Chemoselective Preparation of Ketones by the Grignard Reaction of *N*-Acylpyrazoles

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N-Acylpyrazoles afford chemoselectively the corresponding ketones in good yields by the use of equimolar amounts of Grignard reagent. In the case of an optically active *N*-acylpyrazole, optical asymmetry was retained in comparable optical yield. Ketone formation by the Grignard reactions can be regarded as an important functionalization in a synthetic loop using pyrazoles as the auxiliary compound.

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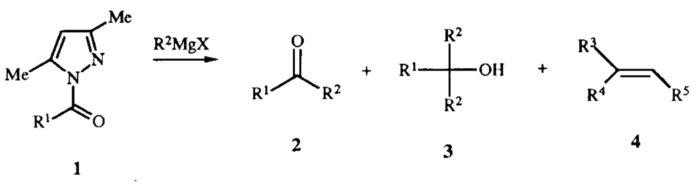
Recently we reported that *N*-acylpyrazoles are easily prepared from carboxylic acids and their acyl chlorides stereoselectively [1,2], and are diastereoselectively alkylated on the α-position of the acyl moiety [1,3]. These behaviors are regarded to be the activation and the modification reaction in the synthetic loop using pyrazoles [4]. As the remarkable functionalization reaction in this synthetic loop, the aminolysis [4], the alcoholysis [2] and the Reformatsky reactions [5] of *N*-acylpyrazoles are provided, where *N*-acylpyrazoles react chemoselectively with nucleophiles. In order to expand the usefulness of this synthetic loop system, further developments of the functionalization reaction of *N*-acylpyrazoles are highly desired. In this paper, the reaction of *N*-acylpyrazoles with Grignard reagents will be discussed as a functionalization reaction.

When 1-benzoyl-3,5-dimethylpyrazole (**1a**) was treated with phenylmagnesium bromide in ether at room temperature, benzophenone (**2a**) and triphenylmethanol (**3a**) were obtained without any side reaction. By the use of various amounts of phenylmagnesium bromide, a reaction profile of **1a** was obtained (Figure 1). The formation of **2a** was observed with the consumption of **1a** in the first step and **3a** was consecutively formed after disappearance of **1a**. This fact implied that *N*-acylpyrazoles **1** are rather reactive toward the Grignard reagent. To investigate this situation further, the reactivity of *N*-acylpyrazoles **1** was compared with those of ordinary carbonyl compounds such as ketones and esters. By competitive reaction, **1a** was found to be more reactive than esters and aryl ketones as summarized in Table 1. From these results, the controlled formation of ketones **2** was expected by use of an equimolar amount of Grignard reagent with **1**. Actually various ketones **2** were formed in good yield by the reaction of **1** with 1.2 molar amounts of Grignard reagent, as summarized in Table 2. Excess amounts (2.4 equivalents) of Grignard reagent caused further reaction to form an hydroxy compound **3** or an olefin **4**.

Scheme 1



3a	R^1=R^2=Ph	**4a**	R^3=Ph, R^4=Me, R^5=H
3b	R^1=Ph, R^2=Et	**4b**	R^3=Ph, R^4=Ph, R^5=H
3c	R^1=Ph, R^2=p-Tol	**4c**	R^3=p-Tol, R^4=p-Tol, R^5=H
3d	R^1=p-Tol, R^2=Ph	**4d**	R^3=Ph, R^4=Ph, R^5=Me
3e	R^1=PhCH$_2$CH$_2$, R^2=Ph		
3f	R^1=PhCH(Me), R^2=Ph		

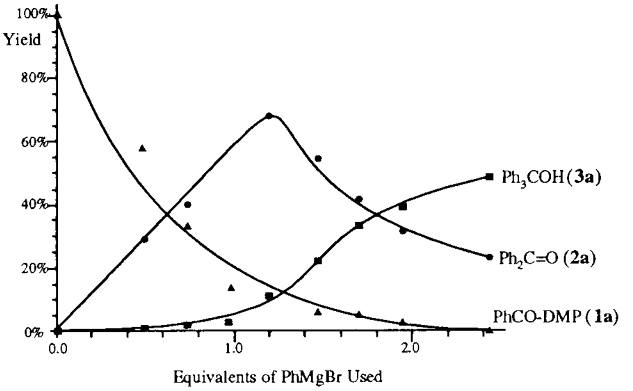


Figure 1. Products of the Reaction of 1-Benzoyl-3,5-dimethylpyrazole with PhMgBr.

Similarly (2'*R*)-2-(2'-phenylpropanoyl)-3-phenyl-*l*-menthopyrazole (*R*-**6**, 53% *de*), which was prepared by the α-methylation of 2-phenylacetyl-3-phenyl-*l*-menthopyrazole (**5**) [1,3], was treated with phenylmagnesium bromide at room temperature. The product was found to be 1,2-diphenyl-1-propanone (*R*-**2**) in 90% yield. By comparison with the authentic $[\alpha]_D$ value [6], the configuration of resulting *R*-**2** was deduced to be *R*-form with 42% *ee*. Also the optical purity of *R*-**2** was evaluated from the ^{1}H nmr spectrum using chiral europium shift reagent [Eu(tfc)$_3$]. These results indicated that the Grignard reaction proceeded with the retention of 66% optical yield. In this asymmetric ketone formation, 3-phenyl-*l*-menthopy-

Table 1

Relative Reactivities of **1a** and Other Carbonyl Compounds with PhMgBr

Substrate	Relative Reactivity
1-(Ph-CO)-DMP* (**1a**)	1.0 [a]
1-(Me-CO)-DMP* (**1b**)	0.9
Ph-CO-Me	0.3
Me_2CO	0.9
p-Tol-CO-Ph	~0
Me-COOEt	0.02
p-Tol-COOMe	~0

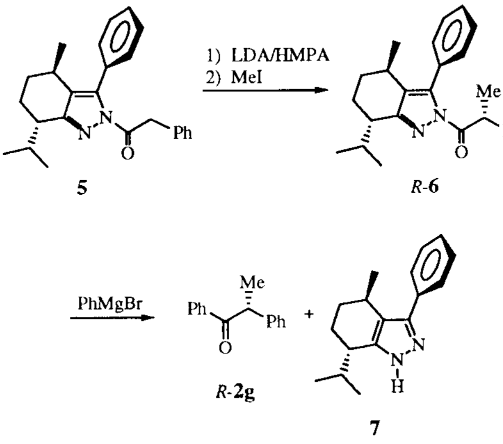
*DPM represents 3,5-dimethylpyrazole. [a] Taken as reference in each reaction.

Table 2

Products from the Grignard Reaction of 1-Acyl-3,5-dimethylpyrazoles **1**

Substrate	R^1	R^2MgX (equivalents used)	Ketone **2** formed (Yield, %)		Other product obtained (Yield, %)	
1a	Ph	PhMgBr (1.2)	**2a**	68	**3a**	11
1a	Ph	PhMgBr (2.4)	**2a**	23	**3a**	48
1a	Ph	MeMgI (1.2)	**2b**	63	**4a**	13
1a	Ph	MeMgI (2.4)	**2b**	2	**4a**	73
1a	Ph	EtMgBr (1.2)	**2c**	65	**3b**	12
1a	Ph	EtMgI (1.2)	**2c**	63	**3b**	10
1a	Ph	*p*-TolMgBr (1.2)	**2d**	62	**3c**	1
1b	Me	PhMgBr (1.0)	**2b**	74	**4b**	26
1b	Me	PhMgBr (2.3)	**2b**	9	**4b**	67
1b	Me	*p*-TolMgBr (1.2)	**2e**	74	**4c**	12
1c	Et	PhMgBr (1.2)	**2c**	67	**4d**	4
1d	*p*-Tol	PhMgBr (1.2)	**2d**	63	**3d**	2
1e	$PhCH_2CH_2$	PhMgBr (1.2)	**2f**	79	**3e**	18
1f	PhCHMe	PhMgBr (1.2)	**2g**	62	**3f**	3

Scheme 2



razole (**7**) was recovered in 63% yield without any loss of chirality.

N-Acylpyrazoles **1** afforded chemoselectively the corresponding ketones **2** in good yields by the use of equimolar amounts of Grignard reagent. In the case of optically active *N*-acylpyrazole (**6**), optical asymmetry was retained in comparable optical yield. Ketone formation by the Grignard reactions can be regarded as an important functionalization. Therefore pyrazoles, especially 3-phenyl-*l*-menthopyrazole (**7**), are demonstrated to be useful as the auxiliary compound in a synthetic loop.

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 a Shimadzu IR-460 spectrophotometer. Specific rotation was measured on a JASCO DIP-360 digital polarimeter. Gas chromatography was performed on a Shimadzu Gas Chromatograph GC-4CM with SE-30 column (2 m) at 250° or in the temperature range of 100-250°.

Materials.

1-Acyl-3,5-dimethylpyrazoles **1** were prepared from 3,5-dimethylpyrazole and the corresponding carboxylic acids or acyl chlorides by the method described in the previous paper [2]. Grignard reagents were prepared under ordinary conditions from magnesium turnings (1.0 g), organo halide (40 mmoles) and dry ether (20 ml) at room temperature under a nitrogen atmosphere. The resulting mixture was stored in a silicone capped bottle under nitrogen. The concentration of the Grignard reagent was determined by titration using 1,10-phenanthroline and 2-butanol [7].

Relative Reactivities of **1a** and Carbonyl Compounds in the Grignard Reaction

To a mixture of **1a** (0.15 mmole), the carbonyl compound (0.15 mmole) and phenanthrene (5 mg) in ether (1 ml) was added 0.15 mmole of phenylmagnesium bromide (1.7 *M* in ether) at room temperature. After being stirred for 1 hour at room temperature, the reaction was interrupted by the addition of methanol. By gc of the reaction mixture, the relative reactivities were evaluated from the ratios of the products. The results are summarized in Table 1.

General Synthetic Procedure.

To a mixture of 1-acyl-3,5-dimethylpyrazole (**1**, 1 mmole) and phenanthrene (10 mg, an internal standard for gc) in dry ether (10 ml) was added the appropriate amount of Grignard solution at room temperature under a nitrogen atmosphere. After stirring for 1 hour at room temperature, the mixture was quenched with acetic acid. In the case of phenylmagnesium bromide, the reaction was interrupted with methanol which caused methanolysis of unreacted starting *N*-acylpyrazole. The yields of the products were evaluated by means of gc. The reaction products were extracted into ether. Ether solutions were washed with dilute hydrochloric acid, water, aqueous sodium hydrogen carbonate and aqueous sodium chloride. The organic layer was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel with a benzene-hexane mixture and/or by Kugelrohr distillation under reduced pressure.

(2'*R*)-2-(2'-Phenyl)propanoyl-3-phenyl-*l*-menthopyrazole (*R*-**6**).

To a solution of diisopropylamine (200 mg) in THF (15 ml), 1.75 mmoles of butyllithium solution (1.67 *M* in hexane) was added under a nitrogen atmosphere at -78°. After stirring for 30 minutes at room temperature, HMPA (2 ml) and 2-phenylacetyl-3-phenyl-*l*-menthopyrazole (**5**, 604 mg) in THF (5 ml) were added at -78° with continuous stirring for 1 hour. Methyl iodide (3 ml) was added at -78°, and then the reaction mixture was warmed to room temperature with stirring for 1 hour. The reaction mixture was quenched with acetic acid and products were extracted with dichloromethane. The organic layer was washed with dilute hydrochloric acid, water, aqueous sodium hydrogen carbonate, and aqueous sodium chloride. After drying over anhydrous magnesium sulfate, the solvent was removed under reduced pressure. The residue was chromatographed on silica gel with hexane-benzene mixture (v/v 1:1), yield 395 mg (63%); *de* 54% (**R**); ^{1}H nmr: δ 0.68 (3H, d, J = 7 Hz), 0.76 (3H, d, J = 7 Hz), 1.01 (3H, d, J = 7 Hz), 1.51 (3H, d, J = 7 Hz), 1.1-1.7 (2H, m), 1.8-2.0 (2H, m), 2.3-2.5 (1H, m), 2.5-2.7 (2H, m), 5.22 (1H, q, J = 7 Hz), 7.1-7.5 (10H, m).

Anal. Calcd. for $C_{26}H_{30}N_2O$: C, 80.79; H, 7.82; N, 7.25. Found: C, 80.70; H, 7.84; N, 7.25.

(*R*)-1,2-Diphenyl-1-propanone (*R*-**2g**).

Phenylmagnesium bromide (1.7 *M*, 0.72 ml) in ether was added to *R*-**6** (394 mg) in ether (10 ml), and the mixture was stirred for 1 hour at room temperature. After quenching with water, the organic layer was washed with dilute hydrochloric acid, water, aqueous sodium hydrogen carbonate and aqueous sodium chloride, dried over anhydrous magnesium sulfate, and concentrated. The products were purified by the column chromatography on silica gel with hexane-benzene mixture (v/v 2:1) and then ethyl acetate as the eluents. (*R*)-1,2-Diphenyl-1-propanone (*R*-**2g**) was isolated from the hexane-benzene fraction, yield 193.2 mg (90%); $[\alpha]_D^{21}$ -87.2° (chloroform, c 0.37, lit -206° [6]), $[\alpha]_D^{26}$ -88.7° (ethanol, c 0.95). The optical purity of *R*-**2g** was deduced to be 35% by the ^{1}H nmr peak at δ 1.53 ppm in the presence of Eu(tfc)$_3$, bp 165-170°/6 mm Hg; ^{1}H nmr: δ 1.53 (3H, d, J = 6.6 Hz), 4.69 (1H, q, J = 6.9 Hz), 7.16-7.50 (8H, m), 7.93-7.97 (2H, m).

3-Phenyl-*l*-menthopyrazole (**7**) was recovered from the ethyl acetate fraction, mp 122.5-124° (from hexane); yield 63%; ^{1}H nmr: δ 0.81 (3H, d, J = 7 Hz), 0.97 (3H, d, J = 7 Hz), 0.98 (3H, d, J = 7 Hz), 1.18-1.37 (1H, m), 1.50-1.63 (1H, m), 1.77-1.88 (1H, m), 1.99-2.22 (2H, m), 2.55-2.65 (1H, m), 2.98-3.14 (1H, m), 7.27-7.39 (3H, m), 7.57-7.65 (2H, m), 11.25 (1H, broad d).

1,1,2-Triphenyl-1-propanol (**3f**) was detected in the ethyl acetate fraction by gc and ^{1}H nmr, yield 2%; ^{1}H nmr: δ 1.33 (3H, d, J = 7.3 Hz), 2.38 (1H, s), 3.99 (1H, q, J = 6.9 Hz), 7.03-7.37 (13H, m), 7.60-7.63 (2H, m).

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