2), 4.29 (2H, q, J=7.1 Hz, OCH_2), 7.40 (1H, br s, NH), 7.49 (2H, t, J=7.5 Hz, ArH), 7.60 (1H, tt, J=7.5, 1.5 Hz, ArH), 7.88 (2H, dd, J=7.5, 1.5 Hz, ArH). ^{13}C-NMR δ: 13.4, 13.8, 39.1, 61.1, 62.7, 78.3, 128.7, 128.8, 131.5, 133.9, 142.7, 161.1, 168.4, 192.1. *Anal.* Calcd for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.14; H, 5.78; N, 8.46. HR-MS m/z: Calcd for $C_{16}H_{18}N_2O_5$: 318.1216. Found: 318.1198.

5-Benzoyl-4,5-dihydro-1*H*-pyrazole-3,5-dicarboxylic Acid 3-Ethyl Ester 5-Isopropyl Ester (**2c**): A yellow oil. IR (neat): 1733, 1691 cm^{-1}. ^{1}H-NMR δ: 1.01 (3H, d, J=6.3 Hz, CH_3), 1.19 (3H, d, J=6.3 Hz, CH_3), 1.34 (3H, t, J=7.2 Hz, CH_3), 3.51 (1H, d, J=18.3 Hz, 4-H), 4.04 (1H, dd, J=18.3, 1.5 Hz, 4-H), 4.29 (2H, q, J=7.2 Hz, OCH_2), 5.06 (1H, heptet, J=6.3 Hz, OCH), 7.37 (1H, br s, NH), 7.48 (2H, t, J=7.5 Hz, ArH), 7.62 (1H, tt, J=7.5, 1.3 Hz, ArH), 7.89 (2H, dd, J=7.5, 1.3 Hz, ArH). ^{13}C-NMR δ: 14.2, 21.1, 21.3, 39.3, 61.6, 71.2, 78.7, 129.0, 129.1, 131.9, 134.2, 143.3, 161.5, 168.1, 192.5. HR-MS m/z: Calcd for $C_{17}H_{20}N_2O_5$: 332.1372. Found: 332.1377.

5-Benzoyl-4,5-dihydro-1*H*-pyrazole-3,5-dicarboxylic Acid 5-Cyclopentyl Ester 3-Ethyl Ester (**2d**): A yellow oil. IR (neat): 1736, 1692 cm^{-1}. ^{1}H-NMR δ: 1.33 (3H, t, J=7.1 Hz, CH_3), 1.18—1.81 (8H, m, CH_2), 3.51 (1H, d, J=18.1 Hz, 4-H), 4.05 (1H, dd, J=18.1, 1.5 Hz, 4-H), 4.29 (2H, q, J=7.1 Hz, OCH_2), 5.21 (1H, m, OCH), 7.35 (1H, br s, NH), 7.48 (2H, t, J=7.3 Hz, ArH), 7.62 (1H, tt, J=7.3, 1.5 Hz, ArH), 7.88 (2H, dd, J=7.3, 1.5 Hz, ArH). ^{13}C-NMR δ: 13.9, 22.9, 23.1, 31.9×2, 39.1, 61.2, 78.4, 80.1, 128.77, 128.80, 131.6, 134.0, 142.9, 161.2, 168.1, 192.2. HR-MS m/z: Calcd for $C_{19}H_{22}N_2O_5$: 358.1529. Found: 358.1527.

5-Benzoyl-4,5-dihydro-1*H*-pyrazole-3,5-dicarboxylic Acid 5-Cyclohexyl Ester 3-Ethyl Ester (**2e**): A yellow oil. IR (neat): 1735, 1692 cm^{-1}. ^{1}H-NMR δ: 1.33 (3H, t, J=7.1 Hz, CH_3), 1.18—1.80 (10H, m, CH_2), 3.52 (1H, d, J=18.3 Hz, 4-H), 4.05 (1H, dd, J=18.3, 1.5 Hz, 4-H), 4.29 (2H, q, J=7.1 Hz, OCH_2), 4.84 (1H, m, OCH), 7.39 (1H, br s, NH), 7.48 (2H, t, J=7.3 Hz, ArH), 7.61 (1H, tt, J=7.3, 1.5 Hz, ArH), 7.88 (2H, dd, J=7.3, 1.5 Hz, ArH). ^{13}C-NMR δ: 13.9, 22.7, 22.8, 24.7, 30.7, 39.1, 61.2, 78.5, 128.7, 128.8, 131.7, 133.9, 142.8, 161.2, 167.9, 192.2. HR-MS m/z: Calcd for $C_{20}H_{24}N_2O_5$: 372.1685. Found: 372.1694.

5-Benzoyl-4,5-dihydro-1*H*-pyrazole-3,5-dicarboxylic Acid 5-Benzyl Ester 3-Ethyl Ester (**2f**): A yellow oil. IR (neat): 1735, 1691 cm^{-1}. ^{1}H-NMR δ: 1.32 (3H, t, J=7.1 Hz, CH_3), 3.51 (1H, d, J=18.1 Hz, 4-H), 4.06 (1H, dd, J=18.1, 1.4 Hz, 4-H), 4.28 (2H, q, J=7.1 Hz, OCH_2), 5.16 (2H, ABq, J=12.3 Hz, OCH_2), 7.05—7.85 (11H, m, ArH and NH). ^{13}C-NMR δ: 14.2, 39.5, 61.6, 68.5, 78.6, 128.1, 128.49, 128.53, 129.0, 129.1, 129.2, 131.6, 134.2, 143.4, 161.4, 168.4, 192.2. HR-MS m/z: Calcd for $C_{21}H_{20}N_2O_5$: 380.1372. Found: 380.1373.

5-Acetyl-5-benzoyl-4,5-dihydro-1*H*-pyrazole-3-carboxylic Acid Ethyl Ester (**2g**): A yellow oil. IR (neat): 1736, 1710, 1691 cm^{-1}. ^{1}H-NMR δ: 1.33 (3H, t, J=7.1 Hz, CH_3), 2.19 (3H, s, CH_3), 3.46 (1H, d, J=18.5 Hz, 4-H), 4.07 (1H, dd, J=18.5, 1.6 Hz, 4-H), 4.29 (2H, q, J=7.1 Hz, OCH_2), 7.49 (2H, t, J=7.3 Hz, ArH), 7.59 (1H, br s, NH), 7.63 (1H, tt, J=7.3, 1.5 Hz, ArH), 7.85 (2H, dd, J=7.3, 1.5 Hz, ArH). ^{13}C-NMR δ: 14.1, 25.6, 37.6, 61.6, 85.2, 129.1, 129.7, 131.9, 134.6, 144.3, 161.4, 194.9, 199.9. HR-MS m/z: Calcd for $C_{15}H_{16}N_2O_4$: 288.1110. Found: 288.1128.

5,5-Dibenzoyl-4,5-dihydro-1*H*-pyrazole-3-carboxylic Acid Ethyl Ester (**2h**): A yellow oil. IR (neat): 1730, 1697, 1678 cm^{-1}. ^{1}H-NMR δ: 1.34 (3H, t, J=7.1 Hz, CH_3), 4.00 (2H, s, 4-H), 4.30 (2H, q, J=7.1 Hz, OCH_2), 7.41 (2H, t, J=7.3 Hz, ArH), 7.52 (1H, br s, NH), 7.54 (1H, tt, J=7.3, 1.5 Hz, ArH), 7.85 (2H, dd, J=7.3, 1.5 Hz, ArH). ^{13}C-NMR δ: 14.2, 39.9, 61.6, 84.1, 129.0, 129.6, 133.4, 134.1, 143.9, 161.5, 193.7. HR-MS m/z: Calcd for $C_{20}H_{18}N_2O_4$: 350.1267. Found: 350.1254.

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