A Novel Cyclization Route to Some Substituted 3(2*H*)-Isoquinolinones

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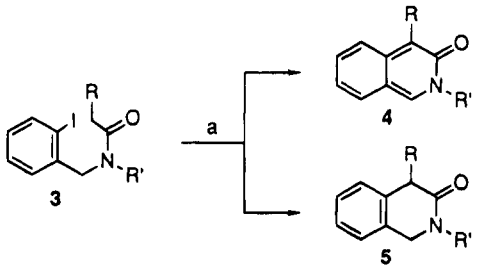
Of seven possible isomeric hydroxyisoquinolines, 3-hydroxyisoquinoline (**1**) is unique in that it is capable of existing in equilibrium (Scheme 1) with the tautomeric lactam structure **2** in which the aromatic sextet is destroyed for both rings.[1] Theoretical calculations have shown that the energy difference between the two tautomers **1** and **2** is quite small, the latter being slightly more stable.[2] The basic framework of compound **2** was first obtained by Boyer and Wolford in 1956 by the decomposition of aqueous diazotized 3-aminoisoquinoline or by treatment of compound **1** with nitrous acid in concentrated sulfuric acid.[3] Both structures interconvert in solution, their relative importance being dependent on the solvent employed; lactim structure **1** predominates in nonpolar solvents, whereas both lactim and lactam structures are important in polar solvent systems.[4–6] Electron-withdrawing substituents at the 1-position favor the lactim structure, while electron-donating substituents work favorably for the lactam structure. The latter structure is subject to facile autoxidation[6–8] and photooxidation.[9]

3(2*H*)-Isoquinolinone (**2**) and its derivatives are not so readily accessible. They have previously been synthesized by the reaction of *o*-acylphenylacetic acid with ammonia[4,5,8,10,11] or amines,[6,12] diazotization of 3-aminoisoquinoline,[3] isomerization of 3-hydroxyisoquinolines,[3,7,13] reaction of 3-isochromanone with amines,[10] alkylative dehydrogenation[14] or isomerization[15] of 1,4-dihydro-3(2*H*)-isoquinolinone derivatives, $POCl_3$-mediated reaction between arylacetic acid and secondary arylamides[16] or its internal variant,[17] and acid-catalyzed cyclization of *o*-acylphenylacetamides.[18] In spite of the multiplicity of synthetic approaches, no method appears to be general as to the variation of substituent group and substitution pattern on the lactam ring. In this paper, we report a novel synthetic route involving a previously unknown dehydrogenative cyclization, which, although limited in scope, may provide convenient access to some types of 3(2*H*)-isoquinolinone and 3-hydroxyisoquinoline derivatives which would be otherwise laborious to obtain. Some 3(2*H*)-isoquinolinone derivatives with a substituent at position 1 or 4 are known to exhibit biological effects such as antidepressant, cardiotonic, or analgesic activity.[1]

Scheme 1

1 2

Scheme 2



3 4 5

a: R = CN, R' = Me **e**: R = CN, R' = Ph
b: R = CN, R' = Et **f**: R = SO_2p-Tol, R' = Et
c: R = CN, R' = *n*-Pr **g**: R = Cl, R' = Et
d: R = CN, R' = CH_2Ph **h**: R = Ph, R' = Et

[a] Key: (a) 0.5 mmol of compound **3**, 1.0 mmol of NaH, 2 mL of solvent, 25 °C, then add 0.75 mmol of CuI, 120 °C, 3 h.

Earlier we have reported that the enolate anions of *N*-(2-haloaryl)- and *N*-(2-haloaryl)methyl-substituted enaminones undergo smooth intramolecular cyclization to give indole and 1,2-dihydroisoquinoline derivatives, respectively (Scheme 2), on being heated in the presence of CuI in hexamethylphosphoric triamide (HMPA).[19] When this methodology was applied to *N*-ethyl-*N*-(2-iodobenzyl)cyanoacetamide (**3b**), we came across an unexpected mode of cyclization which led to the formation of the 3(2*H*)-isoquinolinone framework **2**. The expected 1,4-dihydro-3(2*H*)-isoquinolinone derivative **5b** could not be detected. Thus, when the anion generated from tertiary amide **3b** was heated in HMPA in the presence of CuI at 120 °C for 3 h under argon, a formal displacement of the *ortho* iodine atom by the enolate carbon atom took place, giving cyclization product **4b** in moderate yield. Compound **4b** crystallized as reddish yellow needles (mp 198–199 °C) from benzene and emitted strong yellowish green fluorescence when irradiated. On treatment with lithium aluminum hydride (LAH) in ice-cooled tetrahydrofuran (THF), compound **4b** was reduced to the non-fluorescent 1,4-dihydro derivative **5b**.

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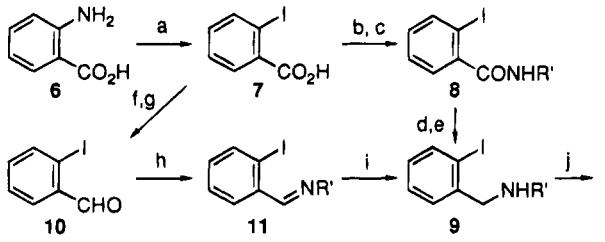
Table 1. Cyclization of Amide 3b to 3(2*H*)-Isoquinolinone 4b[a]

conditions			4b	conditions			4b,
NaH, equiv	CuI, equiv	solvent	yield, %	NaH equiv	CuI, equiv	solvent	yield, %
2	0	HMPA	*b*	5	1.5	HMPA	17
1	1.5	HMPA	32	*c*	1.5	HMPA	43
2	1.5	HMPA	61	2	1.5	NMP	48
2	4	HMPA	55	2	1.5	DMF	64
3	1.5	HMPA	25	2	1.5	TMU	43

[a] All reactions were carried out using the given substrate (0.5 mmol) and solvent (2 mL) at 120 °C for 3 h under argon. [b] A complex mixture resulted. [c] KO-*t*-Bu (2 equiv) was used as a base.

Scheme 3



[a] Key: (a) $NaNO_2$, HCl, KI (70%); (b) $SOCl_2$; (c) $R'NH_2$ (85%); (d) $POCl_3$; (e) $NaBH_4$, HCl (60–70%); (f) $BF_3{\cdot}OEt_2$, $NaBH_4$ (90%); (g) PDC (80%); (h) $R'NH_2$ (100%); (i) $NaBH_4$ (60–80%); (j) $NCCH_2CO_2H$, $(EtO)_2P(O)CN$, Et_3N (77–95%).

The effect of solvents on the reaction has been examined for four dipolar aprotic solvents using compound **3b** as the common substrate (Table 1). As far as can be judged from the product yields, *N*,*N*-dimethylformamide (DMF) and HMPA were the solvents of choice; *N*-methyl-2-pyrrolidinone (NMP) and *N*,*N*,*N*′,*N*′-tetramethylurea (TMU) gave less satisfactory results. In the absence of CuI, the cyclization did not take place, while the use of a large excess of Cu(I) catalyst produced little positive results. Attempts to effect a similar cyclization of amide **3b** and its enolate by using palladium catalysts led to a complex mixture of products.

NaH-induced aromatization of unsaturated cyclic compounds has long been known.[20-22] However, compound **5b** was found to be stable toward the action of NaH in the absence of CuI. When compound **5b** was subjected to the conditions under which **3b** was successfully cyclized to **4b**, it suffered dehydrogenation in part to form the expected **4b**, but a considerable part of **5b** was recovered intact, showing its reluctance to undergo dehydrogenation to the 3(2*H*)-isoquinolinone system.

Tertiary amides **3** were prepared by two different methods. Anthranilic acid (**6**) was converted to 2-iodobenzoic acid (**7**) by the Griess diazo reaction (Scheme 3). Acid **7** was condensed with amines to give secondary amides **8**, which were reduced by a known procedure[23] to secondary amines **9**. Alternatively, acid **7** was converted to 2-iodobenzaldehyde (**10**) by precedented methods.[24,25] Condensation of aldehydes **10** with amines to give imines **11** followed by reduction with $NaBH_4$ afforded the corresponding amines **9**. *N*-Acylation of amines **9** with cyanoacetic acid in the presence of diethylphosphoryl cyanide[26] gave the tertiary amides **3a–e** in good yields. Amides **3g,h** were prepared by the condensation of amine **9b** with corresponding acyl chlorides, and amide **3f** was obtained by treating **3g** with sodium *p*-toluenesulfinate.

Table 2. Cyclization of Amides 3 to 3(2*H*)-Isoquinolinones 4 and Dihydro Derivative 5[a]

	amide 3				
	R	R′	solvent	product	yield,[b] %
a	CN	Me	HMPA	**4a**	40
b	CN	Et	DMF	**4b**	64
c	CN	*n*-Pr	DMF	**4c**	58
d	CN	CH_2Ph	HMPA	**4d**	34
e	CN	Ph	DMF	**4e**	38[c]
f	SO_2-*p*-Tol	Et	HMPA	**5f**	73[d]
g	Cl	Et	HMPA	*e*	0
h	Ph	Et	HMPA	*e*	0

[a] As for reaction conditions, see footnote *a* in Table 1. [b] Isolated yield. [c] Reaction temperature was 100 °C. [d] Reaction time was 6 h. [e] A complex mixture resulted.

Although not examined extensively, the present cyclization reaction appears to be limited in scope, because two tertiary amides **3g** and **3h** led to a complex mixture of products under similar conditions, while amide **3f** was simply cyclized to the expected 1,4-dihydro-3(2*H*)-isoquinolinone derivative **5f** in a good yield, no isoquinolinone compound **4f** being isolated (Table 2). Thus, the mechanism of the copper(I)-mediated dehydrogenative cyclization of amide **3** to 3(2*H*)-isoquinolinone (**4**) is not clear at present.

Experimental Section

General. Copper(I) iodide was purified according to the reported procedure.[27] All other reagents were of commercial quality and purchased from Wako Pure Chemical Industries, Ltd. and Nacalai Tesque, Inc. Reagent-quality solvents were used after distillation. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a 200-MHz NMR spectrometer, using tetramethylsilane as an internal reference. IR spectra were measured as liquid films on NaCl plates or as KBr pellets. Only important peaks below 2500 cm^{-1} are reported. Mass spectra (EI) were determined at 70 eV. Elemental analyses were carried out at Microanalytical Laboratory, Institute for Chemical Research, Kyoto University.

Preparation of *N*-Substituted-*N*-(2-iodobenzyl)cyanoacetamides 3. To a stirred mixture of *N*-substituted 2-iodobenzylamine **9** (5.0 mmol), cyanoacetic acid (0.55 g, 6.5 mmol), and DMF (3 mL) was added diethylphosphoryl cyanide (1.1 g, 6.5 mmol), followed by triethylamine (1.2 g, 12 mmol) at 0 °C. After 30 min the ice bath was removed and the mixture was stirred at room temperature for additional 4 h. The reaction mixture was then diluted with benzene (20 mL), and the organic phase was separated and washed successively with aqueous Na_2CO_3, water, 5% HCl, and brine. Drying of the extract over Na_2SO_4 and subsequent evaporation under reduced pressure gave crude tertiary amide **3**, which was further purified by recrystallization from hexane/ethyl acetate or by column chromatgraphy on silica gel using the same solvent as eluent.

***N*-(2-Iodobenzyl)-*N*-methylcyanoacetamide (3a)**: yield 85%; colorless powder, mp 52–53 °C; ^1H NMR δ 3.01, 3.04 (two s, 3 H), 3.48, 3.58 (two s, 2 H), 4.46, 4.70 (two s, 2 H), 7.0–7.2 (m, 2 H), 7.3–7.5 (m, 1 H), 7.8–7.9 (m, 1 H); IR (KBr) 2210 (CN), 1665 (CO) cm^{-1}; MS (EI) *m*/*z* (rel intensity) 217 (24, C_7H_6I), 187 (100, $M^+ - I$). Anal. Calcd for $C_{11}H_{11}IN_2O$: C 42.1; H, 3.5; N, 8.9. Found: C, 42.0; H, 3.5; N, 8.9.

***N*-(2-Iodobenzyl)-*N*-ethylcyanoacetamide (3b)**: yield 87%; colorless needles, mp 113–114 °C; ^1H NMR δ 1.19, 1.24 (two t, J = 7.2, 3 H), 3.31, 3.49 (two q, J = 7.1, 2 H), 3.43, 3.60 (two s,

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2 H), 4.42, 4.69 (two s, 2 H), 6.9–7.2 (m, 2 H), 7.3–7.5 (m, 1 H), 7.8–7.9 (m, 1 H); IR (KBr) 2260 (CN), 1645 (CO) cm^{-1}; MS (EI) m/z (rel intensity) 217 (35, C_7H_6I), 201 (100, $M^+ - I$). Anal. Calcd for $C_{12}H_{13}IN_2O$: C, 43.9; H,4.0; N, 8.5. Found: C, 43.8; H, 4.0; N, 8.5.

***N*-(2-Iodobenzyl)-*N*-propylcyanoacetamide (3c)**: yield 92%; colorless crystals, mp 84–86 °C; ^1H NMR δ 0.93, 0.94 (two t, J = 7.4, 3 H), 1.5–1.8 (m, 2 H), 3.18, 3.39 (two t, J = 7.9, 2 H), 3.41, 3.59 (two s, 2 H), 4.43, 4.70 (two s, 2 H), 6.9–7.5 (m, 3 H), 7.8–7.9 (m, 1 H); IR (KBr) 2260 (CN), 1640 (CO) cm^{-1}; MS (EI) m/z (rel intensity) 217 (85, C_7H_6I), 215 (100, $M^+ - I$). Anal. Calcd for $C_{13}H_{15}IN_2O$: C, 45.6; H, 4.4; N, 8.2. Found: C, 45.5; H, 4.4, N; 8.2.

***N*-(2-Iodobenzyl)-*N*-benzylcyanoacetamide (3d)**: yield 95%; colorless viscous oil; ^1H NMR δ 3.50, 3.54 (two s, 2 H), 4.37, 4.50 (two s, 2 H), 4.64, 4.78 (two s, 2 H), 7.0–7.4 (m, 8 H), 7.8–7.9 (m, 1 H); IR (neat) 2260 (CN), 1670 (CO) cm^{-1}; MS (EI) m/z (rel intensity) 263 (28, $M^+ - I$), 217 (8, C_7H_6I), 91 (100, C_7H_7). Anal. Calcd for $C_{17}H_{15}IN_2O$: C, 52.3; H, 3.9; N, 7.2. Found: C, 53.1; H, 4.0; N, 7.3.

***N*-(2-Iodobenzyl)-*N*-phenylcyanoacetamide (3e)**: yield 77%; colorless needles, mp 134–135 °C; ^1H NMR δ 3.25 (s, 2 H), 5.05 (s, 2 H), 6.94 (t, J = 7.2, 1 H), 6.9–7.1 (m, 2 H), 7.2–7.4 (m, 5 H), 7.75 (d, J = 7.6, 1 H); IR (KBr) 2260 (CN), 1670 (CO) cm^{-1}; MS (EI) m/z (rel intensity) 249 (100, $M^+ - I$), 217 (87, C_7H_6I). Anal. Calcd for $C_{16}H_{13}IN_2O$: C, 51.1; H, 3.5; N, 7.5. Found: C, 51.2; H, 3.4; N, 7.4.

***N*-(2-Iodobenzyl)-*N*-ethyl((4-methylphenyl)sulfonyl)acetamide (3f).** To a solution of (2-iodobenzyl)ethylamine **(9b)** (2.0 g, 7.7 mmol) and pyridine (1.7 g, 22 mmol) in dichloromethane (20 mL) was added chloroacetyl chloride (1.1 g, 9.5 mmol) at 0 °C. The reaction mixture was allowed to come to room temperature and after 4 h quenched with saturated aqueous Na_2CO_3. The organic phase was extracted with dichloromethane, and the extract was washed with 5% HCl and brine, dried with Na_2SO_4, and concentrated to give crude *N*-(2-iodobenzyl)-*N*-ethylchloroacetamide **(3g)** (2.1 g, 6.3 mmol) as a colorless oil. The oil was then stirred overnight with sodium *p*-toluenesulfinate tetrahydrate (3.2 g, 13 mmol) in EtOH (20 mL) under gentle reflux. The resulting mixture was diluted with water and extracted with benzene. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Chromatography on silica gel (hexane/ethyl acetate) gave compound **3f** as a colorless viscous oil (1.85 g, 64%): bp *ca.* 200 °C dec (oven temperature)/2 mmHg; ^1H NMR δ 1.14, 1.25 (two t, J = 7.1, 3 H), 2.43, 2.46 (two s, 3 H), 3.39, 3.57 (two q, J = 7.2, 2 H), 4.09, 4.31 (two s, 2 H), 4.58, 4.60 (two s, 2 H), 6.9–7.1 (m, 2 H), 7.3–7.4 (m, 3 H), 7.8–7.9 (m, 3 H); IR (neat) 1650 (CO), 1315 (SO_2), 1150 (SO_2) cm^{-1}; MS (EI) m/z (rel intensity) 330 (100, $M^+ - I$), 302 (77, $M^+ - C_7H_7$-SO_2), 217 (54, C_7H_6I), 91 (87, C_7H_7). Anal. Calcd for $C_{18}H_{20}INO_3S$: C, 47.3; H, 4.4; N, 3.1. Found: C, 47.4; H, 4.5; N, 2.9.

Cyclization of Tertiary Amide 3 to 3(2*H*)-Isoquinolinone (4). Typical Procedure. Commercial sodium hydride (60% in mineral oil, 40 mg, 1 mmol) was washed with dry hexane under argon to remove the oil. The solid was then covered with DMF (2 mL), and *N*-(2-iodobenzyl)-*N*-ethylcyanoacetamide **(3b)** (164 mg, 0.5 mmol) was added with stirring. After several minutes, when the evolution of hydrogen had ceased, copper(I) iodide (143 mg, 0.75 mmol) was added to the solution. The color of the solution turned grey, and the resulting mixture was heated at 120 °C for 3 h with stirring. The color darkened as the reaction proceeded. The progress of the reaction was monitored by TLC. When the substrate disappeared, the mixture was cooled to room temperature, diluted with water (20 mL), and filtered to leave a solid residue, which was washed with three 20 mL portions of water and then placed in a thimble and extracted with benzene using a Soxhlet extractor. Aqueous washings and filtrate were also extracted with benzene. The combined extracts were evaporated to give an orange-colored, highly fluorescent residue, which was purified by chromatography on silica gel using chloroform/methanol (200:1) as the eluent to give **4-cyano-2-ethyl-3(2*H*)-isoquinolinone (4b)** (63 mg, 64%) as reddish yellow needles: mp 198–199 °C; ^1H NMR δ 1.53 (t, J = 7.2, 3 H), 4.35 (q, J = 7.2, 2 H), 7.13 (t, J = 7.5, 1 H), 7.5–7.6 (m, 2 H), 7.70 (d, J = 8.7, 1 H), 8.48 (s, 1 H); ^{13}C-NMR δ 15.0, 47.5, 116.7, 122.4, 123.4, 129.0, 135.7, 144.5, 146.2; IR (KBr) 2210 (CN), 1645 (CO) cm^{-1}; MS (EI) m/z (rel intensity) 198 (79, M^+), 170 (100, $M^+ - CO$); UV ($CHCl_3$) λ_{max} 452 nm; fluorescence spectrum (MeOH) λ_{max} 437 nm. Anal. Calcd for $C_{12}H_{10}N_2O$: C, 72.7; H, 5.1; N, 14.1. Found: C, 72.4; H, 5.0; N, 14.1.

4-Cyano-2-methyl-3(2*H*)-isoquinolinone (4a): yield 40%; yellow plates, mp 234–235 °C; ^1H NMR δ 3.91 (s, 3 H), 7.14 (t, J = 7.5, 1 H), 7.5–7.6 (m, 2 H), 7.71 (d, J = 7.6, 1 H), 8.50 (s, 1 H); IR (KBr) 2210 (CN), 1655 (CO) cm^{-1}; MS (EI) m/z (rel intensity) 184 (100, M^+), 156 (95, $M^+ - CO$). Anal. Calcd for $C_{11}H_8N_2O$: C, 71.7; H, 4.4; N, 15.2. Found: C, 71.5; H, 4.3; N, 15.2.

4-Cyano-2-propyl-3(2*H*)-isoquinolinone (4c): yield 58%; yellow needles, mp 169–170 °C; ^1H NMR δ 1.02 (t, J = 7.4, 3 H), 1.8–2.0 (m, 2 H), 4.25 (t, J = 7.4, 2 H), 7.13 (t, J = 7.5, 1 H), 7.5–7.6 (m, 2 H), 7.71 (d, J = 8.6, 1 H), 8.44 (s, 1 H); IR (KBr) 2210 (CN), 1645 (CO) cm^{-1}; MS (EI) m/z (rel intensity) 212 (41, M^+), 184 (7, $M^+ - CO$), 170 (100). Anal. Calcd for $C_{13}H_{12}N_2O$: C, 73.6; H, 5.7; N, 13.2. Found: C, 72.9; H, 5.6; N, 13.0.

2-Benzyl-4-cyano-3(2*H*)-isoquinolinone (4d): yield 34%; yellow needles, mp 219–222 °C; ^1H NMR δ 5.45 (s, 2 H), 7.09 (t, J = 7.5, 1 H), 7.4–7.7 (m, 8 H), 8.37 (s, 1 H); IR (KBr) 2210 (CN), 1650 (CO) cm^{-1}; MS (EI) m/z (rel intensity) 260 (14, M^+), 91 (100, C_7H_7). Anal. Calcd for $C_{17}H_{12}N_2O$: C, 78.4; H, 4.7; N, 10.8. Found: C, 78.2; H, 4.6; N, 10.6.

4-Cyano-2-phenyl-3(2*H*)-isoquinolinone (4e): yield 38%; orange needles, mp 201–205 °C dec; ^1H NMR δ 7.0–7.8 (m, 9 H), 8.50 (s, 1 H); IR (KBr) 2210 (CN), 1655 (CO) cm^{-1}; MS (EI) m/z (rel intensity) 246 (43, M^+), 218 (50, $M^+ - CO$), 91 (100). Anal. Calcd for $C_{16}H_{10}N_2O$: C, 78.0; H, 4.1; N, 11.4. Found: C, 77.0; H, 4.1; N, 11.1. Unsatisfactory analysis may be attributed to deterioration while waiting for analysis.

Cyclization of Tertiary Amide 3f to 2-Ethyl-4-((4-methylphenyl)sulfonyl)-1,4-dihydro-3(2*H*)-isoquinolinone (5f). A mixture of *N*-(2-iodobenzyl)-*N*-ethyl((4-methylphenyl)sulfonyl)-acetamide **(3f)** (1.14 g, 2.50 mmol), sodium hydride (5.50 mmol), copper(I) iodide (0.96 g, 5.04 mmol), and HMPA (2.5 mL) was similarly reacted at 120 °C for 6 h, and the resulting dark-colored mixture was worked up as described above to give 1,4-dihydro-3(2*H*)-isoquinolinone **5f** (0.60 g, 73%) as a colorless powdery solid: mp 185–186 °C; ^1H NMR δ 1.20 (t, J = 7.3, 3 H), 2.46 (s, 3 H), 3.34, 3.41 (two q, J = 7.1, 1 H), 3.69, 3.76 (two q, J = 7.1, 1 H), 4.15 (d, J = 16, 1 H), 4.83 (d, J = 16, 1 H), 4.95 (s, 1 H), 7.2–7.5 (m, 6 H), 7.66 (d, J = 8.4, 2 H); IR (KBr) 1655 (CO), 1305 (SO_2), 1140 (SO_2) cm^{-1}; MS (EI) m/z (rel intensity) 329 (1, M^+), 146 (100). Anal. Calcd for $C_{18}H_{19}NO_3S$: C, 65.6; H, 5.8; N, 4.3. Found: C, 65.9; H, 5.7; N, 4.2.

$LiAlH_4$ Reduction of 4-Cyano-2-ethyl-3(2*H*)-isoquinolinone (4b) to 4-Cyano-2-ethyl-1,4-dihydro-3(2*H*)-isoquinolinone (5b). To a suspension of $LiAlH_4$ (29.1 mg, 0.768 mmol) in THF (3 mL) cooled in an ice bath was added isoquinolinone **4b** (76.1 mg, 0.384 mmol), and the resulting mixture was stirred for 2.5 h at 0 °C. It was then quenched with 5% HCl (10 mL) and extracted with dichloromethane. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was chromatographed on silica gel using chloroform as eluent to give **5b** as a pale yellow solid (48.2 mg, 63%): mp 92–94 °C; ^1H NMR δ 1.22 (t, J = 7.5, 3 H), 3.61 (q, J = 7.5, 2 H), 4.50 (s, 2 H), 4.70 (s, 1 H), 7.2–7.6 (m, 4 H); IR (KBr) 2250 (CN), 1665 (CO) cm^{-1}; MS (EI) m/z (rel intensity) 200 (8, M^+), 129 (100). Anal. Calcd for $C_{12}H_{12}N_2O$: C, 72.0; H, 6.0; N, 14.0. Found: C, 72.1; H, 6.0; N, 14.0.

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