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SYNTHETIC UTILITIES OF *N*-ACYLPYRAZOLES

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Abstract - Little attention had been paid to *N*-acylpyrazoles, because they are 20 times less reactive than the corresponding *N*-acylimidazoles. From this lower reactivity, *N*-acylpyrazoles seem to be sufficiently stable as the starting materials, and should be applied to the controlled reactions such as the chemo-, the regio- and the stereoselective reactions. In this review, the preparation of *N*-acylpyrazoles and their utilities for the organic syntheses are reviewed.

1 Introduction

Imidazole has extensively been investigated as an activating agent for carboxylic acids by the formation of *N*-acylimidazole using carbonyldiimidazole.[1] By the treatment with nucleophiles, *N*-acylimidazoles are converted into a large variety of carboxylic derivatives.[2] For example, the *N*-acylimidazoles derived from amino acids or peptides are used very often for the peptide bond formation. Moreover, these nucleophilic reactions of *N*-acylimidazoles are accelerated by acid catalyst.[3] For applying as an auxiliary, however, *N*-acylimidazoles are too labile to isolate as a pure form, and to control the selective reactions in the modification step.

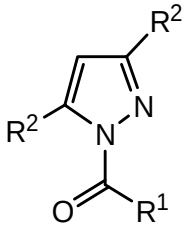
When we started the investigation of *N*-acylpyrazoles in 1992, little attention had been paid to *N*-acylpyrazoles, because they are 20 times less reactive than the corresponding *N*-acylimidazoles.[4] This lower reactivity of *N*-acylpyrazoles is sometimes expected to be the excellent property in organic synthesis. *N*-Acylpyrazoles seem to be sufficiently stable as the starting materials, and this low reactive property should be applied to the controlled reactions such as the chemo-, the regio- and the stereoselective reactions. Moreover, one of two adjacent nitrogen atoms on the pyrazole ring combines with acyl group, and the other should act as a ligand for Lewis acid. Namely, pyrazole compounds are presumed to be suitable as an auxiliary for the selective reactions of carboxylic derivatives. Here, the preparation of *N*-acylpyrazoles, and their utilities for the organic syntheses will be reviewed.

2 Preparation of *N*-Acylpyrazoles[5]

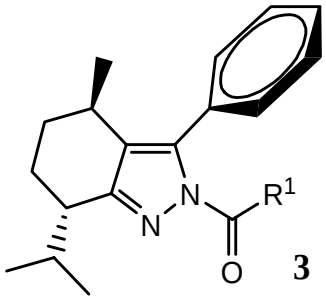
Various pyrazoles were easily prepared from the corresponding β-diketones in good yields, for example 3,5-dimethylpyrazole from acetylacetone.[6] Many *N*-acylpyrazoles were obtained in good yields by the direct *N*-acylation of these pyrazoles using acyl chloride in the presence of triethylamine.[7] By the *in situ* formation of acyl chloride from carboxylic acid using thionyl chloride, *N*-acylpyrazoles were conveniently prepared by one-pot operation. Even though acyl chlorides such as α-keto- and α-hydroxyacyl chlorides were hardly prepared, *N*-acylpyrazoles were yielded by the treatment of pyrazoles with thionyl chloride, followed by the addition of the corresponding carboxylic acids. In this preparation, dipyrazolyl sulfoxide

was postulated to be firstly formed and then followed the acyl exchange reaction. When pyrazoles having two different substituents were acylated by these preparations, two regioisomers of *N*-acylpyrazoles were formed. For example, an isomeric mixture of 3-methyl-5-phenyl- and 5-methyl-3-phenyl-1-acetylpyrazoles was obtained with 1:5 isomer ratio by the acetylation of 5-methyl-3-phenylpyrazole using acetyl chloride.

N-Acylpyrazoles were prepared from β-diketones by the treatment with acylhydrazides.[8] When acetylhydrazide was treated with benzoylacetone, the sole product was found to be 3-methyl-5-phenyl-1-



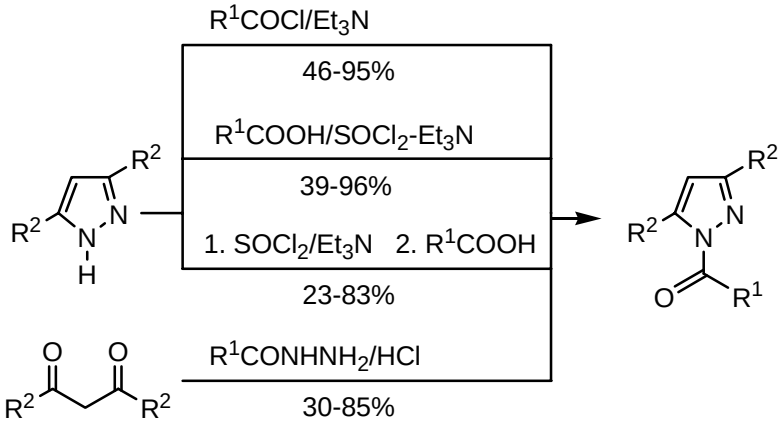
1: R^2=Me
2: R^2=H
4: R^2=Ph



3

a: R^1CO =H **e**: R^1=EtO **i**: R^1=*t*-Bu **n**: R^1=CHMePh
b: R^1=Me **f**: R^1=*t*-BuO **j**: R^1=Ph **o**: R^1=COOEt
c: R^1=Et **g**: R^1=$PhCH_2O$ **k**: R^1=CH_2Ph **p**: R^1=CH_2CH_2COOEt
d: R^1=MeO **h**: R^1=Bu **m**: R^1=CH_2CH_2Ph

acetylpyrazole**.** By the reaction of propionylhydrazide with benzoylacetone, 3-methyl-5-phenyl- and 5-methyl-3-phenyl-1-propionylpyrazoles were obtained with the 5:1 isomer ratio, and the elongation of the reaction time lead to the increase of the minor isomer. The formation of *N*-acylpyrazoles is governed by the steric interaction between the ring substituent groups and the acyl moiety, and isomerized slowly into the thermodynamically stable form. Many *N*-acylpyrazoles were prepared according to the various methods, summarized in Scheme 1.

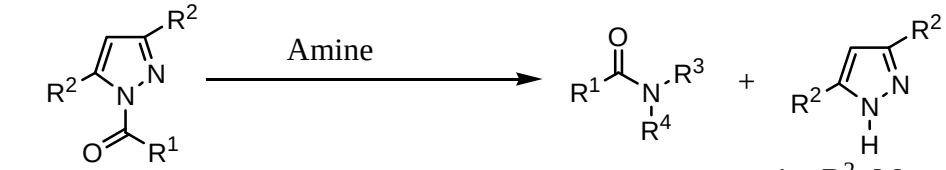


Scheme 1

3 Properties of *N*-Acylpyrazoles

3.1 Aminolysis[9]

As the typical chemical behaviors of *N*-acylpyrazoles toward the nucleophiles including the steric interaction, aminolysis of 1-acyl-3,5-dimethylpyrazole (**1**) is revealed illustrated in Scheme 2. When **1** was treated with various amines, the corresponding amides were formed quantitatively without any by-products. The data listed in Table 1 indicate that the steric interaction between amines and 1-



1c: R^1=Et, R^2=Me
2b: R^1=Me, R^2=H

1a: R^2=Me
2a: R^2=H

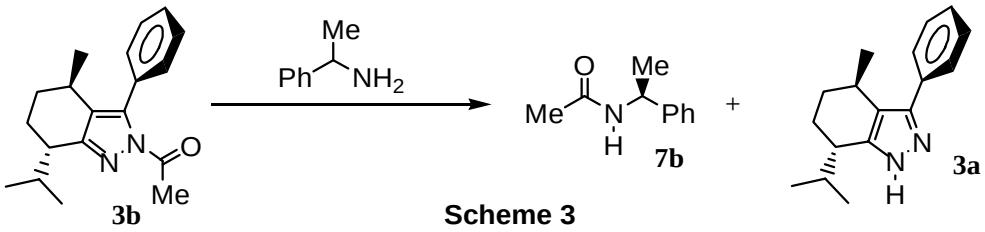
Scheme 2

Table 1. Aminolysis Rates of 1-Acylpyrazoles (**1c** and **2b**) and pKa Values

Run	Amine	pKa	$k_{29.5}$ of **1c** ($s^{-1}M^{-1}$)	$k_{29.5}$ of **2b** ($s^{-1}M^{-1}$)
1	$BnNH_2$	9.34	5.32×10^{-4}	3.47×10^{-4}
2	$PhCH(Me)NH_2$	9.08	3.86×10^{-5}	6.64×10^{-4}
3	$Pr\text{-}NH_2$	10.53	3.16×10^{-4}	4.58×10^{-3}
4	$Ph\text{-}NH_2$	4.58	3.70×10^{-6}	5.15×10^{-5}
5	*p*-$Tol\text{-}NH_2$	5.07	6.99×10^{-6}	6.05×10^{-5}
6	*p*-$Anis\text{-}NH_2$	5.29	8.34×10^{-6}	5.50×10^{-5}
7	*i*-$Pr\text{-}NH_2$	10.63	2.20×10^{-5}	5.45×10^{-4}
8	$Ph_2CH\text{-}NH_2$	7.7	3.51×10^{-5}	2.27×10^{-4}
9	*t*-$Bu\text{-}NH_2$	10.55	4.55×10^{-7}	5.38×10^{-6}
10	Pyrrolidine	11.27	1.48×10^{-3}	
11	$Et_2\text{-}NH$	10.98	5.23×10^{-7}	4.80×10^{-5}
12	Bn-NH-Me	9.58	1.85×10^{-5}	1.03×10^{-3}

acylpyrazoles affected intensively to the aminolysis rates. From the kinetic investigations, the small enthalpy values of activation and the large negative entropies of activation suggested that the aminolysis of 1-acylpyrazoles was much dependent on the structures of amines by the higher steric factor of the transition state.

Therefore the stereoselective aminolysis into chiral amides is expected by the high steric interaction using optically active pyrazoles. When 2-acetyl-3-phenyl-*l*-menthopyrazole (**3b**) was treated with *dl*-1-phenylethylamine (*dl*-**5a**) at room temperature, *N*-(1-phenyl)ethylacetamide (**5b**) was obtained in good chemical yield, accompanied by 3-phenyl-*l*-menthopyrazole (**3a**), shown in Scheme 3. By means of optical rotation, the stereoselective aminolysis was observed with the preference of *S*-configuration, but the stereoselectivity was low.



Scheme 3

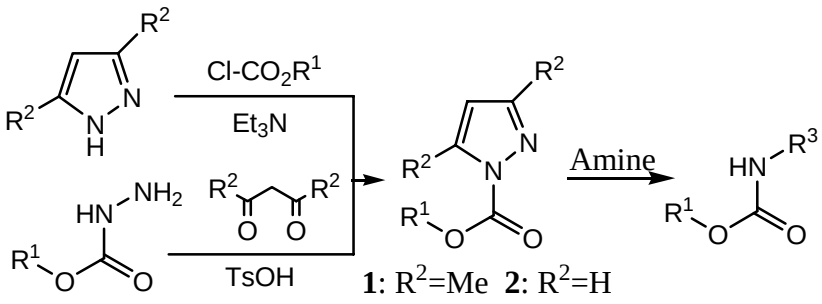
After all, 1-acylpyrazoles reacted with amines having a tiny substituent such as α-unbranched primary group to give the corresponding amides as well as the *N*-unsubstituted pyrazoles. In the cases of the bulky amines such as α-branched primary amines and the secondary amines, the aminolysis of 1-acylpyrazoles was retarded by the steric repulsion. This tendency of aminolysis should be utilized to the modification and functionalization reaction of 1-acylpyrazoles in the synthetic loop.

3.2 Aminolysis of Alkyl Pyrazole-1-carboxylates[10]

Alkyl pyrazole-1-carboxylates were readily prepared by the action of alkyl chloroformates on pyrazoles, or from 2,4-pentanedione with alkyl carbazate, illustrated in Scheme 4. Although benzyl carbazate was not available commercially, benzyl 3,5-dimethylpyrazole-1-carboxylate (**1g**) was also prepared in good yield by the reaction of carbohydrazide, benzyl alcohol and 2,4-pentanedione in the presence of equimolar amount of *p*-toluenesulfonic acid.

Generally, the particular attention should be paid to the handling of conventional alkoxycarbonylating agents because of their labile properties toward the moisture. From Table 2, 3,5-dimethylpyrazole-1-carboxylates (**1d-g**) were quite stable, and able to be stored under ordinary conditions without any decomposition. Even in the cases of unsubstituted pyrazole derivatives (**2d-g**), the stabilities were equivalent to that of Boc-SDP, which was regarded as the moderately stable alkoxycarbonyl-ating agent.

When **1g** was treated with propylamine, benzyl *N*-propylcarbamate (**6ga**) was afforded in good yield. Also **6ga** was obtained from **1g** by the neutralization of propylamine hydrochloride with triethylamine. Moreover, various carbamates (**6**) were yielded in the reaction of **1d**-**g** or **2d**-**g** with primary and secondary amines as summarized in Table 3.



Scheme 4

Table 2. The Stabilities of Alkyl Pyrazole-1-carboxylates (**1d**-**g** or **2d**-**g**) in Aqueous Ethanol at 40°C.

Run	Pyrazolecarboxylate			Half Life (τ) (h)	Rel. Stability[a]
		R^1	R^2		
1	**1d**	Me	Me	924	28.9
2	**1e**	Et	Me	569	17.8
3	**1f**	*t*-Bu	Me	144	4.5
4	**1g**	Bn	Me	344	10.8
5	**2d**	Me	H	282	8.8
6	**2f**	*t*-Bu	H	30	0.9
7	**2g**	Bn	H	141	4.4
8	**1b**	1-Acetyl-3,5-dimethylpyrazole		36	1.1
9		Methyl Imidazole-1-carboxylate		68	2.1
10		Boc-SDP[a]		32	—

a: Relative stabilities were evaluated based on that of 2-(*t*-butoxycarbonylthio)-4,6-dimethylpyrimidine (Boc-SDP)

Table 3. The Reaction of Alkyl Pyrazole-1-carboxylates (**1d-g** or **2d-g**) with Amines.

Run	**1d-g** or **2d-g**			Amine	Temp	Carbamate	Yield	Opt. Yield
		R^1	R^2				(%)	(%)
1	**1g**	Bn	Me	NH_4OH	60°C	H_2N-CO_2Bn	71	—
2	**1g**	Bn	Me	$PrNH_2$	60°C	PrNH-CO_2Bn	92	—
3	**1g**	Bn	Me	$PrNH_2$·HCl/Et_3N	60°C	PrNH-CO_2Bn	97	—
4	**1e**	Et	Me	$BnNH_2$	60°C	BnNH-CO_2Et	87	—
5	**1g**	Bn	Me	Pyrrolidine	60°C	$(CH_2)_4N$-CO_2Bn	86	—
6	**1e**	Et	Me	$PhNH_2$	60°C	PhNH-CO_2Et	5	—
7	**1e**	Et	Me	$HOCH_2CHBnNH_2$	60°C	$HOCH_2CHBnNH$-CO_2Et	26	—
8	**1d**	Me	Me	Gly-OEt·HCl/Et_3N	rt	MeO_2C-Gly-OEt	74	—
9	**1f**	*t*-Bu	Me	Gly-OEt·HCl/Et_3N	rt	Boc-Gly-OEt	10	—
10	**1g**	Bn	Me	Gly-OEt·HCl/Et_3N	rt	Cbz-Gly-OEt	75	—
12	**2f**	*t*-Bu	H	Gly-OEt·HCl/Et_3N	rt	Boc-Gly-OEt	60	—
13	**2f**	*t*-Bu	H	Ala-OEt·HCl/Et_3N	rt	Boc-Ala-OEt	21	100
14	**1g**	Bn	Me	Ala-OEt·HCl/Et_3N	rt	Cbz-Ala-OEt	73	100
15	**1d**	Me	Me	Phe-OMe·HCl/Et_3N	rt	MeO_2C-Phe-OMe	63	100
16	**2f**	*t*-Bu	H	Phe-OMe·HCl/Et_3N	rt	Boc-Phe-OMe	trace	—
17	**2g**	Bn	H	Phe-OMe·HCl/Et_3N	rt	Cbz-Phe-OMe	86	100
18	**1d**	Me	Me	Phe-OH/NaH	rt	MeO_2C-Phe-OH	0	—
19	**1f**	*t*-Bu	Me	Phe-OH/NaH	rt	Boc-Phe-OH	52	85
20	**1g**	Bn	Me	Ala-OH/NaH	rt	Cbz-Ala-OH	95	19
21	**1g**	Bn	Me	Phe-OH/NaH	rt	Cbz-Phe-OH	41	100
23	**1g**	Bn	Me	Gly-OH/NaH	-5°C	Cbz-Gly-OH	55	—
24	**1g**	Bn	Me	Ala-OH/NaH	-5°C	Cbz-Ala-OH	98	93
26	**1g**	Bn	Me	Phe-OH/NaH	-5°C	Cbz-Phe-OH	46	100
28	**1g**	Bn	Me	Val-OH/NaH	-5°C	Cbz-Val-OH	31	100
30	**1g**	Bn	Me	Leu-OH/NaH	-5°C	Cbz-Leu-OH	72	100

In consequence of the high stability toward moisture, Schotten-Baumann type reaction could be performed to obtained benzyl urethane (**6gb**) in good yield from **1g** by the prolonged heat with aqueous ammonia.

The results of these reactions suggested that **1d**-**g** also acted as a very convenient alkoxycarbonylating agent for the preparation of carbamates, even under the aqueous conditions.

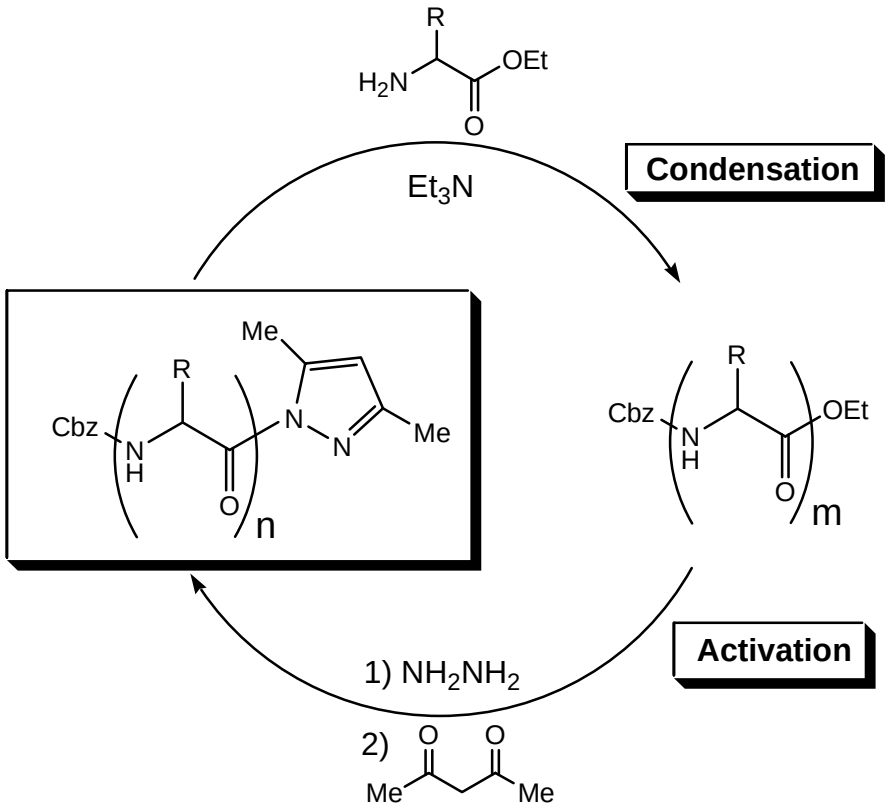
For amino acid ester hydrochlorides, **1g** acted as the alkoxycarbonylating agent to give *N*-Cbz amino esters in good yield as summarized in Table 3. The property of high stability toward water allowed the reaction of **1g** with ethyl glycinate hydrochloride even in the aqueous ethanol to give N-Cbz glycinate (**6gc**). On the contrary, **1f** gave *N*-Boc amino ester in poor yields, due to the steric hindrance of *t*-butyl group. During these alkoxycarbonylating reactions, the stereostructure on the chiral center was completely retained.

Because of the zwitterionic state of amino acids, the nucleophilicity of amino group was insufficient for the reaction with **1d**-**g**, and no product of *N*-alkoxycarbonylation was obtained by the reaction of **1d** with phenylalanine in the presence of triethylamine. By neutralization of acid function with NaH, amino group of phenylalanine increased their nucleophilicities and was sufficiently reactive toward **1d**-**g**. As shown in Table 3, the reaction of **1g** with free amino acids was accomplished optimally at -5°C in THF or DMF to afford Cbz-protected amino acids without any racemization.

When these chemical properties of 1-pyrazolecarboxylates were combined with the preparative method of pyrazole ring from carboxylic esters, the new system of peptide bond formation is constituted.[11] The reaction of various Cbz-amino esters with hydrazine hydrate in methanol afforded Cbz-amino acid hydrazides, which was treated with 2,4-pentanedione under weakly acidic conditions to give 1-(α-Cbz-aminoacyl)-3,5-dimethylpyrazoles in good yield. By this step by step preparation in one pot, dipeptide esters and tripeptide esters were also converted into the corresponding *N*-acylpyrazoles.

The consequent *N*-acylpyrazoles were extractable from aqueous reaction mixture with ordinary organic solvent. Further these compounds were very stable crystalline compounds and easily purified by means of chromatography or recrystallization. On the HPLC using the chiral column, the optical resolution was observed with remarkable separability factors. Moreover the strong UV absorption of these compounds led to the high sensitivity on the UV detector of HPLC, compared with those of *N*-protected amino esters. From these characteristics, pyrazole moiety of *N*-protected α-aminoacylpyrazoles was practically regarded as the useful marker for the quantitative analysis of amino acid and peptide derivatives especially for the evaluation of enantiomer ratio.

Further, *N*-protected α-amino-acylpyrazoles was treated with various amino esters, and obtained the corresponding dipeptide esters with the retention of optical asymmetry in moderate to good yield. Similarly *N*-protected α-amino-acylpyrazoles reacted with various amino ester hydro-chloride in the presence of triethylamine to give the corresponding dipeptide esters. The consequent peptide esters were applicable to the further conversion into the corresponding *N*-acylpyrazoles. After all, new system of peptide synthesis was constituted of this peptide bond formation and the direct preparation of *N*-acylpyrazoles from the corresponding esters, as illustrated in Scheme 5. The extension of one amino acid unit on the peptide chain was required only 2 steps of independent reactions, the conversion from esters to *N*-acylpyrazoles and the subsequent aminolysis with amino esters. This new system was distinctive from the conventional peptide synthesis, which was consisted of 3 steps of the deprotection, the activation and the condensation. Moreover, the key intermediate *N*-acylpyrazoles exhibited the excellent properties of high sensitivity and separability for the chiral column on HPLC using the UV detector.



Scheme 5 New Peptide Synthetic System

3.3 Alcoholysis[12]

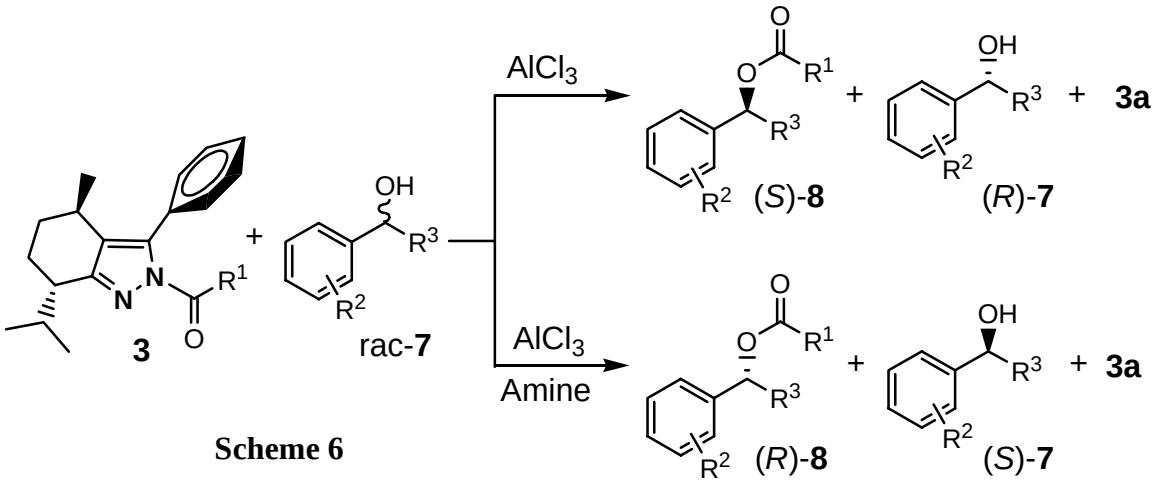
In order to demonstrate the stability of *N*-acylpyrazoles, alcoholysis of *N*-acylpyrazoles was investigated. When the benzene solution of benzyl alcohol and 1-pentanoyl-3,5-dimethylpyrazole (**1h**) was heated at

60°C for 20 h, benzyl pentanoate was formed only in 20 % yield. Even in the presence of triethylamine, this reaction went on very slowly.

The alcoholysis was accelerated 1700 times by the addition of sodium hydride. The alcoholysis of *N*-acylpyrazoles was also catalyzed by the addition of $BF_3{\cdot}OEt_2$. Furthermore, the alcoholysis of *N*-acylpyrazoles was accelerated in the presence of various kinds of Lewis acids having the coordination number. The data of the Table 4 showed that the reaction of 1-acetyl-3,5-dimethylpyrazole (**1b**) with 1-phenylethanol (**7a**) was remarkably accelerated more than 1500 times by $TiCl_4$, $FeCl_3$ and $AlCl_3$, which usually behaved as higher coordination number elements. These Lewis acids should enable the alcoholysis with secondary alcohols under mild conditions, even in their presence of less than 50 mol %. This high chemoselectivity of *N*-acylpyrazoles under various reaction conditions should be the useful properties for the selective synthesis of a wide variety of carboxylic acid derivatives.

Table 4. The Effect of Lewis Acid on Reaction of **1b** with **7a**.

Catalyst	Half Life of **1b** (min)
None	7600
Et_3N	7600
NaH	~5
p-TsOH	384
$BF_3{\cdot}OEt_2$	191
$ZnCl_2$	188
$CuBr_2$	88
$TiCl_4$	13
$FeCl_3$	7
$AlCl_3$	6



Scheme 6

Phenyl group caused the chiral environment on the acyl moiety of 2-acyl-3-phenyl-*l*-menthopyrazoles (**3**), and allowed the diastereofacial attacks of reagent on the α-position of acyl moiety.[13] These diastereofacial attacks might be allowed on the carbonyl carbon, which was much closer to the chiral center of **3**. Thus we firstly attempted the reaction of 2-acetyl-3-phenyl-*l*-menthopyrazole (**3b**) with racemic 1-phenylethanol (**7a**). When **3b** was treated with 20 molar amounts of **7a** in the presence of equimolar $AlCl_3$ at room temperature for 3 h, (S)-1-phenylethyl acetate ((*S*)-**8ba**) was afforded in 87 % yield with 48 % ee. After optimization of the reaction in various solvents with some Lewis acid, (*S*)-**8ba** was predominantly obtained in 94 % yield with 71 % ee in toluene-hexane mixture at -5°C, where the selectivity factor (s) was found to be 5.9.

By the use of 2.4 molar amount of racemic **7a**, (*S*)-**8ba** was obtained in 99 % yield with 66 % ee. In this reaction, unreacted (*R*)-**7a** was recovered in 64 % yield with 46 % ee as well as the chiral auxiliary **3a** in 93 % yield. Similarly some secondary alcohols were enantioselectively acetylated by the use of **3b** in good yields summarized in Scheme 6 and Table 5.

When the strongly basic amines were added, the configuration of **8ba** was dramatically changed in the reaction of **3b** with **7a** as summarized in Table 6. When **3b** was treated with **7a** in the presence of

Table 5. Optical Resolution of *sec*-Alcohols by Enantioselective Acylation with **3** in Toluene-Hexane Mixture (3:1).

Run	**3**		*Rac*.-**7**			Product (*S*)-**8**			Unreacted (*R*)-**7**		**3a**
		R^1		R^2	R^3		Yield(%)	Ee(%)	Yield(%)	Ee(%)	Yield (%)
1	**3b**	Me	**7a**	H	Me	**8ba**	99	66	64	46	93
2	**3c**	Et	**7a**	H	Me	**8ca**	54	66	40	57	88
3	**3i**	*t*-Bu	**7a**	H	Me	**8ia**	3	1	58	1	51
4	**3j**	Ph	**7a**	H	Me	**8ja**	trace	—	22	—	95
5	**3b**	Me	**7b**	*p*-Cl	Me	**8bb**	85	60	81	30	86
6	**3b**	Me	**7c**	*p*-Me	Me	**8bc**	79	53	24	13	83
7	**3b**	Me	**7d**	*o*-Me	Me	**8bd**	29	69	58	16	37
8	**3b**	Me	**7e**	H	Et	**8be**	89	66	65	42	90

equimolar amounts of $AlCl_3$ and diisopropylamine in toluene at -5°C, (*R*)-**8ba** was optimally obtained in 89 % yield with 64 % ee, and unreacted (*S*)-**7a** was recovered in 60 % yield with 41 % ee.

Table 6. Optical Resolution of **7a** with **3b** in the Presence of $AlCl_3$ and Amines in Toluene

Run	Amine		Temp.	Product (**8ba**)			Unreacted **7a**			**3a**
		eq	(°C)	Yield	Ee	Conf.	Yield	Ee	Conf.	Yield
1	none	0	40	77	13	(*S*)	31	7	(*R*)	84
2	*i*-Pr_2NH	1.0	40	99	15	(*R*)	56	7	(*S*)	87
3	none	0	-5	90	49	(*S*)	58	30	(*R*)	94
4	*i*-Pr_2NH	0.5	-5	98	5	(*R*)	70	9	(*S*)	89
5	*i*-Pr_2NH	1.0	-5	89	64	(*R*)	60	41	(*S*)	83
6	*i*-Pr_2NH	1.2	-5	69	61	(*R*)	76	23	(*S*)	67
7	*i*-Pr_2NH	1.5	-5	100	64	(*R*)	77	38	(*S*)	82
8	*i*-Pr_2NH	2.0	-5	82	61	(*R*)	58	24	(*S*)	58

3.4 Grignard Reaction of *N*-Acylpyrazoles[14]

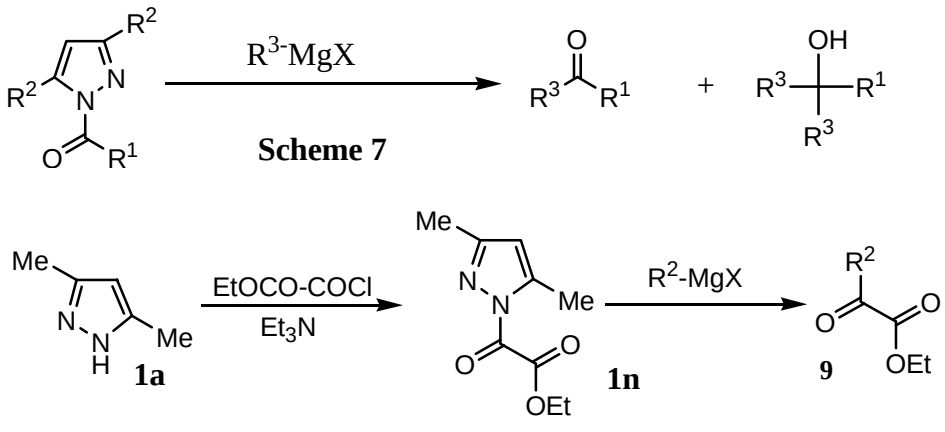
When 1-benzoyl-3,5-dimethylpyrazole (**1j**) was treated with phenylmagnesium bromide in ether at room temperature, benzophenone and triphenylmethanol were formed without any side reaction. Excess amount of Grignard reagent to *N*-acylpyrazoles caused further reaction to afford the complicated mixture of hydroxyl compounds and olefins. By competitive reaction, *N*-acylpyrazoles was found to be more reactive than esters and aryl ketones as summarized in Table 7. After detailed studies, the controlled formation of ketones was succeeded by the use of an equimolar amount of Grignard reagent with *N*-acylpyrazoles, summarized in Scheme 7 and Table 8. Also the Grignard reaction of alkyl pyrazolecarboxylates gave one carbon higher carboxylic esters.[9]

α-Keto esters have been paid attention to their biological activities such as the inhibitor of proteolytic enzymes [15] and leukotriene A4 hydrase. [16] Also α-keto esters are regarded as the important synthon of α-keto acids and α-hydroxy acids. As an extensive studies about the chemistry of *N*-acylpyrazoles, the convenient preparative method of α-keto esters (**9**) was succeeded by the Grignard reaction of *N*-acylpyrazoles (**1**), summarized in Scheme 8. This short step reaction conveniently afforded various α–keto esters in good yields.[17]

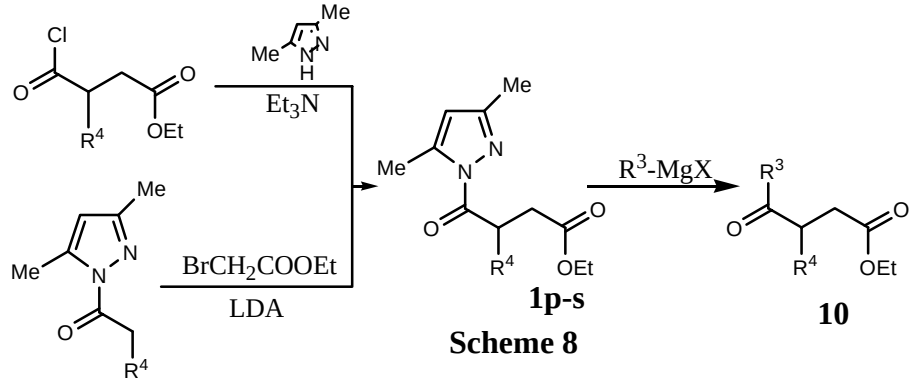
γ-Keto esters are regarded as the important synthons of γ-lactones which are paid attention to their biological activities. By the treatment with phenylmagnesium bromide, ethyl 4-phenyl-4-oxobutanoate (**10oa**) was obtained in good yield from ethyl 4-(3,5-dimethylpyraz-o1-yl)-4-oxobutanoate (**1o**) which was directly prepared from succinic acid

Table 7. Relative Reactivities of *N*-Acylpyrazoles and Other Carbonyl Compounds with PhMgBr

Substrate	Reactivity
1-Benzoyl-3,5-dimethylpyrazole (**1b**)	1.0
1-Acetyl-3,5-dimethylpyrazole (**1j**)	0.9
Acetophenone	0.3
Acetone	0.9
p-Methylbenzophenone	~0
Ethyl Acetate	0.02
Methyl *p*-Toluate	~0



Scheme 7



Scheme 8

Table 8. The Grignard Reaction of *N*-Acylpyrazoles.

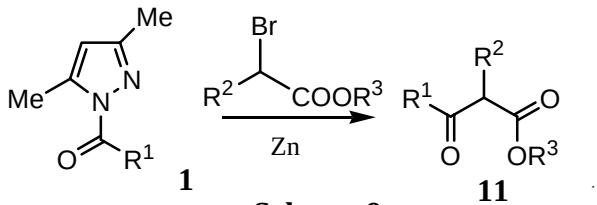
Run	*N*-Acylpyrazole			Product	yield
		R^1	R^2		(%)
1	**1j**	Ph	Me	Ph-CO-Ph	68
2	**1j**	Ph	Me	Ph-CO-Me	63
3	**1j**	Ph	Me	Ph-CO-Et	65
4	**1j**	Ph	Me	*p*-Tol-CO-Ph	62
5	**1b**	Me	Me	Ph-CO-Me	74
6	**1m**	$PhCH_2CH_2$	Me	$PhCH_2CH_2$-CO-Ph	79
7	**1n**	PhCHMe	Me	PhCHMe-CO-Ph	62
8	**1e**	EtO	Me	Ph-COOEt	86
9	**1f**	*t*-BuO	Me	Ph-COO(*t*-Bu)	63
10	**1g**	$PhCH_2O$	Me	Ph-$COOCH_2Ph$	47
11	**1g**	$PhCH_2O$	Me	Bu-$COOCH_2Ph$	40
12	**1d**	MeO	Me	$PhCH_2CH_2$-COOMe	42
13	**1g**	$PhCH_2O$	Me	*i*-Pr-$COOCH_2Ph$	51
14	**2o**	COOEt	H	Ph-CO-COOEt (**9a**)	57
15	**1o**	COOEt	Me	Ph-CO-COOEt (**9a**)	64
16	**1o**	COOEt	Me	*p*-Tol-CO-COOEt (**9b**)	57
17	**1o**	COOEt	Me	Me-CO-COOEt (**9c**)	69
18	**1o**	COOEt	Me	Et-CO-COOEt (**9d**)	66
19	**1o**	COOEt	Me	*i*-Pr-CO-COOEt (**9e**)	51
20	**1o**	COOEt	Me	*c*-Hex-CO-COOEt (**9f**)	80
21	**1o**	COOEt	Me	$PhCH_2CH_2$-CO-COOEt (**9g**)	76
22	**1p**	CH_2CH_2COOEt	Me	Ph-CO- CH_2CH_2COOEt (**10pa**)	53
23	**1p**	CH_2CH_2COOEt	Me	*p*-Tol-CO- CH_2CH_2COOEt (**10pb**)	48
24	**1p**	CH_2CH_2COOEt	Me	Me-CO- CH_2CH_2COOEt (**10pc**)	64
25	**1p**	CH_2CH_2COOEt	Me	Et-CO- CH_2CH_2COOEt (**10pd**)	63
26	**1p**	CH_2CH_2COOEt	Me	Bu-CO- CH_2CH_2COOEt (**10ph**)	51
27	**1q**	$CH_2CHMeCOOEt$	Me	Ph-CO- $CH_2CHMeCOOEt$ (**10qa**)	51
28	**1q**	$CH_2CHMeCOOEt$	Me	Me-CO- $CH_2CHMeCOOEt$ (**10qc**)	17
29	**1r**	$CH_2CHPhCOOEt$	Me	Ph-CO- $CH_2CHPhCOOEt$ (**10ra**)	63
30	**1r**	$CH_2CHPhCOOEt$	Me	Me-CO- $CH_2CHPhCOOEt$ (**10rc**)	67
31	**1s**	$CH_2CH(CH_2Ph)COOEt$	Me	Me-CO- $CH_2CH(CH_2Ph)COOEt$ (**10sc**)	52

derivatives and 3,5-dimethylpyrazole. Alkylation of 1-acyl-3,5-dimethylpyrazole (**1c**, **1k**, and **1m**) with

bromoacetates afforded 3-substituted 4-(3,5-dimethylpyrazol-1-yl)-4-oxobutanoic esters (**1p-r**) in good yields. The subsequent Grignard reaction afforded various β–substituted γ–keto esters (**10**) summarized in Scheme 8.[18]

3.5 Reformatsky Reaction of *N*-Acylpyrazoles[19]

The Reformatsky reaction of 1-benzoyl-3,5-dimethylpyrazole (**1j**) was observed under refluxing in THF to afford ethyl 3-phenyl-3-oxopropanoate in high yield, while the reaction did not occur at room temperature. Similarly the Reformatsky reaction of various 1-acyl-3,5-dimethylpyrazoles (**1**) with α-bromoacetates afforded β-keto esters (**11**) in high yields, summarized in Scheme 9 and Table 9. Even in the use of α-bromopropanoates, the corresponding α-methyl-β-keto esters were formed. This reaction was applicable to the synthesis of statines, where optical



Scheme 9

Table 9. The Reformatsky Reaction of 1-Acyl-3,5-dimethylpyrazoles (**1**)

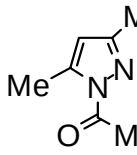
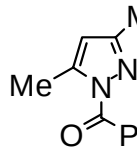
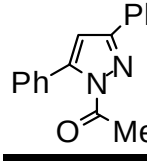
Run	R^1	R^2	R^3	Product	Yield (%)
1	Ph	H	Et	Ph-CO-CH_2-COOEt	73
2	Ph	H	Me	Ph-CO-CH_2-COOMe	67
3	Ph	H	CH_2Ph	Ph-CO-CH_2-COOCH_2Ph	62
4	Ph	Me	Et	Ph-CO-CHMe-COOEt	71
5	Me	H	Et	Me-CO-CH_2-COOEt	62
6	Me	Me	Et	Me-CO-CHMe-COOEt	100
7	Et	H	Et	Et-CO-CH_2-COOEt	74
8	*i*-Pr	H	Et	*i*-Pr-CO-CH_2-COOEt	73
9	*t*-Bu	H	Et	*t*-Bu-CO-CH_2-COOEt	11
10	$PhCH_2CH_2$	H	Et	$PhCH_2CH_2$-CO-CH_2-COOEt	81
11	$PhCH_2CH$(NHBoc)	H	Et	$PhCH_2CH$(NHBoc)-CO-CH_2-COOEt	47
12	$PhCH_2CH$(NHBoc)	H	Me	$PhCH_2CH$(NHBoc)-CO-CH_2-COOMe	38
13	$PhCH_2CH$(NHCbz)	H	Et	$PhCH_2CH$(NHCbz)-CO-CH_2-COOEt	64
14	*i*-$BuCH_2CH$(NHCbz)	H	Et	*i*-$BuCH_2CH$(NHCbz)-CO-CH_2-COOEt	41

purities were retained completely.

3.6 Behaviours of *N*-Acylpyrazoles toward $MgBr_2$[20]

The diastereoselective α-replacement reactions of 2-acyl-3-phenyl-*l*-menthopyrazoles (**3**) were elucidated by the attack of electrophiles on the lithium enolate intermediate, which was rigidly fixed by the intramolecular chelation between lithium and *N*-1 atom.[21] Since magnesium ion has very similar Van der Waals radius with lithium ion and $MgBr_2$ is recently paid much attention as the divalent Lewis acid having the small atomic size,[22] the interaction between *N*-acylpyrazoles and $MgBr_2$ was studied by means of IR spectra, and the chelation of $MgBr_2$ with the carbonyl oxygen of 1-acyl-3,5-dimethylpyrazole (**1**) in $CHCl_3$ was observed, while no chelation was observed in THF solution. From GC of **1** toward various amounts of $MgBr_2 \cdot OEt_2$ and in the various concentrations, the equilibrated chelation was deduced with approximately K= 15 l/mol in $CHCl_3$ and K= 20 l/mol in CH_2Cl_2 at room temperature, respectively. Moreover, the formation of the complex among **1** and $MgBr_2$ was proved in the ^1H NMR spectra, where

Table 10. The Chemical Shifts of **1** and Their $MgBr_2$ Complexes

	Assignment	δ of **1**	δ of $MgBr_2$ Complex	$\Delta\delta^{\dagger}$
 (**1b**)	3-Me	2.24	2.55	0.31
	4-H	5.96	6.35	0.39
	5-Me	2.54	2.77	0.23
	Ac	2.66	3.02	0.36
 (**1j**)	3-Me	2.55	2.51	0.26
	4-H	6.06	6.33	0.27
	5-Me	2.63	2.15	-0.48
 (**4b**)	4-H	6.71	6.73	0.02
	Ac	2.79	2.53	-0.26

†: The upper field shifts in the complex formation were represented as the negative value.

all peaks of **1b** were shifted to the down field by the addition of $MgBr_2 \cdot OEt_2$. In the case of 1-benzoyl-3,5-

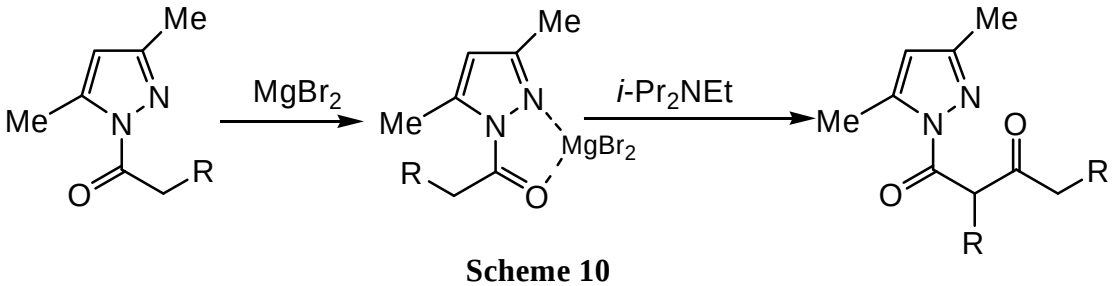
dimethylpyrazole (**1j**), 5-Me resonance was shifted to the upper field, while 3-Me and 4-H proton signals appeared in the lower field, summarized in Table 10. This upper field shift was illustrated to be caused by the anisotropic effect of adjacent benzene ring, which was fixed in the syn conformation due to the 5-membered chelation of C=O···Mg···N-2. Similar upper field anisotropic shift was observed in the acetyl protons of 1-acetyl-3,5-diphenylpyrazole (**4b**).

Next, the molecular orbital calculation of **1b** and the $MgBr_2$ complex was carried out by PM3 method listed in Table 11. The predominant conformer of **1b** was postulated to be anti form 3 kcal/mol more stable than *syn*-conformer. In the case of $MgBr_2$ complex, *syn*-**1b**-$MgBr_2$ was rather stable according to the 5-membered chelation of C=O···Mg···N-2. The results of these calculations supported the postulated conformation based on the chromatographic and spectroscopic data.

Table 11. PM3 calculation of **1b** and Its $MgBr_2$ Complex.

		Anti-**1b**	*Syn*-**1b**	*Anti*-**1b**-$MgBr_2$	*Syn*-**1b**-$MgBr_2$
Heat of Formation (Kcal/mol)		-11.10	-7.74	-100.22	-117.41
Charge	2-**N**	-0.2182	-0.1586	-0.2045	0.0804
	3-Me-**H**	0.0598	0.0518	0.0665	0.0783
	4-**H**	0.1404	0.1395	0.1531	0.1554
	5-Me-**H**	0.0528	0.0544	0.0702	0.0717
	1-Ac-**O**	-0.3347	-0.2771	-0.2797	-0.1995
	1-Ac-**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 α-position by the action of weak base such as tertiary amines.[23] In the Table 11, the positive charges on acetyl protons of **1b** were much increased by the formation of the $MgBr_2$ complex. When the mixture of 1-propanoyl-3,5-dimethylpyrazole (**1c**) and $MgBr_2{\cdot}OEt_2$ was treated with *N*-ethyldiisopropylamine (**2**) in CH_2Cl_2 at room temperature, 1-(2-methyl-3-oxo)pentanoyl-3,5-dimethylpyrazole (**1t**) was obtained in good yield through the Claisen condensation of **1c**, illustrated in Scheme 10. This reaction mechanism was presumed that **1c** was firstly deprotonated from α−position of acyl group to form enolate by the action of $MgBr_2$, and then the nucleophilic attack of the subsequent enolate was caused on carbonyl of **1c** to afford **1t**.



Scheme 10

4 Conclusion

We have recently developed a method of preparation for 3-phenyl-*l*-menthopyrazole (**3a**) as a new chiral auxiliary, which has unique structure and properties that are different from the conventional chiral auxiliaries. As an analogue of the *N*-acylheteroaromatics, *N*-acylpyrazoles are comparably stable and are easily prepared either from acid chlorides and pyrazoles or from β-diketones and acylhydrazides. *N*-Acylpyrazoles are easily converted into acyl derivatives by the action of nucleophiles such as alcohols, amines, Grignard reagents, or organozinc compounds under basic or acidic conditions. In the case of alcoholysis, *N*-acyl-3-phenyl-*l*-menthopyrazoles (**3**) act as the chiral acylating agent, and bring the optical resolution of secondary alcohols. From these chemical properties, *N*-acylpyrazoles exhibit high utilities in the reaction on synthetic loop using 3-phenyl-*l*-menthopyrazole (**3a**). Moreover *N*-acylpyrazoles are applicable for the convenient peptide syntheses, where one amino acid unit is extended on the peptide chain through 2 steps, namely the preparation and the aminolysis of *N*-Acylpyrazole derivatives.

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