

New Facile Alkoxy-carbonylating Agent, Alkyl Pyrazole-1-carboxylates. The Preparation and the Utilities.

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Abstract: Alkyl pyrazole-1-carboxylates (**2**), which were readily prepared from alkyl chloroformate or carbazate in good yields, were provided as the new facile alkoxy-carbonylating agents toward the Grignard reagents for the synthesis of one carbon higher carboxylic esters. Also amines were alkoxy-carbonylated by **2** to produce the corresponding urethanes even in an aqueous medium. Benzyl 3,5-dimethylpyrazole-1-carboxylate (**2d**) could be utilized for the Cbz-protection of amino acids and esters in good yield without any racemization. © 1998 Elsevier Science Ltd. All rights reserved.

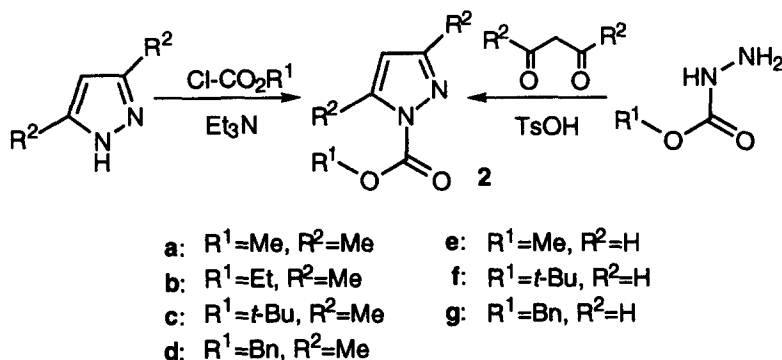
Generally the alkoxy-carbonylation reaction of nucleophiles is regarded as one of the most important reactions for the synthetic strategy of the complex organic compounds. Especially, introduction of benzyloxycarbonyl (Cbz) and *t*-butoxycarbonyl (Boc) groups on amino functions have been widely applied as the protection of amino acids and peptides in the peptide synthesis. Although the various alkoxy-carbonylating reagents have been investigated such as benzyl chloroformate (Cbz-Cl),¹ di-*t*-butyl pyrocarbonate (Boc anhydride),² 2-(*t*-butoxycarbonylthio)-4,6-dimethylpyrimidine (Boc-SDP),³ 2-(*t*-butoxycarbonyloxyimino)-2-phenylacetonitrile (Boc-ON)⁴ and alkyl imidazole-1-carboxylate,⁵ each of these reagents suffers from the defects of unstable toward the moisture and sometimes showed explosive properties. Also some alkoxy-carbonylating agents such as *t*-butyl azidoformate (Boc-Azide)⁶ are known as a carcinogenic substance. Therefore, development of new facile alkoxy-carbonylating agent is still desired at this moment.

Recently we have developed the preparation and the utilities of 3-phenyl-*l*-menthopyrazole (**1**) as a new chiral auxiliary,⁷ which has unique structure and properties different from the conventional chiral auxiliaries.⁸ The most important characteristics of this auxiliary are that the substrate terminates to nitrogen atom of heteroaromatic pyrazole ring and that the substrate is surrounded by the chiral atmosphere. This structural feature causes the diastereofacial attack on the substrate moiety in the reactions with alkyl halides,⁹ diphenyldisulfide,¹⁰ acyl chloride,¹¹ aldehydes,¹² and C=N compounds.¹³ Moreover, the asymmetric additions of Grignard reagents,¹⁴ dienes¹⁵ and 1,3-dipolar compounds¹⁶ on 2-(α,β -unsaturated)acyl-3-phenyl-*l*-menthopyrazoles have been reported. Otherwise, *N*-Acyloxyheteroaromatics such as *N*-acylimidazoles are utilized as the activated acyl

moiety in the wide varieties of organic syntheses.¹⁷ As an analogue of these *N*-acylheteroaromatics, *N*-acylpyrazoles are easily converted into acyl derivatives by the action of nucleophiles such as alcohols,¹⁸ amines,¹⁹ Grignard reagents,²⁰ or organozinc compounds²¹ under basic or acidic conditions. As a part of the investigations concerning to the *N*-acylpyrazoles, we report here the preparation and the nucleophilic reactions of alkyl pyrazole-1-carboxylates. These compounds will be regarded as the new type of facile alkoxyacetylating agent for various nucleophiles.

Results and Discussion

Alkyl pyrazole-1-carboxylates (**2**) were readily prepared by the action of alkyl chloroformates on pyrazoles. Because of labile and explosive properties of chloroformates to the moisture, another preparative method of **2** was provided from the handy substances. By heating mixture of alkyl carbazate and 2,4-pentanedione for several hours under azeotropic conditions by the catalyst of *p*-toluenesulfonic acid, **2a-c** were produced in good yields. Although benzyl carbazate was not available commercially, benzyl 3,5-dimethylpyrazole-1-carboxylate (**2d**) was obtained in good yield by the reaction of carbonylhydrazide, benzyl alcohol and 2,4-pentanedione in the presence of equimolar amount of *p*-toluenesulfonic acid. The preparation of unsubstituted pyrazole-1-carboxylates (**2e-g**) from 1,1,3,3-tetramethoxypropane and alkyl carbazates was successful by trapping methanol using Soxhlet extractor containing CaH_2 .



Scheme 1

In order to reveal the chemical behaviors of **2**, **2b** was treated with phenylmagnesium bromide as a nucleophile, and ethyl benzoate (**3b**) was obtained exclusively. Similarly, one carbon higher carboxylic esters (**3-6**) were variously obtained in good yields from Grignard reagent by the treatment with **2** as listed in Table 1. From these facts, any further Grignard reaction on the ester function was not detected, and **2** was served as a very convenient alkoxyacetylating agent in the preparation of carboxylic esters.

Generally, the particular attention should be paid to the handling of conventional alkoxycarbonylating agents because of their labile properties toward the moisture. Thus, the high stability and good handling should promote the general utilities of alkoxycarbonylating agent. Therefore, the stability of **2** was estimated from their half-lives in aqueous ethanol at 40°C. From Table 2, 3,5-dimethylpyrazole-1-carboxylates (**2a-d**) were quite stable, and able to be stored under ordinary conditions without any decomposition. Even in the cases of unsubstituted pyrazole derivatives (**2e-g**), the stabilities were equivalent to that of Boc-SDP, which was regarded as the moderately stable alkoxycarbonylating agent. Comparing with the half life of the analogous methyl imidazole-1-carboxylate, the high stability and good handling was proved.

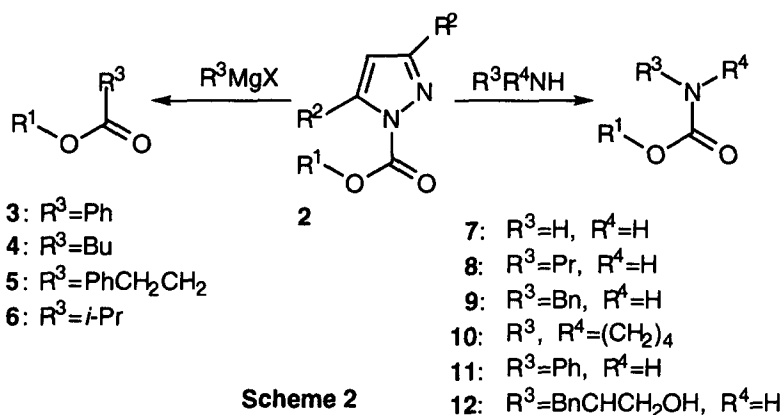


Table 1. The Grignard Reaction of Alkyl 3,5-Dimethylpyrazole-1-carboxylates (**2a-d**).

Run	Pyrazolecarboxylate	R ¹ R ²		R ³ MgX	Product	Yield (%)
		R ¹	R ²			
1	2a	Me	Me	PhMgBr	3a PhCO ₂ Me	49
2	2b	Et	Me	PhMgBr	3b PhCO ₂ Et	86
3	2c	<i>t</i> -Bu	Me	PhMgBr	3c PhCO ₂ <i>t</i> -Bu	63
4	2d	Bn	Me	PhMgBr	3d PhCO ₂ Bn	47
5	2d	Bn	Me	BuMgBr	4d BuCO ₂ Bn	40
	2a	Me	Me	PhCH ₂ CH ₂ MgBr	5a PhCH ₂ CH ₂ CO ₂ Me	42
7	2d	Bn	Me	<i>i</i> -PrMgBr	6d <i>i</i> -PrCO ₂ Bn	51

When **2d** was treated with propylamine, benzyl *N*-propylcarbamate (**8d**) was afforded in good yield. Also **8d** was obtained from **2d** by the neutralization of propylamine hydrochloride with triethylamine. Moreover,

various carbamates were yielded in the reaction of **2** with primary and secondary amines as summarized in Table 3. In consequent of the high stability toward moisture, Schotten-Baumann type reaction could perform to obtained benzyl urethane (**7d**) in good yield from **2d** by the prolonged heat with aqueous ammonia. The results of these reactions suggested that **2** also acted as a very convenient alkoxycarbonylating agent for the preparation of carbamates, even under the aqueous conditions.

Since the conventional alkoxycarbonylating agents were most widely used for the protection of *N*-terminal of amino acids and peptides, the reaction of **2** was particularly performed with amino acids and their derivatives. When **2a** was treated with ethyl glycinate hydrochloride in toluene in the presence of excess amount of triethylamine, ethyl *N*-methoxycarbonylglycinate (**13a**) was obtained in good yield. Also **2d** acted as the alkoxycarbonylating agent for amino acid ester hydrochlorides to give *N*-Cbz amino esters (**13d**, **14d**) in good yield as summarized in Table 4. The property of high stability toward water allowed the reaction of **2d** with ethyl glycinate hydrochloride even in the aqueous ethanol to give **13a**. On the contrary, **2c** gave *N*-Boc amino ester (**13c**) in poor yields, due to the steric hindrance of *t*-butyl group. By the use of **2f** instead of **2c**, some improvement of the yields was observed on the Boc- protection of amino esters (**13c**, **14c**). During these alkoxycarbonylating reactions, the stereostructure on the chiral center was completely retained.

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

Run	Pyrazolecarboxylate		Half Life (τ)	Rel. Stability ^a	
	R ¹	R ²	(h)		
1	2a	Me	Me	924	28.9
2	2b	Et	Me	569	17.8
3	2c	<i>t</i> -Bu	Me	144	4.5
4	2d	Bn	Me	344	10.8
5	2e	Me	H	282	8.8
6	2f	<i>t</i> Bu	H	30	0.9
7	2g	Bn	H	141	4.4
8	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 3,5-Dimethylpyrazole-1-carboxylates (**2b,d**) with Amines.

Run	Pyrazolecarboxylate	R ¹ R ²		Amine	Time ^a (h)	Product	Yield (%)
1	2d	Bn	Me	NH ₄ OH	24	7d H ₂ N-CO ₂ Bn	71
2	2d	Bn	Me	PrNH ₂	5.5	8d PrNH-CO ₂ Bn	92
3	2d	Bn	Me	PrNH ₂ ·HCl/Et ₃ N	5.5	8d PrNH-CO ₂ Bn	97
4	2b	Et	Me	BnNH ₂	5.5	9b BnNH-CO ₂ Et	87
5	2d	Bn	Me	(CH ₂) ₄ NH	5.5	10d (CH ₂) ₄ N-CO ₂ Bn	86
6	2b	Et	Me	PhNH ₂	15 ^b	11b PhNH-CO ₂ Et	5
7	2b	Et	Me	HOCH ₂ CHBnNH ₂	17.5	12b HOCH ₂ CHBnNH-CO ₂ Et	26

a: The reaction was carried out in THF at 60°C. b: The reaction was carried out in toluene at 100°C.

Table 4. The Reaction of Alkyl Pyrazole-1-carboxylates (**2**) with Amino Ester Hydrochlorides in Toluene.

Run	Pyrazolecarboxylate	R ¹ R ²		Amino Ester		R ³ R ⁴		Product	Yield (%)	Opt. Yield (%)
1	2a	Me	Me	Gly-OEt·HCl	H	Et		13a MeO ₂ C-Gly-OEt	74	---
2	2c	<i>t</i> -Bu	Me	Gly-OEt·HCl	H	Et		13c Boc-Gly-OEt	10	---
3	2d	Bn	Me	Gly-OEt·HCl	H	Et		13d Cbz-Gly-OEt	75	---
4	2d	Bn	Me	Gly-OEt·HCl	H	Et		13d Cbz-Gly-OEt	36 ^a	---
5	2f	<i>t</i> -Bu	H	Gly-OEt·HCl	H	Et		13c Boc-Gly-OEt	60	---
6	2f	<i>t</i> -Bu	H	Ala-OEt·HCl	Me	Et		14c Boc-Ala-OEt	21	100
7	2d	Bn	Me	Ala-OEt·HCl	Me	Et		14d Cbz-Ala-OEt	73	100
8	2a	Me	Me	Phe-OMe·HCl	Bn	Me		15a MeO ₂ C-Phe-OMe	63	100
9	2f	<i>t</i> -Bu	H	Phe-OMe·HCl	Bn	Me		15c Boc-Phe-OMe	trace	b
10	2g	Bn	H	Phe-OMe·HCl	Bn	Me		15d Cbz-Phe-OMe	86	100

a: The reaction was carried out in aqueous ethanol. b: The optical purity could not be measured.

Because of the zwitterionic state of amino acids, the nucleophilicity of amino group was insufficient for the reaction of **2**, and no product of *N*-alkoxycarbonylation was obtained by the reaction of **2a** with phenylalanine in the presence of triethylamine. By neutralization of acid function, amino group of amino acids was expected to

increase their nucleophilicities and to be sufficiently reactive toward **2**. By the action of NaH, Cbz-protected phenylalanine (**18d**) was obtained from **2d** with phenylalanine at room temperature in high optical yield. Although alanine gave Cbz-protected alanine (**17d**) in good yield, the optical yield was very poor according to the strongly basic conditions. As shown in Table 5, the reaction of **2d** with free amino acids was accomplished optimally at -5°C in THF or DMF to afford Cbz-protected amino acids (**16d-20d**) without any racemization.

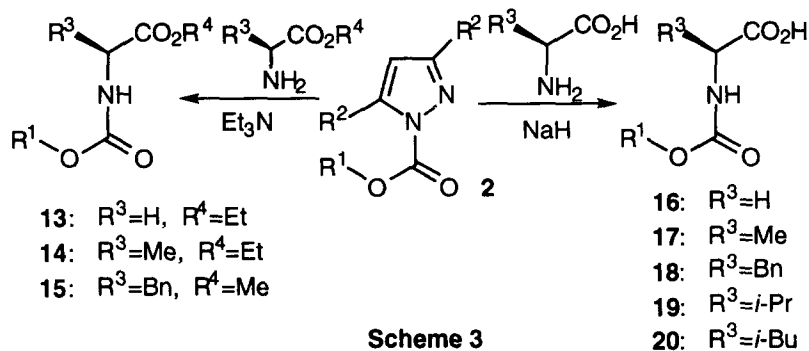


Table 5. The Reaction of Alkyl Pyrazole-1-carboxylates (**2**) with Amino Acids.

	Pyrazolecarboxylate		Amino Acid		Condition		Product		Yield (%)	Opt. Yield (%)
	R ¹	R ²		R ³		Temp				
2a	Me	Me	Phe-OH	Bn	PhH/Et ₃ N	rt.	18a	MeO ₂ C-Phe-OH	0	a
2c	<i>t</i> -Bu	Me	Phe-OH	Bn	THF/NaH	rt.	18c	Boc-Phe-OH	52	85
2d	Bn	Me	Ala-OH	Me	THF/NaH	rt.	17d	Cbz-Ala-OH	95	19
2d	Bn	Me	Phe-OH	Bn	THF/NaH	rt.	18d	Cbz-Phe-OH	41	100
2d	Bn	Me	Gly-OH	H	THF/NaH	-5°C	16d	Cbz-Gly-OH	24	----
2d	Bn	Me	Gly-OH	H	DMF/NaH	-5°C	16d	Cbz-Gly-OH	55	----
2d	Bn	Me	Ala-OH	Me	THF/NaH	-5°C	17d	Cbz-Ala-OH	98	93
2d	Bn	Me	Ala-OH	Me	DMF/NaH	-5°C	17d	Cbz-Ala-OH	66	68
2d	Bn	Me	Phe-OH	Bn	THF/NaH	-5°C	18d	Cbz-Phe-OH	46	100
2d	Bn	Me	Phe-OH	Bn	DMF/NaH	-5°C	18d	Cbz-Phe-OH	45	100
2d	Bn	Me	Val-OH	<i>i</i> -Pr	THF/NaH	-5°C	19d	Cbz-Val-OH	31	100
2d	Bn	Me	Val-OH	<i>i</i> -Pr	DMF/NaH	-5°C	19d	Cbz-Val-OH	27	100
2d	Bn	Me	Leu-OH	<i>i</i> -Bu	THF/NaH	-5°C	20d	Cbz-Leu-OH	72	100
2d	Bn	Me	Leu-OH	<i>i</i> -Bu	DMF/NaH	-5°C	20d	Cbz-Leu-OH	72	100

a: The optical purity was not measured.

In conclusion, alkyl pyrazole-1-carboxylates (**2**), which were easily prepared from alkyl chloroformate or carbazate in good yields, were provided as the new facile alkoxycarbonylating agents toward the Grignard reagents for the synthesis of one carbon higher carboxylic esters. Also amines were alkoxycarbonylated by **2** to produce the corresponding urethanes even in an aqueous medium. Particularly **2d** could be utilized for the Cbz-protection of amino acids and esters in good yield without any racemization.

Experimental Section

NMR data were collected on a Varian NMR Gemini-200 (200 MHz) spectrometer in deuteriochloroform with tetramethylsilane as an internal standard. Optical rotations were observed using a JASCO DIP-370 digital polarimeter. HPLC analysis was carried out by SIL-C18 (JASCO) column on JASCO BIP-I chromatograph and by CHIRALCEL OD-R (Daicel Chemical Industries) column on JASCO GULLIVER chromatograph series using aqueous methanol. Melting points are uncorrected.

Preparation of Alkyl 3,5-Dimethylpyrazole-1-carboxylates (2a-c). The mixture of alkyl carbazate (22 mmol), 2,4-pentanedione (20 mmol), and *p*-toluenesulfonic acid (0.3 mmol) in toluene (40 ml) was heated under the azeotropic conditions for 16 h. The reaction mixture was washed with dilute hydrochloric acid, water, aqueous NaHCO₃, and saturated NaCl solution and dried over anhydrous MgSO₄. After removal of the solvent, the product was purified by the distillation under reduced pressure and/or the recrystallization from hexane.

Methyl 3,5-Dimethylpyrazole-1-carboxylate (2a). Mp 43.5–45.0°C (from hexane); yield 90 %; ¹H NMR; δ 2.27 (3H, s), 2.53 (3H, d, *J*=1.0 Hz), 4.02 (3H, s), 5.98 (1H, d, *J*=0.6 Hz).

Anal. Calcd for C₇H₁₀N₂O₂: C, 54.54; H, 6.54; N, 18.17. Found: C, 54.34; H, 6.67; N, 18.09.

Ethyl 3,5-Dimethylpyrazole-1-carboxylate (2b). Bp 130–140°C/ 5 mmHg; yield 76 %; ¹H NMR; δ 1.46 (3H, t, *J*=7.2 Hz), 2.27 (3H, s), 2.52 (3H, s), 4.49 (2H, q, *J*=7.0 Hz), 5.98 (1H, s); ¹³C NMR; δ 13.3 (CH₃), 13.6 (CH₃), 13.8 (CH₃), 63.4 (CH₂), 110.2 (CH), 144.5 (C), 152.2 (C).

Anal. Calcd for C₈H₁₂N₂O₂: C, 57.13; H, 7.19; N, 16.66. Found: C, 56.91; H, 7.32; N, 16.70.

***t*-Butyl 3,5-Dimethylpyrazole-1-carboxylate (2c).** Bp 175°C/ 3 mmHg; yield 64 %; ¹H NMR; δ 1.64 (9H, s), 2.25 (3H, s), 2.47 (3H, d, *J*=1.0 Hz), 5.93 (1H, s).

Anal. Calcd for C₁₀H₁₆N₂O₂: C, 61.20; H, 8.22; N, 14.27. Found: C, 60.80; H, 8.24; N, 14.31.

Preparation of Alkyl Pyrazole-1-carboxylates (2e,f). The mixture of alkyl carbazate (20 mmol), 1,1,3,3-tetramethoxypropane (20 mmol), and *p*-toluenesulfonic acid (4.0 mmol) in toluene (50 ml) was heated for 16 h. Methanol, which was formed as a by-product, was trapped by Soxhlet extractor containing CaH₂. The reaction mixture was washed with dilute hydrochloric acid, water, aqueous NaHCO₃, and saturated NaCl solution and dried over anhydrous MgSO₄. After removal of the solvent, the product was purified by the distillation under reduced pressure.

Methyl Pyrazole-1-carboxylate (2e). Bp 145°C/ 3 mmHg; yield 44 %; ¹H NMR; δ 4.09 (3H, s), 6.44 (1H, q, *J*=1.4 Hz), 7.59 (1H, t, *J*=1.0 Hz), 8.17 (1H, q, *J*=1.1 Hz).

Anal. Calcd for $C_5H_6N_2O_2$: C, 47.62; H, 4.8; N, 22.21. Found: C, 47.51; H, 4.94; N, 21.97.

***t*-Butyl Pyrazole-1-carboxylate (2f).** Bp 130°C/ 2 mmHg; yield 64 %; 1H NMR; δ 1.66 (9H, s), 6.39 (1H, q, $J=1.4$ Hz), 7.72 (1H, d, $J=1.0$ Hz), 8.11 (1H, dd, $J=0.6, 0.8$ Hz).

Anal. Calcd for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.66. Found: C, 56.83; H, 7.42; N, 16.58.

Preparation of Benzyl Pyrazole-1-carboxylates (2d,g). *From Benzyl Chloroformate.* To the mixture of pyrazole or 3,5-dimethylpyrazole (5.0 mmol) and triethylamine (7.5 mmol) in toluene (10ml) was added the toluene solution (5 ml) of benzyl chloroformate (6.5 mmol) gradually at -5°C. After stirring was continued for 1 h at -5°C, the mixture was washed with dilute hydrochloric acid, water, aqueous $NaHCO_3$, and saturated NaCl solution. The organic layer was dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by the recrystallization from hexane or silica gel column chromatography with hexane-ethyl acetate mixture (v/v 7:1).

Benzyl 3,5-Dimethylpyrazole-1-carboxylate (2d). Mp 41.0-42.0°C (from hexane); yield 60 %; 1H NMR; δ 2.26 (3H, s), 2.49 (3H, s), 5.44 (2H, s), 5.96 (1H, s), 7.26-7.52 (5H, m).

Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 68.02; H, 6.23; N, 12.15.

Benzyl Pyrazole-1-carboxylate (2g). Mp. 69.5-73.0°C (from hexane); yield 56 %; 1H NMR; δ 5.48 (2H, s), 6.42 (1H, dd, $J=1.6, 1.4$ Hz), 7.37-7.52 (5H, m), 7.75 (1H, t, $J=7.0$ Hz), 8.16 (1H, dd, $J=0.6, 0.8$ Hz).

Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.31; H, 5.07; N, 13.79.

From Carbohydrazide. The mixture of carbohydrazide (5.0 mmol), 2,4-pentanedione (10.8 mmol), benzylalcohol (5.8 mmol), and *p*-toluenesulfonic acid (5.5 mmol) in toluene (40 ml) was heated under the azeotropic conditions for 21 h. The mixture was worked up as described above. Product **2d** was isolated in 68 % yield.

Evaluation of the Half Lives of 2 in Aqueous Ethanol. The solution (6 ml) of **2** (0.3 mmol) in the mixture of EtOH- H_2O (v/v 2:1) was stirred at 40.0°C with biphenyl (ca. 30 mg) as an internal standard. The content of **2** was monitored at appropriate time interval by HPLC using the UV detector at 232 nm, and evaluated the half life of **2** as listed in Table 2.

The Grignard Reaction of 2. The Grignard solution (0.71 mmol, ca. 1 mol/l) was added to the solution of **2** (0.65 mmol) in anhydrous Et_2O (2 ml). The mixture was stirred for 3 h at room temperature, and quenched with water. The organic layer was washed with dilute hydrochloric acid, water, aqueous $NaHCO_3$, and saturated NaCl solution. The organic layer was dried over anhydrous $MgSO_4$, and concentrated. The products (**3-6**) were identified by the comparison with authentic samples. The yields were estimated by means of gas chromatography as summarized in Table 1.

The Reaction of 2 with Amines. The mixture of **2** (1.0 mmol) and amine (1.0 mmol) in dry THF (2 ml) was heated for 5.5 h at 60°C under nitrogen atmosphere. In the cases of aqueous ammonia, aniline and phenylalaninol, the reaction time was prolonged to about 20 h. The product mixture was quenched with dilute hydrochloric acid and extracted with Et_2O . The organic layer was washed with dilute hydrochloric acid, water,

aqueous NaHCO_3 , and saturated NaCl solution. The organic layer was dried over anhydrous MgSO_4 , and concentrated. The residue was purified by silica gel column chromatography with hexane-ethyl acetate (v/v 4:1). The yields were estimated by means of HPLC as summarized in Table 3.

The Reaction of 2 with Amino Ester Hydrochlorides. The mixture of **2** (10 mmol), amino ester hydrochloride (10 mmol), triethylamine (12 mmol) in toluene (20 ml) was heated for 24 h at 80°C . The reaction mixture was quenched with dilute hydrochloric acid, and extracted with Et_2O . The organic layer was washed with dilute hydrochloric acid, water, aqueous NaHCO_3 , and saturated NaCl solution. The organic layer was dried over anhydrous MgSO_4 , and concentrated. The products were purified by silica gel column chromatography with hexane-ethyl acetate (v/v 2:1), and identified by the comparison with authentic samples. The yields and the optical purities were estimated by means of HPLC as summarized in Table 4.

The Reaction of 2 with Amino Acids. The THF (2 ml) solution of amino acid (0.5 mmol) was treated with the suspension of NaH (50 mg, >60 % in oil) for 30 min at room temperature. To this mixture, **2** (2.0 mmol) in THF (1 ml) was added and stirred for 5 h at room temperature. In the case of glycine, DMF as the solvent instead of THF improved the yield. The reaction mixture was quenched with dilute hydrochloric acid, and extracted several times with ethyl acetate. The organic layer was dried over anhydrous MgSO_4 , and concentrated. The products were identified by the comparison with authentic samples. The yields and the optical purities were estimated by means of HPLC as summarized in Table 5.

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