AMINOLYSIS OF *N*-ACYLPYRAZOLES

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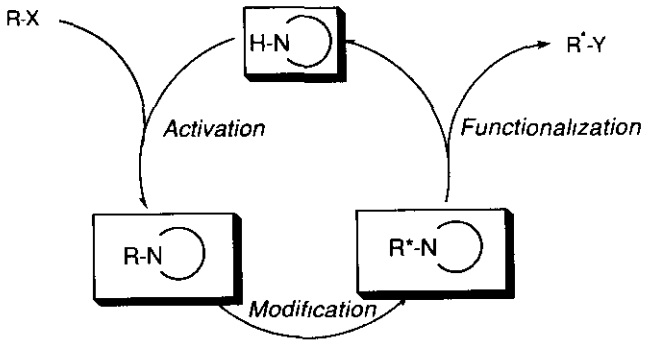
Abstract-- 1-Acylpyrazoles reacted with amines having a tiny substituent to afford the corresponding amides. The aminolysis with bulky amines was controlled to be retarded by the steric factors. Due to this steric interaction, the stereoselective aminolysis was observed. This selectivity of aminolysis should increase the utility of pyrazoles as auxiliary compounds in the synthetic loop.

Many compounds such as Oppolzer's sultams[1] and Evans's oxazolidinones[2] have been used as the auxiliary compounds in a wide variety of the synthetic strategies. As illustrated in Scheme 1, these examples are summarized in the synthetic loop concept, in which two essential reaction steps are included. One is the activation of the substrate with an auxiliary compound. The other is the conversion of the substrate into the desired functionality accompanied by the recovery of the auxiliary compound. Moreover, the utility of an auxiliary compound in the synthetic loop should be raised by the modification of substrate moiety under the influences of the auxiliary.



Scheme 1. The Synthetic Loop

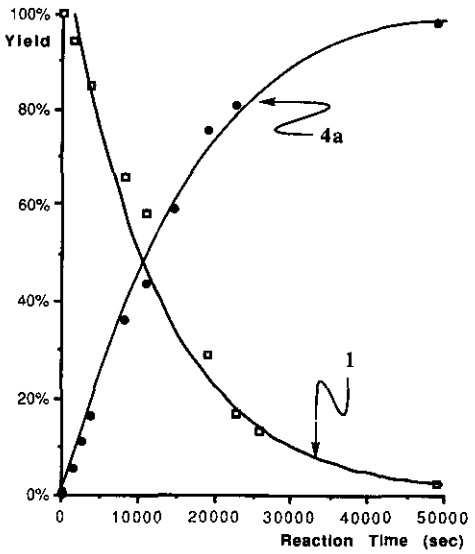
Recently we have investigated the utility of *N*-acylpyrazoles as the auxiliary compounds in the synthetic loop. The activation reaction was accomplished through the acylation of pyrazoles by the action of carboxylic acids or their acid chlorides.[3] In the case of an optically active pyrazole such as 3-phenyl-*l*-menthopyrazole, acylation

reaction proceeded regio- and stereoselectively to give the diastereomerically pure 2-acyl-3-phenyl-*l*-menthopyrazoles were prepared.[4]

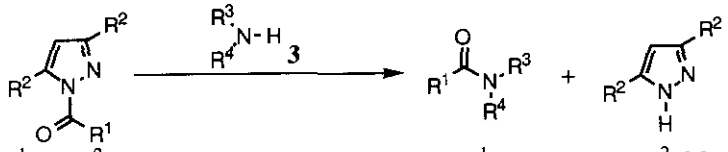
In a meanwhile, imidazole was extensively used as an auxiliary compound in the synthetic loop, where carboxylic acids were activated by the formation of *N*-acylimidazole using carbonyldiimidazole. By treatment with nucleophiles, *N*-acylimidazoles were converted into a large variety of compounds.[5] Owing to the structural analogy to *N*-acylimidazoles, *N*-acylpyrazoles were expected to show the analogous behaviors toward the nucleophiles. However a small number of papers in the literature have appeared in the chemical behaviors of *N*-acylpyrazoles due to their low reactivity.[6] In order to expand the usefulness of *N*-acylpyrazoles as auxiliary compounds in the synthetic loop, the development of a wide variety of conversion reactions is highly desired. So far as we know, the reaction of *N*-acylpyrazoles with amines was reported in only one paper without enough information about their characteristics.[7] Here, we reexamined the aminolysis of *N*-acylpyrazoles to reveal their chemical behaviors toward the nucleophiles including the steric interaction.

When 1-propionyl-3,5-dimethylpyrazole (**1**) was treated with benzylamine (**3a**) in dry benzene, *N*-benzylpropionamide (**4a**) and 3,5-dimethylpyrazole (**6**) were formed quantitatively. The decrease of **1** and the formation of **4a** was followed by gc, as summarized in Figure 1. Similarly the aminolysis of **1** with various amines was compared by the evaluation of their reaction rates. When these aminolysis rates were plotted against their pKa values, those of the unbranched primary amines and anilines were correlated on the straight line (Figure 2). In the cases of α-branched primary amines and secondary amines, analogous linearity could not be found. This tendency was also observed in the aminolyses of 1-acetylpyrazole (**2**), where the aminolyses proceeded about 10 times faster than those of **1**. These data listed in Table 1 indicate that the steric interaction between amines and 1-acylpyrazoles affected intensively to the aminolysis rates. Furthermore the kinetic parameters were evaluated in order to clarify the reaction tendency having the higher steric interaction. The kinetic parameters of the aminolysis of **1** with benzylamine (**3a**) were given to be Ea= 5.1

Figure 1 Aminolysis of**1** with **3a**



kcal/mol, $\Delta G^{\neq}$= 4.5 kcal/mol and $\Delta S^{\neq}$= -59 cal/K at 30°C, while those of **1** with 1-phenylethylamine (**3b**) were Ea= 5.6 kcal/mol, $\Delta G^{\neq}$= 5.0 kcal/mol and $\Delta S^{\neq}$= -62 cal/K at 30°C. Here, the small enthalpy values of activation and the large negative entropies of activation suggested to be caused by the higher steric factor of the transition state. From these facts, it was concluded that the aminolysis of 1-acylpyrazoles was much dependent on the structures of amines.



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

4: R^1=Et
5: R^1=Me

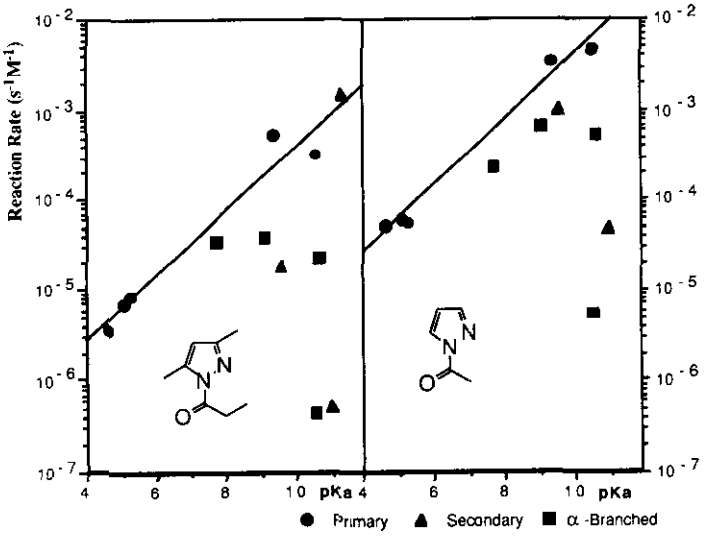
6: R^2=Me
7: R^2=H

	R^3	R^4		R^3	R^4
a:	$PhCH_2$	H	**g**:	i-Pr	H
b:	PhCH(Me)	H	**h**:	Ph_2CH	H
c:	Pr	H	**i**:	t-Bu	H
d:	Ph	H	**j**:	$(CH_2)_4$	
e:	p-Tol	H	**k**:	Et	Et
f:	p-Anis	H	**m**:	$PhCH_2$	Me

Scheme 2

As described in the previous paper,[4] the steric hindrance between 3-phenyl and 4-methyl groups of 3-phenyl-*l*-menthopyrazole (**9**) is relaxed by twisting the phenyl ring, which overlays on the *N*-2 nitrogen atom. This structural feature should extend the steric effect of the chirality of (4R)-methyl group by the induction of the torsional asymmetry. Therefore 2-acyl-3-phenyl-*l*-menthopyrazoles are expected to be aminolyzed stereoselectively into the optically active amide by the high steric interaction in the aminolysis. When 2-acetyl-3-phenyl-*l*-menthopyrazole (**8**) was treated with *dl*-1-phenylethylamine

Figure 2 Aminolysis Rates of **1** and **2** *vs* pKa

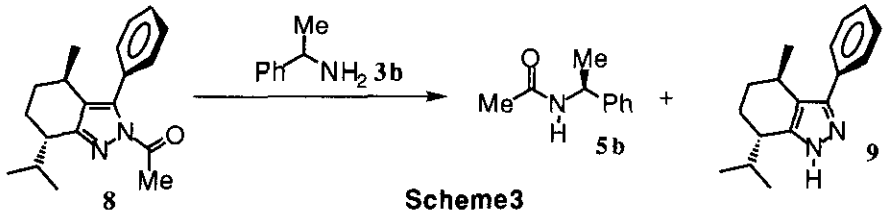


(*dl*-**3b**) at room temperature, *N*-(1-phenyl)ethylacetamide (**5b**) was obtained in good chemical yield, accompanied by 3-phenyl-*l*-menthopyrazole (**9**). By means of specific rotation, the stereoselective aminolysis was observed with the preference of S-configuration,[8] although the stereoselectivity was low. The optical yield of this reaction was evaluated to be 10 % from the ^{1}H nmr spectrum using the chiral europium shift reagent (Eu(tfc)3).

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

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

a Reference 9. b Reference 10. c Reference 11.



Scheme3

In conclusion, 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 controlled to be retarded by the steric repulsion. Due to this steric repulsion, the stereoselective aminolysis was observed in the reaction of *dl*-1-phenylethylamine with optically active 1-acetyl-3-phenylmenthopyrazole. This tendency of aminolysis should be utilized to the modification and functionalization reaction of 1-acylpyrazoles in the synthetic loop.

EXPERIMENTAL

Nmr spectra were obtained on JEOL JNM-EX270 (270 MHz) spectrometers in $CDCl_3$ with TMS as an internal standard. Specific Rotations were measured on a JASCO DIP-360 digital polarimeter. Gas chromatography was performed on Shimadzu GC-4CM Gas chromatography using SE-30 (2 m) column at 100° to 250°C (temperature rising rate 15°C/min).

Aminolysis of 1 and 2 with 3: General Procedure. An amine (**3**, 0.6-1.4 mmol) and 1-acylpyrazole (**1** or **2**, 0.12 mmol) were dissolved in dry benzene (7 ml). As an internal standard for gc, an appropriate aromatic hydrocarbon (5 mg) such as phenanthrene was added to the solution. The solution was kept at 29.5±0.2°C, and contents of the solution were followed by gc. Also the resulting amide was identified with the authentic samples by gc. The kinetic parameters were given by the reactions at between 30-50°C.

Aminolysis of 8 with 3b. A mixture of 2-acetyl-3-phenyl-*l*-menthopyrazole (**8**, 290 mg) and *dl*-1-phenylethylamine (*dl*-**3b**, 500 mg) was dissolved in dry THF (10 ml) and kept at 56°C for 18 h. The mixture was quenched with 2N hydrochloric acid and extracted with CH_2Cl_2. The organic layer was washed with saturated sodium hydrogen carbonate and sodium chloride solutions, dried over anhydrous magnesium sulfate and evaporated. The residue was chromatographed on silica gel with benzene-ethyl acetate (1:1 v/v) mixture. 3-Phenyl-*l*-menthopyrazole (**9**) was eluted as the first fraction, yield 244 mg (98 %). The second fraction was found to be *N*-(1-phenyl)ethylacetamide; yield 116 mg (73 %); $[\alpha]_D^{29°}$ -11.4° (c=3.9, EtOH, Ref. 8 reported -168.1° for S-enantiomer). In the ^1H nmr spectrum using $Eu(tfc)_3$, the peaks assigned to the α-methyl protons were separated to a pair of peaks. From the peak intensity of these peaks, the optical yield was evaluated to be 10 %.

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Received, 8th February, 1994