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The conversion of *N*-acylpyrazoles into β -keto esters was accomplished efficiently by the treatment with α -bromo esters and zinc dust. Using this Reformatsky reaction of *N*-acylpyrazoles, 4-(protected amino)-3-oxoalkanoic acid derivatives were conveniently prepared as the key intermediates in the synthesis of statines.

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As one of the organic syntheses utilizing various chiral auxiliaries, we have recently investigated the reactions of *N*-acylpyrazoles. The formation of auxiliary-substrate intermediate was performed through the acylation of pyrazoles with carboxylic acids or their acid chlorides [1]. In the case of an optically active pyrazole such as 3-phenyl-*l*-menthopyrazole [(4*R*,7*S*)-3-phenyl-4-methyl-7-isopropyl-4,5,6,7-tetrahydroindazole] (**1**), *N*-acylation proceeded regio- and stereoselectively to give the diastereomerically pure 2-acyl-3-phenyl-*l*-menthopyrazoles (**2**) [2]. By the treatment with LDA followed by alkyl halides, the α -alkylation of *N*-acylpyrazoles was accom-

plished, especially the diastereoselective α -alkylation up to 95% using **1** [3]. As the functionalization reactions, the nucleophilic reactions such as aminolysis [4], alcoholysis [1] and the Grignard reactions [5] proceeded chemoselectively under very mild conditions. In order to expand the usefulness of pyrazoles as auxiliary compounds, a wide variety of the functionalization reactions of *N*-acylpyrazoles are highly desired. Meanwhile, we have reported [6] that β -keto esters are conveniently prepared by the Reformatsky reaction of 3-acyloxazolidin-2-ones and -thiazolidine-2-thiones. Here, we report the Reformatsky reaction of *N*-acylpyrazoles to afford β -keto esters in an extension of our synthetic applications of pyrazoles.

The Reformatsky reaction of 1-benzoyl-3,5-dimethylpyrazole (**3a**) was observed under refluxing in THF, while the reaction did not occur at room temperature. After optimization of the reaction conditions, ethyl 3-phenyl-3-oxopropanoate (**5a**) was obtained in high yield without by-product by one hour refluxing in THF using an excess amount of ethyl α -bromoacetate (**4a**) and zinc dust. Similarly, the Reformatsky reaction of various 1-acyl-3,5-dimethylpyrazoles **3** with α -bromoacetates **4** was carried out to give β -keto esters **5** in high yields as summarized in Table 1. Even in the use of α -bromopropanoates, the corresponding α -methyl- β -keto esters were afforded in high yields.

As the practical examples of this Reformatsky reaction, the convenient synthesis of 4-(protected amino)-3-oxoalkanoic acid derivatives **7**, which were desired to be prepared as the key intermediates in the synthesis of statines

Table 1

The Reformatsky Reaction of 1-Acyl-3,5-dimethylpyrazoles

1-Acylpyrazole	α -Bromo Ester			Product	Yield (%) [a]
	R ¹	R ²	R ³		
3a	Ph	4a	H Et	5a	73 (82)
3a	Ph	4b	H Me	5b	67
3a	Ph	4c	H PhCH ₂	5c	62
3a	Ph	4d	Me Et	5d	71
3b	Me	4a	H Et	5e	62
3b	Me	4b	H Me	5f	50
3b	Me	4d	Me Et	5g	100
3c	Et	4a	H Et	5h	74
3c	Et	4d	Me Et	5i	92
3d	<i>i</i> -Pr	4a	H Et	5j	73
3d	<i>i</i> -Pr	4d	Me Et	5k	98
3e	<i>t</i> -Bu	4a	H Et	5m	11
3f	PhCH ₂ CH ₂	4a	H Et	5n	81

[a] Isolated yield and gc yield in parentheses were shown.

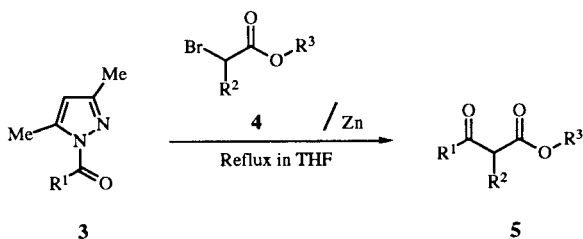
Table 2

The Reformatsky Reaction of 1-(2'-Protected Amino)acyl-3,5-dimethylpyrazoles

Substrate	α -Bromoacetate			Yield (%) [a]	[α] _D	Ee (%) [b]	Configuration	
	R ¹	R ²	R ³					
6a	PhCH ₂	<i>t</i> -BuOCO	4a	Et	47	-52.6°	>95 (93)	<i>S</i>
6a	PhCH ₂	<i>t</i> -BuOCO	4b	Me	38	-62.1°	>95	<i>S</i>
6b	PhCH ₂	PhCH ₂ OCO	4a	Et	64	-56.2°	>95	<i>S</i>
6c	<i>t</i> -Bu	PhCH ₂ OCO	4a	Et	41	-37.4°	>95	<i>S</i>

[a] Isolated yield. [b] Ee value from the specific rotation was shown in parentheses.

Scheme 1



3	R ¹	4	R ²	R ³	5	R ¹	R ²	R ³
a	Ph	a	H	Et	a	Ph	H	Et
b	Me	b	H	Me	b	Ph	H	Me
c	Et	c	H	PhCH ₂	c	Ph	H	PhCH ₂
d	<i>i</i> -Pr	d	Me	Et	d	Ph	Me	Et
e	<i>t</i> -Bu				e	Me	H	Et
f	PhCH ₂ CH ₂				f	Me	H	Me
					g	Me	Me	Et
					h	Et	H	Et
					i	Et	Me	Et
					j	<i>i</i> -Pr	H	Et
					k	<i>i</i> -Pr	Me	Et
					m	<i>t</i> -Bu	H	Et
					n	PhCH ₂ CH ₂	H	Et

[7], was demonstrated from the corresponding α -amino acids. 1-(2'-Protected amino)acyl-3,5-dimethylpyrazoles **6** were prepared in good yields from optically active *N*-protected α -amino acid and 3,5-dimethylpyrazole in the presence of thionyl chloride. By the action of α -bromoacetates and zinc dust, **6** were easily converted into **7** under refluxing in THF. The structure of **7b** was found to be *S*-configuration with 93% *ee* from the data of the specific rotation [7]. The products **7** were also determined to be more than 95% *ee* by the ¹H nmr spectral analysis using chiral europium shift reagent. This fact suggested that the enantiomeric configuration on acyl moiety was retained completely during the formation of *N*-acylpyrazoles and the Reformatsky reaction.

In conclusion, the conversion of *N*-acylpyrazoles into

β -keto esters was accomplished in good yields by the treatment with α -bromo esters and zinc dust. During this reaction, the stereo structure on acyl moiety of *N*-acylpyrazoles was retained completely. These behaviors under the Reformatsky conditions extended the significance of *N*-acylpyrazoles as one of the useful auxiliaries in the organic synthesis.

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 Shimadzu IR-460 spectrophotometer. Specific rotations were measured on a JASCO DIP-360 digital polarimeter.

1-Acyl-3,5-dimethylpyrazole.

1-Acyl-3,5-dimethylpyrazoles were prepared from 3,5-dimethylpyrazole and the corresponding acyl chloride by the method described in the previous paper [3]. In the cases of **6**, the mixture of *N*-protected α -amino acid (10 mmoles), 3,5-dimethylpyrazole (10.6 mmoles), and triethylamine (43 mmoles) in dry benzene (40 ml) was treated with thionyl chloride (13 mmoles) for 3 hours at 5°. After quenching with water, the organic layer was washed with dilute hydrochloric acid, water, aqueous sodium hydrogen carbonate and aqueous sodium chloride, dried over magnesium sulfate, and concentrated. The residue was purified by the recrystallization.

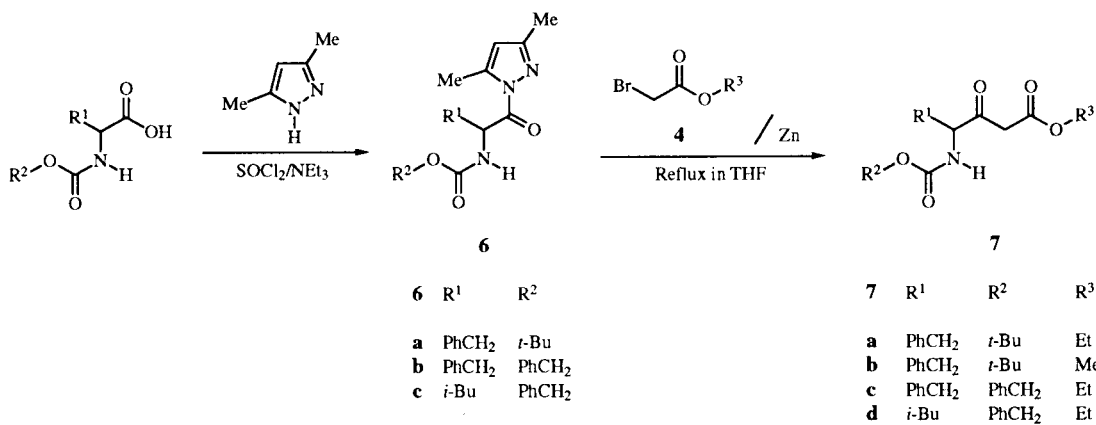
(*S*)-1-(2'-*t*-Butoxycarbonylamino-3'-phenylpropanoyl)-3,5-dimethylpyrazole (**6a**).

This compound showed mp 86-87° (from hexane), yield 70%; [α]_D²⁵: 71.2° (c 0.702, methanol); ¹H nmr: δ 1.39 (9H, s), 2.25 (3H, s), 2.49 (3H, s), 2.99-3.07 (1H, m), 3.31 (1H, dd, *J* = 13.9, 4.6 Hz), 5.22 (1H, m), 5.81 (1H, m), 5.97 (1H, s), 7.10-7.30 (5H, m).

Anal. Calcd. for C₁₉H₂₅N₃O₃: C, 66.45; H, 7.34; N, 12.24. Found: C, 66.46; H, 7.29; N, 12.11.

(*S*)-1-(2'-Benzyloxycarbonylamino-3'-phenylpropanoyl)-3,5-dimethylpyrazole (**6b**).

Scheme 2



6	R ¹	R ²	7	R ¹	R ²	R ³
a	PhCH ₂	<i>t</i> -Bu	a	PhCH ₂	<i>t</i> -Bu	Et
b	PhCH ₂	PhCH ₂	b	PhCH ₂	<i>t</i> -Bu	Me
c	<i>i</i> -Bu	PhCH ₂	c	PhCH ₂	PhCH ₂	Et
			d	<i>i</i> -Bu	PhCH ₂	Et

This compound showed mp 141-142° (from hexane-benzene), yield 84%; $[\alpha]_D^{25}$: 73.3° (c 0.488, methanol); ^1H nmr: δ 2.26 (3H, s), 2.47 (3H, s), 3.09 (1H, dd, $J = 13.9, 7.3$ Hz), 3.34 (1H, dd, $J = 13.5, 4.3$ Hz), 5.07 (2H, AB-q, $J = 12.9$ Hz), 5.48 (1H, d, $J = 8.6$ Hz), 5.82-5.89 (1H, m), 5.98 (1H, s), 7.05-7.08 (2H, m), 7.18-7.36 (8H, m).

Anal. Calcd. for $\text{C}_{22}\text{H}_{23}\text{N}_3\text{O}_3$: C, 70.01; H, 6.14; N, 11.13. Found: C, 70.01; H, 6.18; N, 11.15.

(*S*)-1-(2'-Benzyloxycarbonylamino-4'-methylpentanoyl)-3,5-dimethylpyrazole (**6c**).

This compound showed mp 56-57° (from aqueous methanol), yield 84%; $[\alpha]_D^{25}$: -2.4° (c 0.82, methanol); ^1H nmr: δ 0.93 (3H, d, $J = 5.9$ Hz), 1.04 (3H, d, $J = 5.3$ Hz), 1.50-1.60 (1H, m), 1.74-1.78 (2H, m), 2.22 (3H, s), 2.50 (3H, s), 5.11 (2H, s), 5.47-5.50 (1H, m), 5.60-5.66 (1H, m).

Anal. Calcd. for $\text{C}_{19}\text{H}_{25}\text{N}_3\text{O}_3$: C, 66.45; H, 7.34; N, 12.24. Found: C, 66.14; H, 7.46; N, 12.17.

General Procedure.

The mixture of *N*-acylpyrazole (2 mmoles), α -bromo ester (5 mmoles), and zinc dust (15 mg-atoms) in dry THF (10 ml) was refluxed with stirring under nitrogen atmosphere for 1 hour. After quenching with dilute hydrochloric acid, the unreacted zinc was filtered off and was washed with methanol. The combined filtrate was extracted with dichloromethane. The organic layer was washed with water and aqueous sodium chloride, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by Kugelrohr distillation under reduced pressure or by silica gel column chromatography with benzene-ethyl acetate mixture as an eluent.

Ethyl (*S*)-4-*t*-Butoxycarbonylamino-3-oxo-5-phenylpentanoate (**7a**).

This compound showed mp 64-65° (from hexane), yield 47%; $[\alpha]_D^{25}$: -52.6° (c 1.48, methanol, lit [7] -56.3°).

Methyl (*S*)-4-*t*-Butoxycarbonylamino-3-oxo-5-phenylpentanoate (**7b**).

This compound showed mp 88.5-89.5° (from hexane), yield 38%; $[\alpha]_D^{25}$: -62.1° (c 0.483, methanol); ^1H nmr: δ 1.40 (9H, s), 2.98 (1H, dd, $J = 14.2, 7.3$ Hz), 3.15 (1H, dd, $J = 13.9, 5.9$ Hz),

3.49 (2H, AB-q, $J = 16.2$ Hz), 3.72 (3H, s), 4.57 (1H, t, $J = 7.3$ Hz), 4.99 (1H, s), 7.16-7.35 (5H, m).

Anal. Calcd. for $\text{C}_{17}\text{H}_{23}\text{NO}_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.61; H, 7.31; N, 4.41.

Ethyl (*S*)-4-Benzyloxycarbonylamino-3-oxo-5-phenylpentanoate (**7c**).

This compound showed mp 67-68° (from hexane-benzene), yield 64%; $[\alpha]_D^{25}$: -56.2° (c 0.463, methanol); ^1H nmr: δ 1.24 (3H, t, $J = 7.3$ Hz), 3.08 (2H, ABX-m, $J = 14.1, 5.9$ Hz), 3.46 (2H, AB-q, $J = 16.2$ Hz), 4.15 (2H, q, $J = 6.9$ Hz), 4.67 (1H, q, $J = 6.6$ Hz), 5.07 (2H, s), 5.35 (1H, d, $J = 7.6$ Hz), 7.13-7.40 (10H, m).

Anal. Calcd. for $\text{C}_{21}\text{H}_{23}\text{NO}_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.33; H, 6.36; N, 3.84.

Ethyl (*S*)-4-Benzyloxycarbonylamino-3-oxo-6-methylheptanoate (**7d**).

This compound shows yield 41%; $[\alpha]_D^{25}$: -37.4° (c 0.69, methanol); ^1H nmr: δ 0.95 (6H, t, $J = 7.6$ Hz), 1.26 (3H, t, $J = 6.9$ Hz), 1.36-1.46 (1H, m), 1.59-1.73 (2H, m), 3.55 (2H, AB-q, $J = 15.8$ Hz), 4.18 (2H, q, $J = 7.3$ Hz), 4.44-4.50 (1H, m), 5.11 (2H, s), 5.27 (1H, d, $J = 8.3$ Hz), 7.28-7.38 (5H, m).

Anal. Calcd. for $\text{C}_{18}\text{H}_{25}\text{NO}_5$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.27; H, 7.67; N, 4.31.

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