A Facile Synthesis of 1-Oxo-1,2-dihydroisoquinoline-3-carboxylate and 2-Pyridone-6-carboxylate Derivatives[1]

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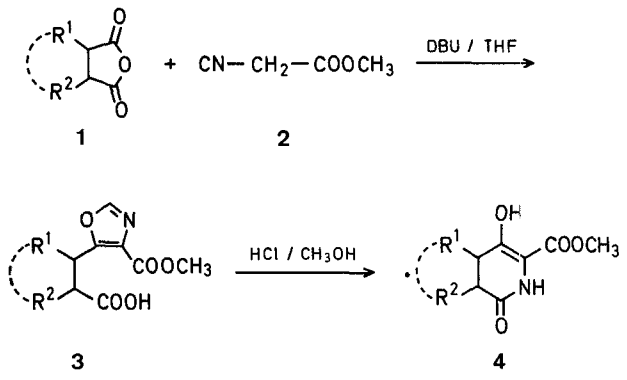
In the course of our studies on reactions of heterocyclic compounds with isocyano compounds, we have previously reported syntheses of pharmaceutically interesting compounds such as amino-carbostyril compounds[2] and amino-coumarin compounds[3] by the reactions of methyl isocyanoacetate with anthranilic and salicylic acid derivatives. The reaction has now been extended to a synthesis of 1-oxo-1,2-dihydroisoquinoline-3-carboxylate or 2-pyridone-6-carboxylate derivatives by the reaction of methyl isocyanoacetate with acid anhydrides such as phthalic or maleic anhydrides.



1 2 3 4

The reaction of methyl isocyanoacetate (**2**) with the acid anhydride **1** was carried out in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in tetrahydrofuran at room temperature to give 4-methoxycarbonyl-1,3-oxazole derivatives **3** in good yields as listed in Table. The structures of the resultant products **3a, b,** and **d** were confirmed by spectral and analytical data and the products **3c** and **3e** were subsequently hydrolyzed without purification. Hydrolysis of the 1,3-oxazole **3** with methanolic hydrochloric acid at 50–55° afforded the desired methyl 4-hydroxy-1-oxo-1,2-dihydroisoquinoline-3-carboxylates **4a, b** and methyl 5-hydroxy-2-pyridone-6-carboxylates **4c–e** in good yields (see Table). The reaction probably proceeds via the cleavage of the oxazole ring and the subsequent intramolecular cyclization.

The I.R. spectra of the products **4** showed the characteristic absorption of the ester C=O band, the amide C=O band, and the C=C double bond at 1685–1695, 1640–1650, and 1590–1600 cm^{-1}, respectively. Furthermore, the structure of the compounds **4** was supported by the microanalyses and these results are summarized in Table.

In the case of the reaction of 4-nitrophthalic anhydride (**1b**) with **2**, the oxazole compound **3b** was obtained as a mixture of 5-(2-carboxy-4-nitro)- and 5-(2-carboxy-5-nitro)-phenyl-4-methoxycarbonyl-1,3-oxazole, the ratio was not clarified. In contrast in the reaction of quinolinic anhydride (**1c**) with **2**, the final product **4c** was obtained as the single product methyl 1-oxo-4-hydroxy-2,5-naphthyridine-3-carboxylate identical to that reported by Ochiai et al.[4] in physicochemical properties.

Table. Preparation of 1,3-Oxazoles **3**, Methyl 1-Oxo-1,2-dihydroisoquinoline-3-carboxylates (**4a, b**), and Methyl 2-Pyridone-6-carboxylates (**4c–e**)

Product	R^1, R^2	Yield [%]	m.p. (Lit. m.p.)	I.R. (nujol) ν [cm^{-1}]	Molecular formula[a]
3a		89	134–135°	1735, 1710, 1630	$C_{12}H_9NO_5$ (247.2)
3b[b]		79	155–163°	1730, 1700, 1610	$C_{12}H_8N_2O_7$ (292.2)
3d		75	125–127°	1720, 1700, 1598	$C_{12}H_{15}NO_5$ (253.3)
4a		95	217–219° (221–222°)[5]	1685, 1640, 1600	$C_{11}H_9NO_4$ (219.2)
4b[c]		97	>280°	1690, 1650, 1600	$C_{11}H_8N_2O_6$ (264.2)
4c		65	218–220° (dec.) [219–220° (dec.)][4]	1695, 1650, 1590	$C_{10}H_8N_2O_4$ (220.2)
4d		41	160–162°	1690, 1650	$C_{11}H_{15}NO_4$ (225.3)
4e		40	268–270°	1690, 1650, 1595	$C_7H_5Cl_2NO_4$ (238.0)

[a] All compounds gave satisfactory microanalyses (C ±0.32%, H ±0.20%, N ±0.18%, Cl ±0.34%).
[b] Mixture of 4- and 5-nitro compounds.
[c] Mixture of 6- and 7-nitro compounds.

Preparation of 4-Methoxycarbonyl-1,3-oxazoles 3; Typical Procedure:

A mixture of phthalic anhydride (**1a**; 4.44 g, 0.03 mol) and methyl isocyanoacetate (**2**, 2.97 g, 0.03 mol) dissolved in tetrahydrofuran (40 ml) is added dropwise to a stirred solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (4.56 g, 0.03 mol) in tetrahydrofuran (20 ml) at 30–35°. Stirring is continued for 1 h at room temperature, water (50 ml) is added to the mixture, and the solvent is removed under reduced pressure. The resultant residue is adjusted to pH 3 with 10% hydrochloric acid and the separated oily products are extracted with ethyl acetate. The extract is washed with water, dried with sodium sulfate, and evaporated in vacuo. The resultant crystals are washed with hexane and recrystallized from ethyl acetate/hexane to afford *5-(2-carboxyphenyl)-4-methoxycarbonyl-1,3-oxazole* (**3a**) as colorless needles; yield: 6.56 g (89%); m.p. 134–135°.

^{1}H-N.M.R. (DNSO-d_6): δ = 8.56 (s, 1H, oxazole-CH); 7.55–8.18 (m, 4H_{arom}); 3.67 ppm (s, 3H, $COOCH_3$).

Preparation of Methyl 4-Hydroxy-1-oxo-1,2-dihydroisoquinoline-3-carboxylate Derivatives (4a, b) or Methyl 5-Hydroxy-2-pyridone-6-carboxylate Derivatives (4d, e); Typical Procedure:

Compound **3a** (4.94 g, 0.02 mol) is dissolved in a mixture of methanol (30 ml) and concentrated hydrochloric acid (6 ml) is added at 50–55° with stirring. Stirring is continued for 4 h at the same temperature, and then the resultant precipitates are isolated by suction under cooling and washed with methanol. Recrystallization from dimethylformamide gives *methyl 4-hydroxy-1-oxo-1,2-dihydroiso-*

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quinoline-3-carboxylate (**4a**) as colorless needles; yield: 4.16 g (95%); m.p. 217–219°; Lit.[5] 221–222°.

^{1}H-N.M.R. (CF_3COOD): $\delta = 7.90$–8.75 (m, $4H_{arom}$); 4.25 ppm (s, 3H, $COOCH_3$).

M.S.: $m/e = 219$ (M^+).

Methyl 4-Hydroxy-1-oxo-2,5-naphthyridine-3-carboxylate (4c): The reaction of quinolinic anhydride (**1c**; 3.87 g, 0.023 mol) with **2** (2.32 g, 0.023 mol) is carried out as described above to afford *5-(3-carboxy-2-pyridyl)-4-methoxycarbonyl-1,3-oxazole hydrochloride* (**3c**) as a crude oil. Subsequently, the product **3c** is dissolved in a mixture of concentrated hydrochloric acid (4 ml) and methanol (20 ml), stirring is continued for 2 h at room temperature, and then the resultant precipitates are isolated by suction filtration. Recrystallization from methanol gives the hydrochloride of **4c** as yellow needles; yield: 3.85 g (65% from **1c**); m.p. 163–165° (dec.).

I.R. (nujol): $\nu_{max} = 3460, 1690, 1658, 1600\,cm^{-1}$.

The product is treated with saturated sodium hydrogen carbonate to afford **4c**; m.p. 218–220° (dec.); Lit.[4] 219–220° (dec.).

^{1}H-N.M.R. (CF_3COOD): $\delta = 9.62$ (dd, 1H, $J = 2$ and 8 Hz); 9.42 (dd, 1H, $J = 2$ and 6 Hz); 8.40 (dd, 1H, $J = 6$ and 8 Hz); 4.25 ppm (s, 3H, $COOCH_3$).

M.S.: $m/e = 220$ (M^+).

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[1] Synthesis of Heterocyclic Compounds using Isocyano Compounds; 3. Part 2: Ref.[2b].

[2] (a) K. Matsumoto, M. Suzuki, N. Yoneda, M. Miyoshi, *Synthesis* **1976**, 805.
(b) M. Suzuki, K. Matsumoto, M. Miyoshi, N. Yoneda, *Chem. Pharm. Bull.* **25**, 2602 (1977).

[3] K. Matsumoto, M. Suzuki, M. Miyoshi, K. Okumura, *Synthesis* **1974**, 500.

[4] E. Ochiai, I. Arai, *Yakugaku Zasshi* **59**, 458 (1939); *C.A.* **34**, 108 (1940).

[5] S. Gabriel, J. Colman, *Ber. Dtsch. Chem. Ges.* **33**, 980 (1900).

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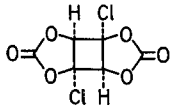
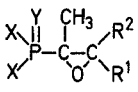
Errata 1978

A. H. Schmidt, W. Ried, *Synthesis* **1978** (1), 1–22;
The structure for product **17a** (p. 3) should be:



17a

P. Coutrot, P. Savignac, *Synthesis* **1978** (1), 34–36;
The structure for product **3** (p. 35) should be:

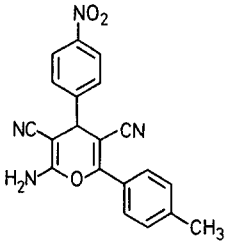


3

K. Burger, R. Ottlinger, *Synthesis* **1978** (1), 44;
Compounds **3** should be named 5-aryl-3,3-bis[trifluoromethyl]-3*H*-1,2,4-thiaselenazoles.

F. Huet, A. Lechevalier, M. Pellet, J. M. Conia, *Synthesis* **1978** (1), 63–65;
The first two entries in the Table (p. 64) should be:

A. J. Fatiadi, *Synthesis* **1978** (4), 241–282;
The formula for product **346** (p. 273) should be:



346

P. Tundo, *Synthesis* **1978** (4), 315–316;
The title and first sentence of the fifth experimental procedure (p. 316) should read as follows:

Preparation of *n*-Octyl Phenyl Sulphide from 1-Bromooctane and Potassium Benzenethiolate:
1-Bromooctane (19.30 g, 100 mmol), dichloromethane (50 ml), and resin **3** (1.20 g corresponding to 1.0 mmol of phosphonium salt) are stirred for 15 min at 20° to condition the resin; then a 3.0 molar aqueous solution of potassium benzenethiolate (50 ml, corresponding to 150 mmol of C_6H_5SK) is added and stirring is continued for 2.0 h.

Abstract no. 5171, *Synthesis* **1978** (4), 325;
The title should be:
Synthesis of Alkanoic, Arylacetic, and 3-Alkenoic Acids

C. Giordano, A. Belli, V. Bellotti, *Synthesis* **1978** (6), 443–445;
The pressures of hydrogen sulphide given in the experimental procedures (pp. 444–445) should be 1.2 ata (912 torr).

Table. Hydrolysis of Various Saturated and Unsaturated Acetals using Wet Silica Gel.

Entry	Acetal	Carbonyl Compound[a]	Method	Reaction time[b]	Yield [%]	Other method	Yield [%]	m.p. or b.p./torr (Lit. m.p. or b.p./torr)
1			B	3 h	98	—	—	130–131°/760 (130.6°/760)
2			A B	24 h 0.5 h	73 77	H_2O/H_2SO_4	65[4]	61°/24 (68.5–69°/23)[4]

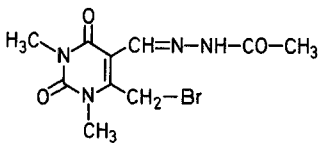
A. J. Fatiadi, *Synthesis* **1978** (3), 165–204;
On page 185, the first paragraph in the right hand column and the heading for Table 5 should read as follows:
Recently Zacharias and Junek[153] extended the related study to include 2-phenylhydrazone derivatives. Thus, reaction of 2-phenylhydrazones of 1,2,3-cyclohexanetriones with malononitrile produced 3-amino-4-cyano-8-dicyanomethylene-2-phenyl-2,8-dihydrocinnolines (50–54% yield, Table 5). Similar treatment of 2-phenylhydrazones of 1,2,3-indanetrione, however, gave 4-cyano-9-dicyanomethylene-3-imino-2-phenyl-2,3-dihydro-9*H*-indeno[2,1-*c*]pyridazines (69–90% yield, Table 6). The plausible pathways of the product formation are shown in the following Tables.

Table 5. Synthesis of Dihydrocinnolines via Reaction of 2-Phenylhydrazones of 1,2,3-Cyclohexanetriones with Malononitrile[153]

R	m.p.	Yield [%] of dihydrocinnoline

M. Suzuki, K. Nunami, K. Matsumoto, N. Yoneda, M. Miyoshi, *Synthesis* **1978** (6), 461–462;
The correct name for compound **4c** should be as follows:
8-hydroxy-7-methoxycarbonyl-5-oxo-5,6-dihydro-1,6-naphthyridine.

S. Senda, K. Hirota, T. Asao, Y. Yamada, *Synthesis* **1978** (6), 463–465;
The formula for compound **4** (p. 464) should be:



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