mm), and the residue was purified by column chromatography on silica gel (hexane–ether eluent) to give a colorless liquid: 32 mg, 0.082 mmol (21%); ^{1}H NMR ($CDCl_3$) δ 1.20 (t, J = 7 Hz, 6 H), 2.40 (s, 3 H), 3.23 (s, 2 H), 3.76 (s, 2 H), 3.96 (q, J = 7 Hz) and 4.04 (q, J = 7 Hz) (total 4 H), 6.18 (m, 1 H), 7.08 (m) and 7.20 (d, J = 8 Hz) (total 3 H), 7.61 (d, J = 8 Hz, 2 H). Anal. $C_{19}H_{23}NO_4S$: m/e calcd 393.1244, found 393.1204.

Preparation of Pyrrole 7d. Claisen ortho ester rearrangement of **5** with triethyl orthopropionate was carried out as described above; purification by column chromatography on silica gel (hexane–ether eluent) gave a colorless liquid: 22 mg, 0.054 mmol (18%); ^{1}H NMR ($CDCl_3$) δ 1.18 (t, J = 7 Hz), 1.23 (t, J = 7 Hz), and 1.38 (d, J = 6 Hz) (total 9 H), 2.48 (s, 3 H), 3.45 (m, 1 H), 3.83 (s) and 4.05 (overlapping q) (total 6 H), 6.31 (m, 1 H), 7.15 (m) and 7.30 (d, J = 8 Hz) (total 3 H), 7.73 (d, J = 8 Hz, 2 H).

Preparation of Thiophene 7g. A solution of ethyl 2-thiopheneglycolate (372 mg, 2.00 mmol), trimethyl orthovalerate (1.62 g, 10.0 mmol), and hexanoic acid (23 mg, 0.20 mmol) in a 25-mL flask fitted with a 15-cm Vigreux column topped with a short-path distillation head was heated at 170 °C for 8 h with stirring in an argon atmosphere; methanol was allowed to distill out of the reaction as it was formed. The Vigreux column was removed, o-dichlorobenzene (2 mL) was added, the short-path distillation head was placed on the reaction flask, and heating was continued at 200 °C for 10 h. Excess ortho ester and o-dichlorobenzene were removed (25 °C, 0.001 mm), and the residue was purified by flash chromatography[15] on 40–63 μm silica gel (10% EtOAc–hexane eluent) to give a colorless liquid: 346 mg, 1.22 mmol (61%); no ester exchange could be detected by VPC (5% OV 101 or 5% DEGS) or ^{1}H NMR; ^{1}H NMR ($CDCl_3$) δ 0.80–1.50 (m) and 1.21 (t, J = 7 Hz) (total 10 H), 3.55 (s, 3 H), 3.62 (m) and 3.70 (s) (total 3 H), 4.11 (q, J = 7 Hz, 2 H), 6.92 (d, J = 5 Hz) and 7.09 (d, J = 5 Hz) (total 2 H). Anal. $C_{14}H_{20}O_4S$: m/e calcd 284.1081, found 284.1094.

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Registry No.—**10**, 27472-43-1; **11**, 69551-49-1; **12**, 4075-58-5.

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One-Step Synthesis of 1-Oxo-1,2-dihydroisoquinoline-3-carboxylic Acid Derivatives[1]

Ken-ichi Nunami, Mamoru Suzuki,* and Naoto Yoneda

Research Laboratory of Applied Biochemistry, Tanabe Seiyaku Co., Ltd., 16-89 Kashima-3-chome, Yodogawa-ku, Osaka 532, Japan

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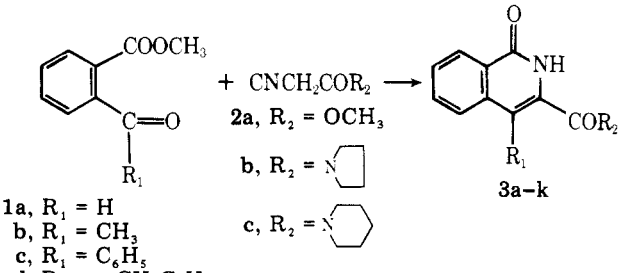
Recently, a number of synthetic studies using isocyanides have been reported and many versatile synthetic methods based on these compounds have been developed.[2] Of these, the reactions of isocyanoacetates with aldehydes or ketones, have been frequently investigated, and a variety of products, e.g., α-*N*-formylaminoacrylates,[3] oxazolines,[4] pyrroles,[5] α-isocyano-β-hydroxybutyrates,[6] and amidines,[7] have been prepared under various reaction conditions.

In the present paper, we wish to report a one-step synthesis of 1-oxo-1,2-dihydroisoquinoline(isocarbostyril)-3-carboxylic acid derivatives by the reaction of methyl 2-acylbenzoates with methyl isocyanoacetate or isocyanoacetamide.

Reaction of methyl isocyanoacetate (**2a**) with methyl 2-formylbenzoate (methyl phthalaldehydate) (**1a**)[8] in the presence of sodium hydride in dimethylformamide at 30–40 °C gave a product whose spectra and melting point showed it to be methyl isocarbostyril-3-carboxylate (**3a**) (Scheme I).[9] To establish the generality of this process, a number of other examples were carried out with both the isocyano ester **2a** and

Scheme I



1a, R_1 = H
b, R_1 = CH_3
c, R_1 = C_6H_5
d, R_1 = p-$CH_3C_6H_4$
e, R_1 = p-$CH_3OC_6H_4$

Scheme II

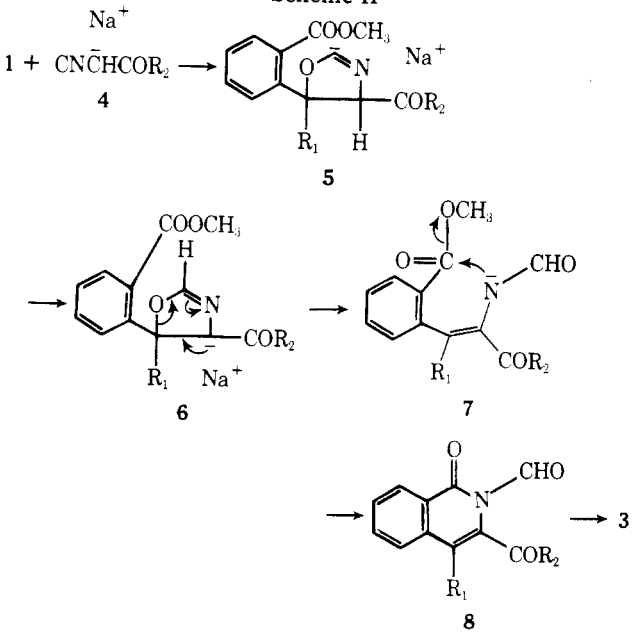


Table I. Formation of Isocarbostyrils (3)[d]

compd	R_1	R_2	yield, %	mp, °C	IR ν_{max} (Nujol), cm^{-1}	^1H NMR (Me_2SO-d_6), δ NH[a]	C_8-H[b]
3a	H	OCH_3	42	158–159.5	1720, 1650, 1600	11.15	8.2–8.5
3b	H		57	213–214	1660, 1620, 1600	11.14	8.15–8.4
3c	H		52	172–173	1650, 1620, 1600	11.51	8.1–8.4
3d	CH_3		47	254–256	1658, 1635, 1605	11.41	8.1–8.35
3e	CH_3		43	234–236	1658, 1605	11.45	8.1–8.35
3f	C_6H_5	OCH_3	46	165–167	1740, 1665, 1600	9.65	8.35–8.55[c]
3g	C_6H_5		57	252–254	1660, 1605	11.35	8.35–8.6
3h	p-$CH_3C_6H_4$	OCH_3	61	219–220.5	1740, 1660, 1600	11.39	8.25–8.5
3i	p-$CH_3C_6H_4$		62	269–271	1655, 1605	11.70	8.2–8.4
3j	p-$CH_3OC_6H_4$		63	258–261	1660, 1605	11.69	8.2–8.4
3k	p-$CH_3OC_6H_4$		43	263–266	1650, 1605	11.70	8.2–8.4

[a] Broad singlet. [b] Multiplet. [c] $CDCl_3$ as solvent. [d] Satisfactory analytical values (±0.3% for C, H, N) were submitted for all products.

the amides[10] **2b** and **2c**. The results are summarized in Table I.

The mechanism for the formation of the isocarbostyrils can be proposed as in Scheme II. Nucleophilic attack of the metalated isocyanide **4** as suggested by Schöllkopf et al.[3] gives the 2-metalated oxazoline **5**. Subsequently, ring opening and further cyclization afford 2-formylisocarbostyrils **8**, followed by hydrolysis of the labile formyl group to give **3**.

Experimental Section

All the melting points were uncorrected and measured with a Yamato melting point apparatus. The IR spectra were recorded with a Shimadzu IR-27G infrared spectrophotometer. The ^1H NMR spectra were obtained using a Hitachi Perkin-Elmer R-20A high-resolution NMR spectrometer with tetramethylsilane as an internal standard.

Materials 1a–e. 2-Substituted benzoic acids were commercially available. 2-Formylbenzoic acid, 2-acetylbenzoic acid, and 2-(4-hydroxybenzoyl)benzoic acid were treated with ethereal diazomethane to give methyl 2-formylbenzoate (**1a**), methyl 2-acetylbenzoate (**1b**), and methyl 2-(4-methoxybenzoyl)benzoate (**1e**), respectively. Methyl 2-benzoylbenzoate (**1c**) and methyl 2-(4-methylbenzoyl)benzoate (**1d**) were prepared by esterification of the corresponding 2-substituted benzoic acids with thionyl chloride in methanol. **1a:** 92%; bp 135–136 °C (12 mm) [lit.[8] bp 135–136 °C (12 mm)]. **1b:** 96%; bp 112–113 °C (1 mm) [lit.[11] bp 114 °C (1 mm)]. **1c:** 90%; mp 51–52 °C (lit.[8] mp 52 °C). **1d:** 93%; mp 61–63 °C (lit.[12] mp 63–66 °C). **1e:** 96%; mp 80–82 °C (lit.[13] mp 81–82 °C).

Typical Procedure for Preparation of Isocarbostyrils (3a–k). To a suspension of sodium hydride (65% in oil; 0.44 g, 0.012 mol) in dimethylformamide (5 mL) was added dropwise a mixture of methyl 2-formylbenzoate (**1a**; 1.64 g, 0.01 mol) and methyl isocyanoacetate (**2a**; 0.99 g, 0.01 mol) in dimethylformamide (7.5 mL) at 30–40 °C. After stirring was continued for 5 h at room temperature, the solution was neutralized with 10% acetic acid and the solvent was removed in vacuo. The resulting residue was dissolved in ethyl acetate, and the solution was washed with water and then dried over magnesium sulfate. The dried solution was concentrated in vacuo, and the residue was recrystallized from ethyl acetate–hexane to give methyl isocarbostyril-3-carboxylate (**3a**) as colorless needles: yield 0.89 g (42%); mp 158–159.5 °C (lit.[9] mp 157–158 °C); IR (Nujol) 3180 (NH), 1720 ($COOCH_3$), 1650 (CONH) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 11.15 (broad s, 1, NH), 8.2–8.5 (m, 1, C_8-H), 7.5–8.0 (m, 3, $C_{5,6,7}$-H), 7.43 (s, 1, C_4-H), 3.91 (s, 3, OCH_3).

Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.16; H, 4.56; N, 6.76.

In the same manner other isocarbostyrils (**3b–k**) were obtained, and these results are summarized in Table I.

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Registry No.—1a, 4122-56-9; **1b,** 1077-79-8; **1c,** 606-28-0; **1d,** 6424-25-5; **1e,** 5449-71-8; **2a,** 105-34-0; **2b,** 67434-30-4; **2c,** 67434-28-0; **3a,** 69454-42-8; **3b,** 69454-43-9; **3c,** 69454-44-0; **3d,** 69454-45-1; **3e,** 69454-46-2; **3f,** 69454-47-3; **3g,** 69454-48-4; **3h,** 69454-49-5; **3i,** 69454-50-8; **3j,** 69454-51-9; **3k,** 69454-52-0; 2-formylbenzoic acid, 119-67-5; 2-acetylbenzoic acid, 577-56-0; 2-(4-hydroxybenzoyl)benzoic acid, 85-57-4; 2-benzoylbenzoic acid, 85-52-9; 2-(4-methylbenzoyl)-benzoic acid, 85-55-2.

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