The Magnesium Bromide Induced Claisen Condensation Reaction of *N*-Acylpyrazoles

Choji Kashima,* Katsumi Takahashi, and Kiyoshi Fukusaka

Department of Chemistry, University of Tsukuba, Tsukuba, Ibaraki 305, Japan

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N-Acylpyrazoles formed the 5-membered C=O···Mg···N-2 chelate complexes with magnesium bromide which afforded the Claisen condensation products by the action of tertiary amine through the corresponding enolate.

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Recently we have been interested in *N*-acylpyrazoles, especially 2-acyl-3-phenyl-*l*-menthopyrazoles as the chiral synthetic intermediate [1]. By the treatment with various nucleophiles, *N*-acylpyrazoles were converted into the corresponding amides [2], esters [3], ketones [4] and β-ketoesters [5]. Moreover, *N*-acylpyrazoles were allowed to react with LDA or LiHMDS to generate lithium enolates, which were the key intermediates for α-alkylation [6] or α-sulfenylation [7]. The chemical behavior of *N*-acylpyrazoles satisfied the requirements such as the activation of the substrate moiety of the substrate-auxiliary intermediate and the conversion of substrate-auxiliary intermediate into the desired functionalities. In order to expand the utility of *N*-acylpyrazoles as the substrate-auxiliary intermediate, the reactions of *N*-acylpyrazoles are desired to proceed under the more efficient and convenient conditions.

The alcoholysis of *N*-acylpyrazoles was effectively catalyzed by boron trifluoride etherate, where the N-2 atom of the pyrazole ring was chelated to form a pyrazolium complex [3]. Furthermore, the highly diastereoselective α-alkylation of 2-acyl-3-phenyl-*l*-menthopyrazoles was reasonably explained by the electrophilic attack on the lithium enolate intermediate, which was rigidly fixed by the intramolecular chelation between lithium and N-2 atoms [6]. These facts suggested that the N-2 atom of the pyrazole preferred to chelate with various Lewis acids. The magnesium ion has a very similar Van der Waals radius compound with the lithium ion and magnesium bromide recently has received much attention as a divalent Lewis acid having a small atomic size [8]. Under these situations, we attempted to observe the interaction between *N*-acylpyrazoles and magnesium bromide.

Table 1

The Chemical Shifts of **1** and their magnesium bromide Complexes

	Assignment	δ of **1**	δ of $MgBr_2$ Complex	Δδ [a]
1a	3-Me	2.24	2.55	0.31
	4H	5.96	6.35	0.39
	5Me	2.54	2.77	0.23
	Ac	2.66	3.02	0.36
1b	3Me	2.55	2.51	0.26
	4H	6.06	6.33	0.27
	5Me	2.63	2.15	-0.48
1c	4H	6.71	6.73	0.02
	Ac	2.79	2.53	-0.26

[a] The upfield shifts in the complex formation are represented as a negative value.

In the ir spectrum of 1-acetyl-3,5-dimethylpyrazole (**1a**), the carbonyl absorption band at 1727 cm^{-1} was shifted to 1680 cm^{-1} by the addition of magnesium bromide etherate in chloroform solution, while no change was observed in THF solution. This fact suggested chelation with magnesium bromide on the carbonyl oxygen of **1a** in chloroform. The peak intensity of **1a** in the gc was decreased by the addition of magnesium bromide etherate in chloroform. The decrease of the peak intensity was explained by the chelation of **1a** with magnesium bromide and disappearance of the signal of chelated product in the gc. From the peak intensities toward various amounts of magnesium bromide etherate and in various concentrations, the equilibrated chelation was shown to be approximately K= 15 1/mol in chloroform at room temperature. The equilibrium constant was K= 20 1/mol in dichloromethane.

Moreover, the formation of complex among **1** and magnesium bromide was established in the ^1H nmr, where all peaks of **1a** were shifted down field by the addition of magnesium bromide etherate. In the case of 1-benzoyl-3,5-dimethylpyrazole (**1b**), the 5-Me peak was shifted up field, while 3-Me and 4-H proton signals appeared at lower field. This upfield shift was illustrated in Figure 1 was caused by the anisotropic effect of the benzene ring, which was fixed in a closed location of the 5-Me by the

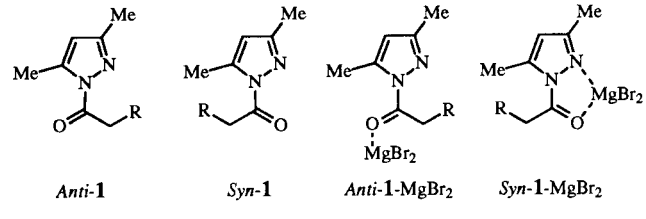


Figure 1.

syn conformation due to the 5-membered chelation of C=O···Mg···N-2. A similar upfield anisotropic shift was observed in the acetyl protons of 1-acetyl-3,5-diphenylpyrazole (**1c**).

The molecular orbital calculations of **1a** and the magnesium bromide complex was carried out by the PM3 method listed in Table 2. The predominant conformer of **1a** was postulated to be the *anti* form 3 kcal/mol more stable than *syn*-conformer. In the case of the magnesium bromide complex, *syn*-**1a**-magnesium bromide was rather stable from the 5-membered chelation of C=O···Mg···N-2. The results of these calculations supported the postulated conformation based on chromatographic and spectroscopic data.

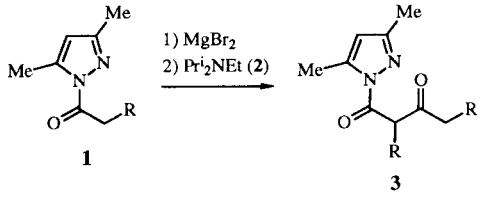
Table 2
PM3 Calculation of **1a** and its Magnesium Bromide Complexes

		Anti-**1a**	*Syn*-**1a**	*Anti*-**1a**-$MgBr_2$	*Syn*-**1a**-$MgBr_2$
Heat of Formation (Kcal/Mol)		-11.10	-7.74	-100.22	-117.41
Charge	2**N**	-0.2182	-0.1586	-0.2045	0.0804
	3Me-**H**	0.0598	0.0518	0.0665	0.0783
	4**H**	0.1404	0.1395	0.1531	0.1554
	5Me-**H**	0.0528	0.0544	0.0702	0.0717
	1Ac-**O**	-0.3347	-0.2771	-0.2797	-0.1995
	1Ac-**H**	0.0754	0.0750	0.1134	0.0932

Recently some amides were reported to be activated by the formation of complexes with Lewis acids, and the subsequent complexes were easily deprotonated on the α-position by the action of a weak base such as tertiary amines [9]. In the Table 2, the positive charges on the acetyl protons of **1a** were much increased by the formation of the magnesium bromide complex. Generally ethanol, which must inhibit the formation of the complex with Lewis acids, is contained in chloroform as the stabilizer. Moreover, the equilibrium constant of the magnesium bromide complex formation in dichloromethane was larger than in chloroform. Therefore, the generation of the enolate was attempted by treating a mixture of **1a** and magnesium bromide etherate with a tertiary amine in dichloromethane.

When the mixture of **1a** and magnesium bromide etherate was treated with *N*-ethyldiisopropylamine (**2**) in dichloromethane at room temperature, **1a** was allowed to react but the remarkable product was hardly isolated. In the case of 1-propanoyl-3,5-dimethylpyrazole (**1d**), 1-(2-methyl-3-oxo)pentanoyl-3,5-dimethylpyrazole (**3d**) was obtained in good yield through the Claisen condensation of **1d**. The structure of **3d** was determined by spectral data and elemental analysis. Also **3d** was converted into the corresponding β-ketoester and β-ketoamide by the treatment with borontrifluoride etherate in methanol and pyrrolidine, respectively. Although neither the mixture of **1d** and magnesium bromide etherate nor **1d** and **2** gave **3d**, the effective formation of **3d** was optimally accomplished by the use of equimolar amounts of magnesium bromide etherate and **2**. This reaction mechanism was presumed that **1d** was deprotonated from the α-position of the acyl group to form an enolate, which caused the nucleophilic attack on the carbonyl of **1d** to afford **3d**. Similarly, 1-butanoyl-**1e** and 1-(3-phenyl)propanoyl-3,5-dimethylpyrazole (**1f**) were allowed to afford the Claisen condensation products in good yields. In the case of 1-(3-methyl)butanoyl-3,5-dimethylpyrazole (**1g**), the reaction proceeded rather slowly owing to their steric hindrance.

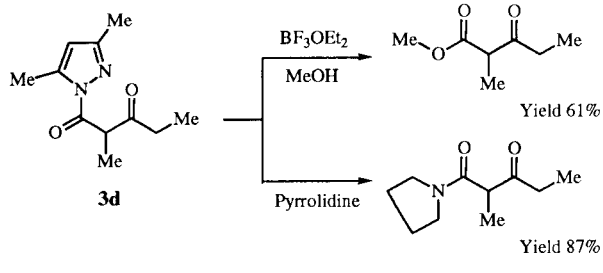
Table 3
Isolated Yields of the Claisen Condensation Products **3**



	R	Time (h)	Yield (%)
a	H	1	trace
d	Me	1	68
e	Et	1	56
f	$PhCH_2$	1	64
g	Pr^i	5	52

After all, *N*-acylpyrazoles formed the chelate complexes with magnesium bromide in chloroform and dichloromethane. From the nmr and PM3 calculation, the structures of these complexes were deduced to be fixed in the *syn* conformer with 5-membered chelation of C=O···Mg···N-2. By the action of tertiary amine, the magnesium bromide complexes afforded the Claisen condensation products through the corresponding enolate. This activation on the α-position of the *N*-acylpyrazoles must expand their utilities as the synthetic intermediate.

Scheme



EXPERIMENTAL

Melting points are uncorrected. The nmr spectra were obtained on JEOL JNM-EX270 (270 MHz) spectrometers in deuteriochloroform with TMS as an internal standard. The ir spectra were measured by a Shimadzu IR-460 spectrophotometer. The gas

chromatograms were obtained by a Shimadzu GC-4CM with FID detector through SE-30 (10%) column (2 m). The THF and dichloromethane were dried over the benzophenone ketyl radical and calcium hydride, respectively. The reagent of magnesium bromide etherate was commercially available from Aldrich Chemicals Co.

General Procedure.

To a mixture of 1-acyl-3,5-dimethylpyrazole (**1**, 1.0 mmole) and magnesium bromide etherate (284 mg, 1.1 mmoles) in dry dichloromethane (2 ml), *N*-ethyldiisopropylamine (258 mg, 2.0 mmoles) in dichloromethane (1 ml) was added and stirred for 1 hour at room temperature. The reaction mixture was washed with diluted hydrochloric acid, water, aqueous sodium hydrogen carbonate and aqueous sodium chloride, dried over anhydrous magnesium sulfate, and concentrated. The residue was chromatographed on silica gel with the mixture of hexane-ethyl acetate (v/v 20:1).

1-(2-Methyl-3-oxo)pentanoyl-3,5-dimethylpyrazole (**3d**).

This compound had bp 30°/2 mm Hg; ^{1}H nmr (deuteriochloroform): δ 1.23 (3H, t, J = 7 Hz), 2.23 (3H, s), 2.54 (3H, d, J = 1 Hz), 3.12 (2H, q, J = 7 Hz), 5.94 (1H, s).

Anal. Calcd. for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 61.69; H, 7.34; N, 14.52.

1-(2-Ethyl-3-oxo)hexanoyl-3,5-dimethylpyrazole (**3e**).

This compound had bp 70-75°/5 mm Hg; ^{1}H nmr (deuteriochloroform): δ 0.91 (3H, t, J = 7.6 Hz), 1.02 (3H, t, J = 7.6 Hz), 1.63 (2H, sextet, J = 7.3 Hz), 1.81-2.08 (2H, m), 2.19 (3H, s), 2.47-2.59 (1H, d-t, J = 17.5, 6.9 Hz), 2.54 (3H, d, J = 0.7 Hz), 2.73-2.85 (1H, d-t, J = 17.5, 6.9 Hz), 4.61 (1H, d-d, J = 8.3, 5.6 Hz), 5.94 (1H, s).

Anal. Calcd. for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.85. Found: C, 66.11; H, 8.73; N, 12.00.

1-(2-Benzyl-5-phenyl-3-oxo)pentanoyl-3,5-dimethylpyrazole (**3f**).

This compound had ^{1}H nmr (deuteriochloroform): δ 2.14 (3H, s), 2.22-2.44 (1H, d-d-d, J = 17.9, 9.2, 5.9 Hz), 2.51 (3H, s), 2.72-2.80 (2H, m), 3.05-3.19 (2H, m), 3.30 (1H, d-d, J = 13.9, 6.9 Hz), 4.93 (1H, t, J = 6.9 Hz), 5.91 (1H, s), 7.03-7.30 (10H, m).

Anal. Calcd. for $C_{23}H_{24}N_2O_2$: C, 76.64; H, 6.71; N, 7.77. Found: C, 76.39; H, 6.76; N, 7.78.

1-(2-Isopropyl-5-methyl-3-oxo)hexanoyl-3,5-dimethylpyrazole (**3g**).

This compound had bp 100°/5 mm Hg; ^{1}H nmr (deuteriochloroform): δ 0.87 (3H, d, J = 7.6 Hz), 8.96 (3H, d, J = 6.6 Hz), 1.02 (6H, d, J = 6.6 Hz), 2.13-2.31 (2H, m), 2.21 (3H, s), 2.36-2.45 (1H, d-d, J = 17.5, 6.6 Hz), 2.54 (3H, s), 2.70-2.79 (1H, d-d, J = 17.5, 6.6 Hz), 4.68 (1H, d, J = 8.9 Hz), 5.95 (1H, s).

Anal. Calcd. for $C_{15}H_{24}N_2O_2$: C, 68.15; H, 9.15; N, 10.6. Found: C, 68.23; H, 9.39; N, 10.76.

Methanolysis of **3d**.

The methanol (2 ml) solution of **3d** (142 mg) and boron trifluoride etherate (167 mg) was refluxed for 2 hours. The mixture was quenched with water and extracted with dichloromethane. The organic layer was washed with water and aqueous sodium chloride, dried over anhydrous magnesium sulfate, and concentrated. The residue was chromatographed on silica gel with benzene-ethyl acetate mixture (v/v 20:1), yield 61%; ^{1}H nmr (deuteriochloroform): δ 1.07 (3H, t, J = 7.3 Hz), 1.34 (3H, d, J = 7.3 Hz), 2.46-2.66 (2H, m), 3.54 (1H, q, J = 7.3 Hz), 3.72 (H, s).

Aminolysis of **3d**.

The mixture of **3d** (96 mg) and pyrrolidine (0.4 ml) in dry THF (2 ml) was stirred for 1 hour at room temperature. The reaction mixture was quenched with water and extracted with dichloromethane. The organic layer was washed with diluted hydrochloric acid, water, aqueous sodium hydrogen carbonate and aqueous sodium chloride, dried over anhydrous magnesium sulfate, and concentrated. The residue was chromatographed on silica gel with benzene-ethyl acetate mixture (v/v 1:1), yield 87%; ^{1}H nmr (deuteriochloroform): δ 1.04 (3H, t, J = 7.3 Hz), 1.37 (3H, d, J = 6.9 Hz), 1.83-2.04 (4H, m), 2.43-2.63 (2H, m), 3.45-3.60 (5H, m).

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