A CONVENIENT PREPARATION OF α-KETO ESTERS BY THE GRIGNARD REACTION ON *N*-ACYLPYRAZOLES†

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Abstract—The α–keto esters were prepared by the formation of *N*-acylpyrazole followed by the appropriate Grignard reaction. These short step reaction conveniently afforded various α–keto esters in good yields.

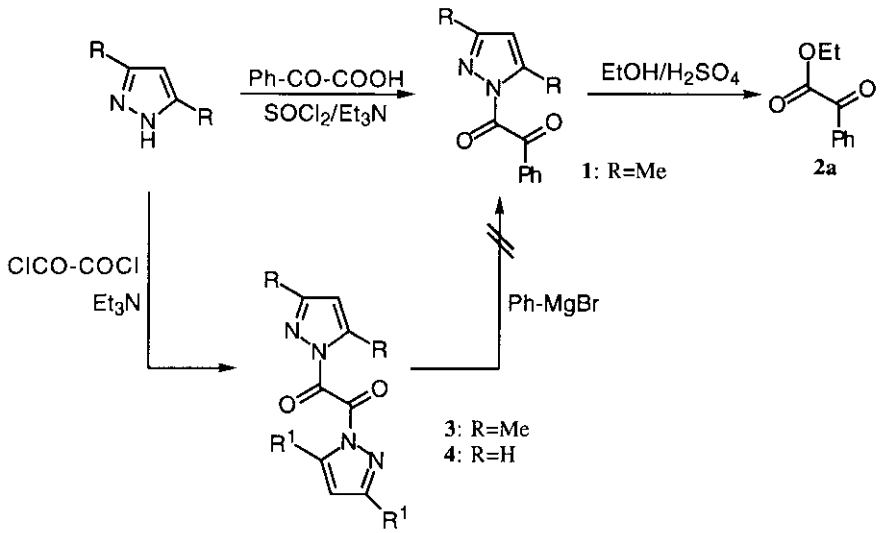
α-Keto esters have been paid attention to their biological activities such as the inhibitor of proteolytic enzymes[1] and leukotriene A4 hydrase.[2] Also α-keto esters are regarded as the important synthon of α-keto acids and α-hydroxy acids. In the literature, the various synthetic methods for these α-keto esters were reported including a few recent papers.[3] Since some defects were remained in these methods, general, convenient and preparative method of α-keto esters was still desired.

In the meantime, we have studied the synthetic utilities concerning to pyrazoles. Particularly 3-phenyl-*l*-menthopyrazole showed the excellent utilities as a new chiral auxiliary,[4] which has some unique structure and properties different from the conventional chiral auxiliaries.[5] The most important characteristic of this auxiliary is that the substrate terminates to nitrogen atom of heteroaromatic pyrazole ring and is surrounded by the chiral atmosphere. This structural characteristic causes the diastereofacial effect in the reactions on the substrate moiety. As the result, the asymmetric induction was caused on acyl group of 2-acyl-3-phenyl-*l*-menthopyrazoles in the reactions with alkyl halides,[6] diphenyl disulfide,[7] acyl chloride,[8] aldehydes,[9] and C=N compounds.[10] Similar diastereomeric selection was observed in the reaction of *N*-(α,β-unsaturated) acylpyrazoles with Grignard reagents[11] and 1,3-dipolar compounds.[12]

Otherwise, *N*-acylpyrazoles are easily converted into various acyl derivatives by the action of nucleophiles such as alcohols,[13] amines,[14] lithium aluminum hydride,[15] or organozinc compounds.[16] As an extensive studies about the chemistry of *N*-acylpyrazoles, we report the convenient preparative method of α-keto esters using *N*-acylpyrazoles.

Firstly, the convenient conversion of α–keto acids into the corresponding α–keto esters was undertaken through the *N*-acylpyrazoles. When the mixture of phenylglyoxylic acid and 3,5-dimethylpyrazole was treated with thionyl chloride in the presence of triethylamine, 1-phenylglyoxyl-3,5-dimethylpyrazole (**1**)

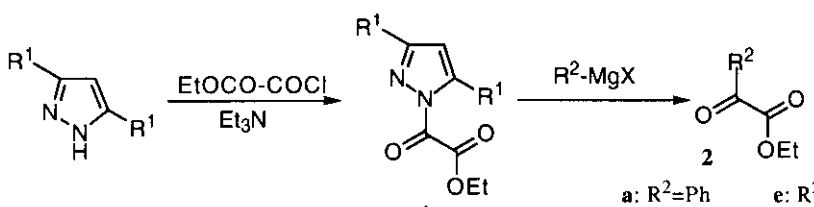
† This paper is dedicated to Professor Bernhard Witkop on the occasion of his 80th birthday for his brilliant achievement in the field of heterocyclic chemistry.



was obtained in 61 % yield. The resulting **1** was easily converted into ethyl phenylglyoxylate (**2**) in acidic ethanol in 64 % yield. Although this esterification reaction is very convenient, the limited sorts of starting α–keto acids are only available and much variety of α–keto esters could not be prepared.

In the Grignard reactions, *N*-acylpyrazoles were reactive rather than either aromatic or aliphatic ketones, and were labile exclusively compared with carboxylic esters.[17] Moreover, the formation of magnesium chelated intermediate in this Grignard reaction afforded selectively the corresponding ketones. On the bases of these chemical behaviors of *N*-acylpyrazoles, the preparation of α–keto esters was attempted by the Grignard reaction of 1,1'-oxalylbispyrazole and pyrazol-1'-ylglyoxylate. In the case of 1,1'-oxalylbis-3,5-dimethylpyrazole (**3**), which was formed from 3,5-dimethylpyrazole and oxalyl chloride, the complex mixture was formed without isolation of the desired **1**. Also the controlled Grignard reaction on 1,1'-oxalylbispyrazole (**4**) was unsuccessful. Next, ethyl 3',5'-dimethylpyrazol-1'-ylglyoxylate (**5**) was prepared from 3,5-dimethylpyrazole and ethyl chloroglyoxylate in the presence of triethylamine. The stability of **5** was enough for the ordinary handling and the long storage as the synthon. Similarly pyrazol-1'-yl- (**6**) and 3',5'-di-*t*-butylpyrazol-1'-ylglyoxylic acid ethyl esters (**7**) were obtained in good yield.

When **5** was treated with phenylmagnesium bromide, desired product (**2**) was obtained accompanied with benzil. The products were identical with the authentic samples by means of spectral and chromatographic comparison. After optimization, the formation of benzil was depressed and the yield of **2** was promoted by the use of 1.2 equimolar amount of Grignard reagent at -90°C, summarized in Table 1. Also the Grignard



5: R^1=Me
6: R^1=H
7: R^1=*t*-Bu

a: R^2=Ph
b: R^2=*p*-Tol
c: R^2=Me
d: R^2=Et
e: R^2=Bu
f: R^2=*i*-Pr
g: R^2=*c*-Hex
h: R^2=$PhCH_2CH_2$

reaction of **6** afforded same product (**2a**) in moderate yield, while **7** was recovered without any reaction by their steric hindrance. Similarly, **5** gave various α–keto esters by the treatment with aliphatic and aromatic Grignard reagents listed in Table 2. The product yield from butylmagnesium bromide was slightly higher than that from iodide due to the preference of the formation of intermediate chelate.

In conclusion, the α–keto esters were prepared by the formation of N-acylpyrazole followed by the appropriate Grignard reaction. These short step reaction conveniently afforded various α–keto esters in good yields.

Table 1. The Reaction of **5** with Ph-MgBr

Ph-MgBr (eq.)	Temp. (°C)	Yield of **2a** (%)	Yield of Benzil (%)
0.5	-5	33	21
0.8	-5	33	20
1.0	rt	36	13
1.0	-5	34	17
1.0	-90	39	19
1.2	-5	40	22
1.2	-90	64	15
1.5	-5	23	37
3.0	-5	4	39

Table 2. Grignard Reaction of 2-(Pyrazol-1'-yl)-2-oxoacetates.

Substrate	R^1	R^2-MgX	α-Keto Ester	Yield (%)
6	H	Ph-MgBr	**2a**	57
5	Me	Ph-MgBr	**2a**	64
7	*t*-Bu	Ph-MgBr	**2a**	
5	Me	*p*-Tol-MgBr	**2b**	57
5	Me	Me-MgI	**2c**	69
5	Me	Et-MgI	**2d**	66
5	Me	Bu-MgI	**2e**	70
5	Me	Bu-MgBr	**2e**	90
5	Me	*i*-Pr-MgBr	**2f**	51
5	Me	*c*-Hex-MgBr	**2g**	80
5	Me	$PhCH_2CH_2$-MgBr	**2h**	76

EXPERIMENTAL

Melting points are uncorrected. NMR spectra were obtained on Varian GEMINI 2000 (200 MHz) spectrometer in $CDCl_3$ with TMS as an internal standard. The IR spectra were recorded in chloroform solution by JASCO FT-IR 300 spectrophotometer. Ether and toluene were dried over benzophenone ketyl radical and calcium hydride, respectively.

1-(Phenylglyoxyl)-3,5-dimethylpyrazole (1). The toluene (20 mL) solution of thionyl chloride (1.8 g, 15 mmol) was gradually added to the mixture of 3,5-dimethylpyrazole (970 mg, 10 mmol), phenylglyoxylic acid (1.5 g, 10 mmol) and triethylamine (4.7 g, 47 mmol) in toluene (40 mL) at -5°C. After stirring for 2 h, the mixture was quenched with water. Toluene layer was washed with 2 % hydrochloric acid, water, saturated $NaHCO_3$ solution, and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated. The residue was chromatographed on silica gel column with hexane-ethyl acetate (v/v 5:1) mixture. bp 140-150°C/5 mmHg; yield 61 %; δ_H ($CDCl_3$): 2.13 (3H, s), 2.67 (3H, s), 6.07 (1H, s),7.48 (2H, t, J=8 Hz), 7.64 (1H, dt, J=1, 6 Hz), 7.92 (2H, dd, J=1, 6 Hz). *Anal.* Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27; Found: C, 68.59; H, 5.33; N, 12.26.

Preparation of Ethyl Phenylglyoxylate (2a) by Ethanolysis of 1. The mixture of **1** (181 mg, 0.8 mmol) and *p*-toluenesulfonic acid (192 mg, 1 mmol) in ethanol (5 mL) was refluxed for 2.5 h. The mixture was poured into water and extracted with Et_2O. The organic layer was washed with water, saturated $NaHCO_3$ solution, and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated. The residue was chromatographed on silica gel with hexane-benzene (v/v 1 : 2) mixture to afford **2a** in yield 64 %.

Preparation of 1,1'-Oxalylbispyrazoles. The toluene (2 mL) solution of oxalyl chloride (500 mg, 4 mmol) was gradually added to the mixture of pyrazole (8 mmol) and triethylamine (1.4 g, 14 mmol) in toluene (6 mL). After stirring for 2 h, the mixture was quenched with water. Toluene layer was washed with 2 % hydrochloric acid, water, saturated $NaHCO_3$ solution, and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated. The residue was recrystallized from benzene-hexane mixture.

1,1'-Oxalylbis-3,5-dimethylpyrazole (**3**).mp 171.5-172.5°C; yield 64 %; δ_H ($CDCl_3$): 2.18 (6H, s), 2.66 (6H, s), 6.05 (2H, s); δ_C ($CDCl_3$): (DEPT) 12.76 (CH_3), 13.38 (CH_3), 111.74 (CH_2), 143.75 (C), 154.50 (C). *Anal.* Calcd for $C_{12}H_{14}N_4O_2$: C, 58.53; H, 5.73; N, 22.75. Found: C, 58.30; H, 5.76; N, 22.58.

1,1'-Oxalylbispyrazole (**4**). mp 137-138°C (decomp); yield 50 %; δ_H ($CDCl_3$): 6.60 (2H, dd, J=1.4, 1.6 Hz), 7.79 (2H, d, J=1.4 Hz), 8.35 (2H, d, J=2.8 Hz); δ_C ($CDCl_3$): (DEPT) 111.0 (CH), 128.0 (CH),

145.8 (CH). *Anal.* Calcd for $C_8H_6N_4O_2$: C, 50.53; H, 3.18; N, 29.46. Found: C, 50.45; H, 3.39; N, 29.33.

General Preparation of Ethyl Pyrazolylglyoxylates. The toluene (15 mL) solution of ethyl chloroglyoxylate (4 g, 30 mmol) was gradually added to the mixture of pyrazole (31 mmol) and triethylamine (4 g, 40 mmol) in toluene (45 mL) at -5°C. After stirring for 1 h, the mixture was quenched with water. Toluene layer was washed with 2 % hydrochloric acid, water, saturated $NaHCO_3$ solution, and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by Kugelrohr distillation under reduced pressure.

Ethyl 3,5-Dimethyl-1-pyrazolylglyoxylate (**5**). bp 170-180°C/ 5 mmHg; mp 55.5-57.0°C (from Hexane); yield 91 %; δ_H ($CDCl_3$): 1.42 (3H, t, J=7.2 Hz), 2.25 (3H, d, J=1.2 Hz), 1.74 (3H, s), 4.48 (2H, q, J=7.2 Hz), 6.06 (1H, s); ν ($CHCl_3$): 1756, 1726 cm^{-1}. *Anal.* Calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16; N, 14.28. Found: C, 54.88; H, 6.19; N, 14.16.

Ethyl 1-Pyrazolylglyoxylate (**6**). bp 135-140°C/ 5 mmHg; yield 83 %; δ_H ($CDCl_3$): 1.43 (3H, t, J=7.2 Hz), 4.51 (2H, q, J=7.2 Hz), 6.58 (1H, dd, J=3.0, 1.4 Hz), 7.86 (1H, d, J=1.4 Hz), 8.26 (1H, d, J=3.0 Hz); ν ($CHCl_3$): 1763, 1733 cm^{-1}. *Anal.* Calcd for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66. Found: C 50.27, H, 4.94; N, 16.56.

Ethyl 3,5-Di-t-butyl-1-pyrazolylglyoxylate (**7**). bp 190°C/ 5 mmHg; yield 71 %; δ_H ($CDCl_3$): 1.26 (9H, s), 1.37-1.44 (12H, m), 4.44 (2H, q, J=7.2 Hz), 6.16 (1H, s); ν ($CHCl_3$): 1757, 1731 cm^{-1}. *Anal.* Calcd for $C_{15}H_{24}N_2O_3$: C, 64.26; H, 8.63; N, 9.99. Found: C, 64.24; H, 8.74; N, 9.91.

Grignard Reaction of Ethyl Pyrazolylglyoxylates. The Grignard reagent (0.84 mmol) was added gradually to ethyl pyrazolylglyoxylate (0.7 mmol) in Et_2O (2 mL) at -90°C, and stirred for another 1 h. After quenching with acetic acid, the mixture was extracted with Et_2O. The organic layer was washed with 2 % hydrochloric acid, water, saturated $NaHCO_3$ solution, and saturated NaCl solution. The yield was appraised by the gas chromatography. The residue was purified by the column chromatography on silica gel with benzene-hexane mixture, and identified with authentic data.

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