

PREPARATION OF β -SUBSTITUTED γ -KETO ESTERS BY THE GRIGNARD REACTION ON *N*-ACYLPYRAZOLES[†]

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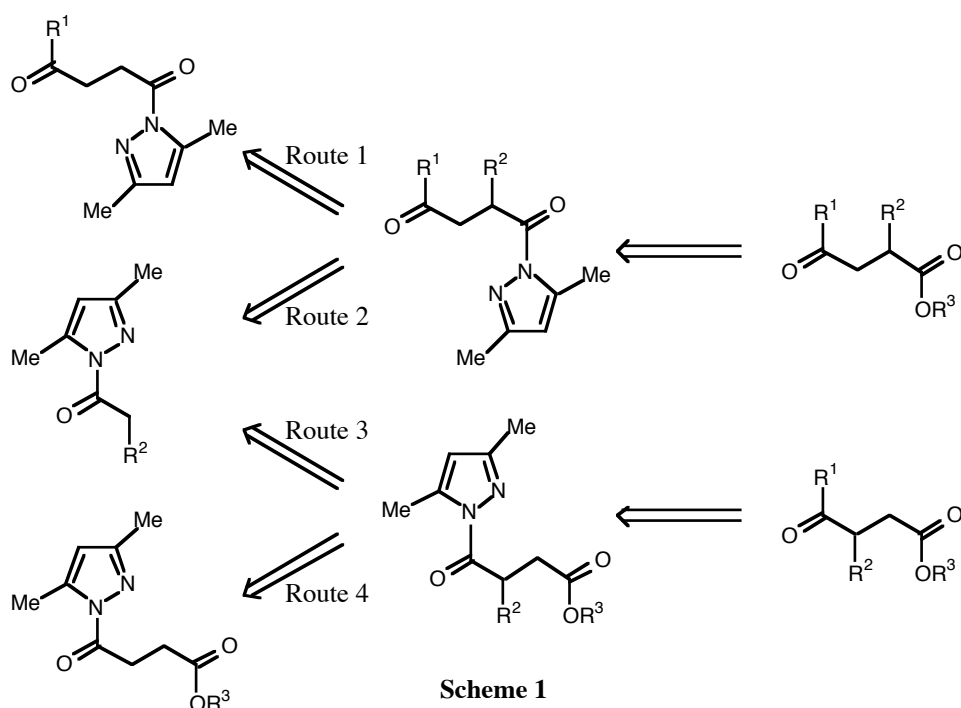
Abstract - Various γ -keto esters were prepared by either the alcoholysis of *N*-(4-oxoalkanoyl)pyrazoles or the Grignard replacement of pyrazole moiety of 4-(*N*-pyrazolyl)-4-oxoalkanoic esters. By using 3-phenyl-*l*-menthopyrazole as a chiral auxiliary, β -substituted γ -keto esters were enantioselectively obtained.

γ -Keto esters are regarded as the important synthons of γ -lactones which are paid attention to their biological activities. Although the various synthetic methods for these γ -keto esters were reported in the literature including a few recent papers,¹ a general, convenient and preparative method of γ -keto esters was still desired, particularly that of optically active γ -keto esters.

Previously we reported the synthetic utilities concerning to pyrazoles, particularly 3-phenyl-*l*-menthopyrazole as a new chiral auxiliary.² The structural peculiarity of this auxiliary 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,³ diphenyl disulfide,⁴ acyl chloride,⁵ aldehydes,⁶ and C=N compounds.⁷ Otherwise, *N*-acylpyrazoles are easily converted into various acyl derivatives by the action of nucleophiles such as alcohols,⁸ amines,⁹ lithium aluminum hydride,¹⁰ organozinc compounds¹¹ and Grignard reagents.¹² On the bases of these reactions, we have previously prepared α -keto esters¹³ and chiral β -keto acid derivatives.⁶ In the course of these preparative studies of keto acid derivatives, we report here the convenient preparative method of β -substituted γ -keto esters using *N*-acylpyrazoles.

On our knowledge of chemical behaviors about *N*-acylpyrazoles, four preparative routes toward γ -keto esters were designed through *N*-acylpyrazoles illustrated in Scheme 1. According to Routes 1 and 2, α -substituted γ -keto esters are expected to be prepared by the alcoholysis of *N*-(4-oxoalkanoyl)pyrazoles, which are obtained by either the α -alkylation of *N*-(4-oxoalkanoyl)pyrazoles (Route 1) or the reaction of

[†] This paper is dedicated to Professor Shô Itô on the occasion of his 77th birthday for his brilliant achievement in the field of heterocyclic chemistry.



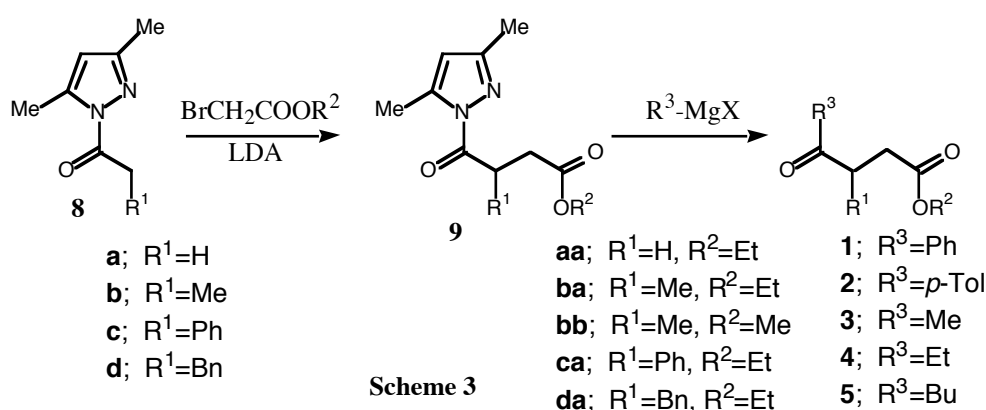
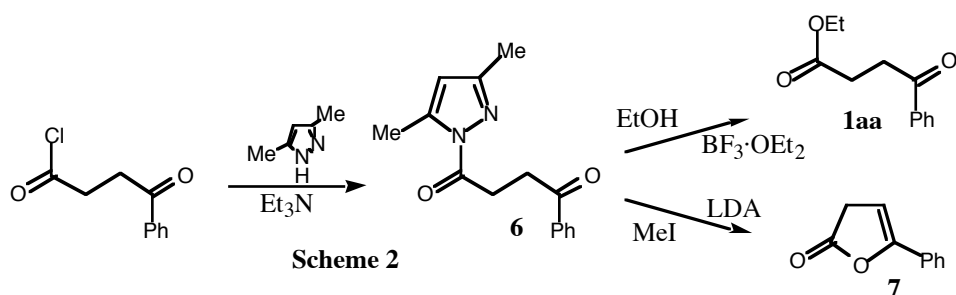
α -bromoketones with *N*-acylpyrazoles (Route 2). The Routes 3 and 4 are consisted of the preparation of the preparation of γ -keto esters was also anticipated by the Grignard reaction. By the treatment with phenylmagnesium bromide, ethyl 4-phenyl-4-oxobutanoate (**1aa**) was obtained in good yield from ethyl 4-(3,5-dimethylpyrazol-1-yl)-4-oxobutanoate (**9aa**) which was directly prepared from succinic acid derivatives and 3,5-dimethylpyrazole. Also ethyl 4-phenyl-4-oxobutanoate (**1aa**) was obtained by the treatment of 1-(4-phenyl-4-oxobutanoyl)-3,5-dimethylpyrazole (**6**) with $\text{BF}_3 \cdot \text{OEt}_2$ in ethanol. These facts

Table 1. Preparation of Alkyl 4-(*N*-Pyrazolyl)-4-oxoalkanoate

Entry		R ¹	R ²	Pyrazole ^a	Yield (%)	De (%)	Config.
1	9aa	H	Et	DMP	88 ^b	----	----
2	9ba	Me	Et	DMP	58	----	----
3	9bb	Me	Me	DMP	57	----	----
4	9ca	Ph	Et	DMP	77	----	----
5	9da	Bn	Et	DMP	64	----	----
6	11ba	Me	Et	3-Ph-MP	69	72	3-(<i>S</i>)
7	11bb	Me	Me	3-Ph-MP	51	78	3-(<i>S</i>)
8	11ca	Ph	Et	3-Ph-MP	74	27	3-(<i>R</i>)
9	11da	Bn	Et	3-Ph-MP	15	72	3-(<i>S</i>)

a: 3,5-Dimethylpyrazol-1-yl and 3-phenyl-*l*-menthopyrazol-2-yl groups are abbreviated to DMP and 3-Ph-MP, respectively.

b: Prepared by direct acylation of 3,5-dimethylpyrazole.



showed the nucleophilic replacement of *N*-acylpyrazoles afforded unsubstituted γ -keto esters.

In Route 1 for α -substituted γ -keto esters, the alkylation of **6** was failed in the presence of LDA and 5-phenyl-2(3*H*)-furanone (**7**) was formed through the cyclization of the enolate derived from keto group. Thereaction of 1-propanoyl-3,5-dimethylpyrazole (**8a**) with α -bromoacetophenone in Route 2 gave the complicated mixture of many products and could not be isolated the desired 1-(2-methyl-4-phenyl-4-oxobutanoyl)-3,5-dimethylpyrazole. The alkylation of **9aa** in Route 3 was also failed and the starting material was recovered even under the force condition using HMPA. In route 4, alkylation of 1-acyl-3,5-dimethylpyrazole (**8**) with bromoacetate esters afforded 3-substituted 4-(3,5-dimethylpyrazol-1-yl)-4-oxobutanoic esters (**9**) in good yields. The subsequent Grignard reaction afforded various β -substituted γ -keto esters (**1-5**) summarized in Tables 1 and 2.

When 3-phenyl-*l*-menthopyrazole was used instead of 3,5-dimethylpyrazole, the formation of ethyl 3-substituted 4-(3-phenyl-*l*-menthopyrazol-2-yl)-4-oxobutanoates (**11**) was accomplished diastereoselectively by the action of 2-acyl-3-phenyl-*l*-menthopyrazoles (**10**) with ethyl bromoacetate in the presence of LDA. According to the previous works,³ the diastereoselectivity was evaluated from the peak intensity of 4methyl

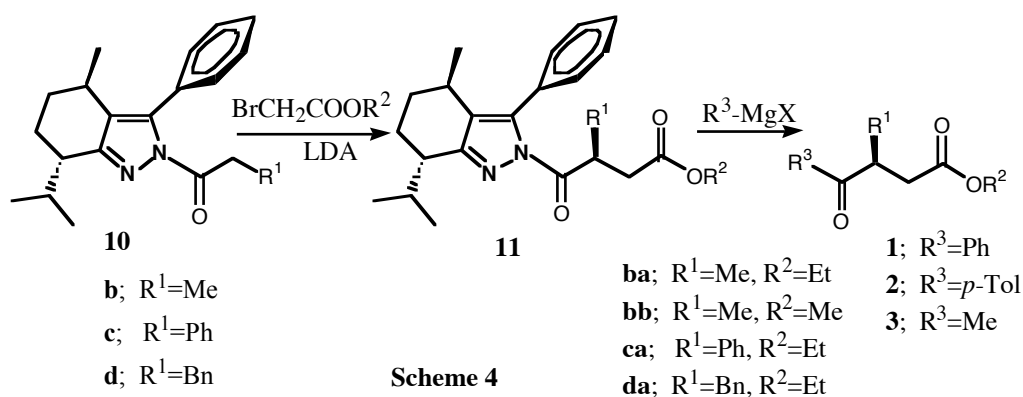


Table 2. Grignard Reaction of Alkyl 4-(*N*-Pyrazolyl)-4-oxoalkanoate

Entry	4-(<i>N</i> -Pyrazolyl)-4-oxoalkanoate			Grignard Reagent		Product		
	Pyrazole ^a	R ¹	R ²	R ³ -MgX		Yield (%)	Opt.	Yield (%)
1	9aa	DMP	H	Et	Ph-MgBr	1aa	53	----
2	9aa	DMP	H	Et	<i>p</i> -Tol-MgBr	2aa	48	----
3	9aa	DMP	H	Et	Me-MgI	3aa	64	----
4	9aa	DMP	H	Et	Et-MgI	4aa	63	----
5	9aa	DMP	H	Et	Bu-MgBr	5aa	51	----
6	9ba	DMP	Me	Et	Ph-MgBr	1ba	51	----
7	9ba	DMP	Me	Et	<i>p</i> -Tol-MgBr	2ba	79	----
8	9ba	DMP	Me	Et	Me-MgBr	3ba	17	----
9	9bb	DMP	Me	Me	Ph-MgBr	1bb	53	----
10	9bb	DMP	Me	Me	<i>p</i> -Tol-MgBr	2bb	53	----
11	9bb	DMP	Me	Me	Me-MgI	3bb	13	----
12	9ca	DMP	Ph	Et	Ph-MgBr	1ca	63	----
13	9ca	DMP	Ph	Et	Me-MgI	3ca	67	----
14	9da	DMP	Bn	Et	Me-MgI	3da	52	----
15	11ba	3-Ph-MP	Me	Et	Ph-MgBr	(<i>S</i>)- 1ba	10	100
16	11bb	3-Ph-MP	Me	Me	Ph-MgBr	(<i>S</i>)- 1bb	51	85
17	11bb	3-Ph-MP	Me	Me	<i>p</i> -Tol-MgBr	(<i>S</i>)- 2bb	44	85
18	11ca	3-Ph-MP	Ph	Et	Me-MgI	(<i>R</i>)- 3ca	0	----
19	11da	3-Ph-MP	Bn	Et	Me-MgI	(<i>S</i>)- 3da	0	----

a: 3,5-Dimethylpyrazol-1-yl and 3-phenyl-*l*-menthopyrazol-2-yl groups are abbreviated as DMP and 3-Ph-MP, respectively.

group on 3-phenyl-*l*-menthopyrazole. The pyrazole derivatives were subsequently converted into β -substituted γ -keto esters (**1-3**) by the action of Grignard reagents. During this conversion, the chiral auxiliary was recovered in high yield without racemization. The absolute configuration of the products was proved to be (*S*)-form by the comparison of optical rotation with authentic data.¹⁴ The enantiomer ratios were deduced by HPLC using chiral column. In the cases of **11ca** and **11da**, the replacement reaction was depressed by the steric hindrance of menthopyrazolyl group.

In conclusion, various γ -keto esters were prepared by either the alcoholysis of *N*-(4-oxoalkanoyl)pyrazoles (**6**) or the Grignard replacement of pyrazole moiety of 3-substituted 4-(3,5-dimethylpyrazol-1-yl)-4-oxoalkanoate esters (**9**). By using 3-phenyl-*l*-menthopyrazole as a chiral auxiliary, β -substituted γ -keto esters (**1-3**) were enantioselectively prepared.

EXPERIMENTAL

Melting points are uncorrected. ^1H NMR and ^{13}C NMR spectra were obtained on JEOL JNM-EX270 (270 MHz) or Varian GEMINI 2000 (200 MHz) spectrometer in CDCl_3 with TMS as an internal standard. Specific rotations were measured on JASCO DIP-370 digital polarimeter. The enantiomer ratios were evaluated from the peak intensity ratios of HPLC on JASCO PU-980 high performance liquid chromatograph using CHIRALCEL OD-R column eluting with aqueous methanol. The yields of the products were evaluated by GL Science GC-353 gas chromatograph using dimethylsiloxane type capillary column (GL Science TC-1, 0.25 mm x 30 m). Ether and THF were dried over benzophenone ketyl radical.

Preparation of 1-Acyl-3,5-dimethylpyrroles. 3,5-Dimethylpyrazole was acylated by carboxylic acid in the presence of thionyl chloride and triethylamine according to the formerly described method.⁸ Also 1-acyl-3,5-dimethylpyrazole was prepared by the action of acid chloride on 3,5-dimethylpyrazole in the presence of triethylamine.

1-(4-Phenyl-4-oxobutanoyl)-3,5-dimethylpyrazole (6).

mp 69-70°C (from hexane); yield 85 %; ^1H -NMR (CDCl_3): δ 2.26 (3H, d, $J=1.7$ Hz), 2.52 (3H, s), 3.42 (2H, t, $J=6$ Hz), 3.58 (2H, t, $J=6$ Hz), 5.97 (1H, s), 7.27-7.59 (3H, m), 8.00-8.04 (2H, m); ^{13}C -NMR (CDCl_3): δ 13.9 (CH_3), 14.5 (CH_3), 29.7 (CH_2), 32.8 (CH_2), 111.2 (CH), 128.3 (CH), 128.7 (CH), 129.0 (C), 133.3 (CH), 144.2 (C), 152.3 (C), 173.2 (C), 198.3 (C). *Anal.* Calcd for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.20; H, 6.42; N, 10.86.

Ethyl 4-(3,5-Dimethylpyrazol-1-yl)-4-oxobutanoate (9aa).

bp 140-150°C/ 5 mmHg; mp 36-37°C (from hexane); yield 90 %; ^1H -NMR (CDCl_3): δ 1.26 (3H, t, $J=7.3$ Hz), 2.23 (3H, s), 2.52 (3H, s), 2.72 (2H, t, $J=6.6$ Hz), 3.44 (2H, t, $J=6.9$ Hz), 4.17 (2H, q, $J=7.3$ Hz), 5.95 (1H, s). *Anal.* Calcd for $\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}_3$: C, 58.91; H, 7.19; N, 12.49. Found: C, 58.94; H, 7.20; N, 12.39.

Ethanolysis of 1-(4-Phenyl-4-oxobutanoyl)-3,5-dimethylpyrazole (6). The mixture of 1-(4-phenyl-4-oxobutanoyl)-3,5-dimethylpyrazole (**6**) (950 mg, 3.7 mmol) and $\text{BF}_3 \cdot \text{OEt}_2$ (738 mg, 5.4 mmol) in EtOH (5 mL) was refluxed for 17 h. The resulting mixture was extracted with ether, and the organic layer was washed with diluted hydrochloric acid (*ca.* 1 %), water, saturated NaHCO_3 solution and NaCl solution. After dried over anhydrous MgSO_4 , the ether was evaporated and ethyl 4-oxo-4-phenylbutanoate (**1aa**) was purified by distillation under reduced pressure; bp 150-155°C/ 5 mmHg; yield 669 mg (88 %); ^1H -NMR (CDCl_3): δ 1.27 (3H, t, $J=7.3$ Hz), 2.76 (2H, t, $J=6.6$ Hz), 3.32 (2H, t, $J=6.6$ Hz), 4.16 (2H, q, $J=7.3$ Hz), 7.27-7.60 (3H, m), 7.98-8.03 (2H, m).

Formation of 5-Phenyl-2(3H)-furanone (7). To the THF solution (5 mL) of LDA which was prepared *in situ* from diisopropylamine (0.25 mL) and butyllithium (1.4 mmol), **6** (262 mg, 1.0 mmol) in THF (1 mL) was added at -5°C. After standing for 30 min at -5°C, methyl iodide (322 mg, 2.3 mmol) in THF (1 mL) was added to the mixture. The reaction was continued stirring for 2 h. The mixture was quenched with acetic acid and water, and extracted with CH_2Cl_2 . The organic layer was washed with diluted hydrochloric acid (*ca.* 1%), water, saturated NaHCO_3 solution and NaCl solution. After dried over anhydrous MgSO_4 , solvent was evaporated. The major product was isolated by silica gel chromatography with hexane-ethyl acetate mixture (v/v 4:1) as elution solvents, and was presumed to be 5-phenyl-2(3H)-furanone (**7**); yield 43

mg (27 %); $^1\text{H-NMR}$ (CDCl_3): δ 3.42 (2H, d, $J=2.8$ Hz), 5.79 (1H, t, $J=2.8$ Hz), 7.34-7.54 (3H, m), 7.57-7.98 (2H, m).

Preparation of 3-Substituted 4-(*N*-Pyrazolyl)-4-oxoalkanoate (9 and 11). To the THF solution (2 mL) of LDA which was prepared *in situ* from diisopropylamine (0.3 mL) and butyllithium (1.2 mmol), the appropriate *N*-acylpyrazole (1.1 mmol) in THF (1 mL) was added at -5°C . After standing at -5°C for 30 min, bromoacetate ester (1.5 mmol) in THF (1 mL) was added at -90°C to the mixture which was kept stirring for 2 h at -5°C . The mixture was quenched with acetic acid and water, and extracted with CH_2Cl_2 . The organic layer was washed with diluted hydrochloric acid (*ca.* 1 %), water, saturated NaHCO_3 solution and NaCl solution. After dried over anhydrous MgSO_4 , solvent was evaporated. 3-Substituted 4-(*N*-pyrazolyl)-4-oxoalkanoate (9 and 11) was purified by silica gel column chromatography with hexane-ethyl acetate mixture (v/v 7:1) as elution solvents.

Ethyl 3-Methyl-4-(3,5-dimethylpyrazol-1-yl)-4-oxobutanoate (9ba).

Oil, yield 58 %; $^1\text{H-NMR}$ (CDCl_3): δ 1.21 (3H, t, $J=7.2$ Hz), 1.30 (3H, d, $J=7.0$ Hz), 2.24 (3H, s), 2.49 (1H, ABX, $J=5.4, 16.6$ Hz), 2.53 (3H, s), 2.92 (1H, ABX, $J=9.4, 16.6$ Hz), 4.1 (2H, q, $J=7.4$ Hz), 4.21-4.29 (1H, m), 5.96 (1H, s). *Anal.* Calcd for $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}_3$: C, 60.49; H, 7.61; N, 11.76. Found: C, 60.24; H, 7.73; N, 11.63.

Methyl 3-Methyl-4-(3,5-dimethylpyrazol-1-yl)-4-oxobutanoate (9bb).

bp $120-125^\circ\text{C}/6$ mmHg; yield 57 %; $^1\text{H-NMR}$ (CDCl_3): δ 1.31 (3H, d, $J=7.3$ Hz), 2.24 (3H, s), 2.50 (1H, ABX, $J=5.6, 16.9$ Hz), 2.53 (3H, d, $J=0.7$ Hz), 2.93 (1H, ABX, $J=8.9, 16.5$ Hz), 3.66 (3H, s), 4.19-4.30 (1H, m), 5.96 (1H, s); $^{13}\text{C-NMR}$ (CDCl_3): δ 14.3 (CH_3), 15.0 (CH_3), 18.1 (CH_3), 35.5 (CH_2), 37.8 (CH), 52.2 (CH_3), 111.7 (CH), 145.0 (C), 152.5 (C), 173.0 (C), 176.3 (C). *Anal.* Calcd for $\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}_3$: C, 58.91; H, 7.19; N, 12.49. Found: C, 58.61; H, 7.37; N, 12.28.

Ethyl 3-Phenyl-4-(3,5-dimethylpyrazol-1-yl)-4-oxobutanoate (9ca).

Oil, yield 77 %; $^1\text{H-NMR}$ (CDCl_3): δ 1.18 (3H, t, $J=7.2$ Hz), 2.20 (3H, s), 2.49 (3H, s), 2.75 (1H, ABX, $J=4.8, 17.0$ Hz), 3.38 (1H, ABX, $J=10.8, 17.0$ Hz), 4.10 (2H, q, $J=7.0$ Hz), 5.60 (1H, ABX, $J=4.8, 10.8$ Hz), 5.89 (1H, s), 7.18-7.34 (3H, m), 7.42-7.47 (2H, m). *Anal.* Calcd for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 68.24; H, 6.77; N, 9.21.

Ethyl 3-Benzyl-4-(3,5-dimethylpyrazol-1-yl)-4-oxobutanoate (9da).

Oil, yield 64 %; $^1\text{H-NMR}$ (CDCl_3): δ 1.16 (3H, t, $J=7.0$ Hz), 2.26 (3H, s), 2.44 (1H, ABX, $J=4.4, 16.8$ Hz), 2.52 (3H, s), 2.68 (1H, ABX, $J=9.2, 13.4$ Hz), 2.86 (1H, ABX, $J=10.4, 16.8$ Hz), 3.24 (1H, ABX, $J=4.8, 13.4$ Hz), 4.04 (2H, q, $J=7.2$ Hz), 4.46-4.61 (1H, m), 5.95 (1H, s), 7.17-7.33 (5H, m). *Anal.* Calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.89; H, 7.05; N, 9.11.

Ethyl 3-Methyl-4-oxo-4-(3-phenyl-1-menthopyrazol-2-yl)butanoate (11ba).

Oil, yield 69 %; $^1\text{H-NMR}$ (CDCl_3): δ 0.69 (3H, d, $J=6.8$ Hz), 0.94 (3H, d, $J=6.8$ Hz), 1.07 (3H, d, $J=6.6$ Hz), 1.13-1.35 (1H, m), 1.26 (3H, t, $J=7.2$ Hz), 1.43-1.61 (1H, m), 1.82 (2H, m), 2.33-2.49 (1H, m), 2.43 (1H, ABX, $J=5.0, 16.8$ Hz), 2.59-2.69 (1H, m), 2.73-2.83 (1H, m), 2.90 (1H, ABX, $J=9.6, 16.8$ Hz), 4.12 (2H, q, $J=7.2$ Hz), 4.21-4.33 (1H, m), 7.26-7.44 (5H, m). *Anal.* Calcd for $\text{C}_{24}\text{H}_{32}\text{N}_2\text{O}_3$: C, 72.7; H, 8.13; N, 7.06. Found: C, 72.63; H, 8.09; N, 6.99.

Methyl 3-Methyl-4-oxo-4-(3-phenyl-1-menthopyrazol-2-yl)butanoate (11bb).

Oil, yield 51 %; ¹H-NMR (CDCl₃): δ 0.69 (3H, d, *J*=6.8 Hz), 0.94 (3H, d, *J*=7.0 Hz), 1.08 (3H, d, *J*=6.8 Hz), 1.21-1.34 (1H, m), 1.26 (3H, d, *J*=7.0 Hz), 1.42-1.63 (1H, m), 1.82-2.00 (2H, m), 2.35-2.60 (1H, m), 2.45 (1H, ABX, *J*=5.4, 16.8 Hz), 2.62-2.70 (1H, m), 2.73-2.81 (1H, m), 2.90 (1H, ABX, *J*=9.4, 16.8 Hz), 3.67 (3H, s), 4.21-4.31 (1H, m), 7.26-7.41 (5H, m). *Anal.* Calcd for C₂₃H₃₀N₂O₃: C, 72.22; H, 7.91; N, 7.32. Found: C, 72.15; H, 7.84; N, 7.32.

Ethyl 4-Oxo-3-phenyl-4-(3-phenyl-l-menthopyrazol-2-yl)butanoate (11ca).

mp 137-138°C (from hexane); yield 74 %; ¹H-NMR (CDCl₃): δ 0.66 (3H, d, *J*=6.8 Hz), 0.72 (3H, d, *J*=6.8 Hz), 0.82-0.92 (1H, m), 1.00 (3H, d, *J*=7.0 Hz), 1.21 (3H, t, *J*=7.1 Hz), 1.36-1.52 (1H, m), 1.79-1.93 (2H, m), 2.41-2.58 (2H, m), 2.60-2.72 (1H, m), 2.67 (1H, ABX, *J*=4.8, 17.0 Hz), 3.15 (1H, ABX, *J*=11.0, 17.0 Hz), 4.12 (2H, q, *J*=7.0 Hz), 5.56 (1H, ABX, *J*=4.8, 11.0 Hz), 7.17-7.46 (10H, m). *Anal.* Calcd for C₂₉H₃₄N₂O₃: C, 75.95; H, 7.47; N, 6.11. Found: C, 76.08; H, 7.61; N, 6.12.

Ethyl 3-Benzyl-4-oxo-4-(3-phenyl-l-menthopyrazol-2-yl)butanoate (11da).

mp 83-84°C (from hexane); yield 15 %; ¹H-NMR (CDCl₃): δ 0.70 (3H, d, *J*=6.6 Hz), 0.97 (3H, d, *J*=6.8 Hz), 1.05-1.38 (1H, m), 1.12 (3H, d, *J*=7.0 Hz), 1.16 (3H, t, *J*=7.0 Hz), 1.44-1.63 (1H, m), 1.84-2.02 (2H, m), 2.31-2.60 (1H, m), 2.33 (1H, ABX, *J*=4, 17.2 Hz), 2.54 (1H, ABX, *J*=10.4, 13.4 Hz), 2.31-2.60 (1H, m), 2.65-2.95 (2H, m), 2.82 (1H, ABX, *J*=11.0, 17.2 Hz), 3.27 (1H, ABX, *J*=4.2, 13.2 Hz), 4.04 (2H, q, *J*=7.2 Hz), 4.51-4.64 (1H, m), 7.16-7.40 (10H, m). *Anal.* Calcd for C₂₉H₃₆N₂O₃: C, 75.62; H, 7.88; N, 6.08. Found: C, 75.81; H, 7.68; N, 5.70.

Conversion of **9** and **11** into γ-Keto Esters.

Under argon atmosphere, 4-(*N*-pyrazolyl-4-oxoalkanoate (**9** and **11**, 1.0 mmol) was stirred with a Grignard reagent (1.2 mmol) in dry ether (1 mL) at rt for 1 h. The mixture was quenched with acetic acid, and the ether solution was washed with diluted hydrochloric acid (*ca.* 1 %), water, a saturated NaHCO₃ solution and NaCl solution. After dried over anhydrous MgSO₄, the ether was evaporated. From the gas chromatography of the residue, the yields of the products were evaluated, as summarized in Table 2. The products were purified by silica gel chromatography with hexane-ethyl acetate mixture (v/v 7:1) as an elution solvent system, and were identified by the means of spectral comparison.

Ethyl 3-Methyl-4-oxo-4-phenylbutanoate (1ba).

Oil, yield 51 %; ¹H-NMR (CDCl₃): δ 1.19 (3H, t, *J*=7.1 Hz), 1.21 (3H, d, *J*=7.2 Hz), 2.44 (1H, ABX, *J*=5.9, 16.8 Hz), 2.95 (1H, ABX, *J*=8.6, 16.8 Hz), 3.91-4.01 (1H, m), 4.08 (2H, q, *J*=7.2 Hz), 7.40-7.56 (3H, m), 7.97-8.00 (2H, m).

Methyl 3-Methyl-4-oxo-4-phenylbutanoate (1bb).

Oil, yield 53 %; ¹H-NMR (CDCl₃): δ 1.23 (3H, d, *J*=7.2 Hz), 2.47 (1H, ABX, *J*=6.0, 16.6 Hz), 2.97 (1H, ABX, *J*=8.2, 16.6 Hz), 3.65 (3H, s), 3.90-4.01 (1H, m), 7.43-7.16 (3H, m), 7.97-8.03 (2H, m). The optical rotation of **1bb**, which was prepared from **11bb**, was measured; [α]_D -4.1° (c 0.24, THF).

Ethyl 3,4-Diphenyl-4-oxobutanoate (1ca).

Oil, yield 63 %; ¹H-NMR (CDCl₃): δ 1.17 (3H, t, *J*=7.2 Hz), 2.70 (1H, ABX, *J*=4.8, 16.8 Hz), 3.37 (1H, ABX, *J*=9.6, 16.8 Hz), 4.08 (2H, q, *J*=7.2 Hz), 5.09 (1H, ABX, *J*=4.8, 9.6 Hz), 7.17-7.46 (8H, m), 7.95-7.99 (2H, m).

Ethyl 4-Oxo-4-(4-methylphenyl)butanoate (2aa).

Oil, yield 47 %; ¹H-NMR (CDCl₃): δ 1.26 (3H, t, *J*=7.2 Hz), 2.41 (3H, s), 2.74 (2H, t, *J*=6.6 Hz), 3.29 (2H, t, *J*=6.6 Hz), 4.16 (2H, q, *J*=7.2 Hz), 7.26 (2H, d, *J*=8.0 Hz), 7.89 (2H, d, *J*=8.2 Hz).

Ethyl 3-Methyl-4-oxo-4-(4-methylphenyl)butanoate (2ba).

Oil, yield 79 %; ¹H-NMR (CDCl₃): δ 1.20 (3H, t, *J*=6.9 Hz), 1.21 (3H, d, *J*=6.9 Hz), 2.40 (3H, s), 2.43 (1H, ABX, *J*=5.9, 16.8 Hz), 2.93 (1H, ABX, *J*=8.2, 16.8 Hz), 3.89-3.97 (1H, m), 4.09 (2H, q, *J*=7.3 Hz), 7.25-7.28 (3H, m), 7.88-7.91 (2H, m).

Methyl 3-Methyl-4-oxo-4-(4-methylphenyl)butanoate (2bb).

Oil, yield 53 %; ¹H-NMR (CDCl₃): δ 1.21 (3H, d, *J*=7.2 Hz), 2.40 (3H, s), 2.44 (1H, ABX, *J*=5.9, 16.5 Hz), 2.95 (1H, ABX, *J*=8.3, 16.5 Hz), 3.64 (3H, s), 3.89-3.99 (1H, m), 7.25-7.43 (3H, m), 7.88-7.97 (2H, m).

Ethyl 4-Oxopentanoate (3aa).

Oil, yield 64 %; ¹H-NMR (CDCl₃): δ 1.26 (3H, t, *J*=7.2 Hz), 2.20 (3H, s), 2.57 (2H, t, *J*=6.2 Hz), 2.76 (2H, t, *J*=6.3 Hz), 4.13 (2H, q, *J*=7.0 Hz).

Ethyl 3-Methyl-4-oxopentanoate (3ba).

Oil, yield 17 %; ¹H-NMR (CDCl₃): δ 1.15 (3H, d, *J*=7.2 Hz), 1.25 (3H, t, *J*=7.2 Hz), 2.23 (3H, s), 2.29 (1H, ABX, *J*=5.4, 16.6 Hz), 2.76 (1H, ABX, *J*=8.6, 16.8 Hz), 2.97-3.07 (1H, m), 4.11 (2H, q, *J*=7.2 Hz).

Methyl 3-Methyl-4-oxopentanoate (3bb).

Oil, yield 13 %; ¹H-NMR (CDCl₃): δ 1.16 (3H, d, *J*=7.2 Hz), 2.28 (3H, s), 2.30 (1H, ABX, *J*=5.4, 16.8 Hz), 2.77 (1H, ABX, *J*=8.6, 16.6 Hz), 2.97-3.08 (1H, m), 3.66 (3H, s).

Ethyl 3-Phenyl-4-oxopentanoate (3ca).

Oil, yield 67 %; ¹H-NMR (CDCl₃): δ 1.21 (3H, t, *J*=7.3 Hz), 2.11 (3H, s), 2.52 (1H, ABX, *J*=4.9, 16.8 Hz), 3.20 (1H, ABX, *J*=9.6, 16.8 Hz), 4.11 (2H, q, *J*=7.3 Hz), 4.18 (1H, ABX, *J*=4.9, 9.6 Hz), 7.18-7.36 (5H, m).

Ethyl 3-Benzyl-4-oxopentanoate (3da).

Oil, yield 18 %; ¹H-NMR (CDCl₃): δ 1.21 (3H, t, *J*=7.2 Hz), 2.10 (3H, s), 2.31 (1H, ABX, *J*=4.3, 17.1 Hz), 2.59 (1H, ABX, *J*=8.2, 13.5 Hz), 2.74 (1H, ABX, *J*=10.2, 17.1 Hz), 2.91 (1H, ABX, *J*=6.9, 13.5 Hz), 3.20-3.32 (1H, m), 4.06 (2H, q, *J*=7.3 Hz), 7.03-7.33 (5H, m).

Ethyl 4-Oxohexanoate (4aa).

Oil, yield 63 %; ¹H-NMR (CDCl₃): δ 1.08 (3H, t, *J*=7.2 Hz), 1.26 (3H, t, *J*=7.2 Hz), 2.49 (2H, q, *J*=7.2 Hz), 2.58 (2H, t, *J*=6.4 Hz), 2.73 (2H, t, *J*=6.6 Hz), 4.13 (2H, q, *J*=7.2 Hz).

Ethyl 4-Oxo-octanoate (5aa).

Oil, yield 51 %; ¹H-NMR (CDCl₃): δ 0.91 (3H, t, *J*=7.4 Hz), 1.23-1.41 (2H, m), 1.25 (3H, t, *J*=7.0 Hz), 1.51-1.65 (2H, m), 2.46 (2H, t, *J*=7.4 Hz), 2.54-2.62 (2H, m), 2.68-2.76 (2H, m), 4.13 (2H, q, *J*=7.0 Hz).

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