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Condensed Heteroaromatic Ring Systems. VIII.[1] Synthesis of 3-Substituted Isocoumarins from *o*-Halobenzoic Acid Derivatives

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The hydration of *o*-ethynylbenzoic acid derivatives, such as ethyl *o*-ethynylbenzoate, *o*-ethynylbenzonitrile, and *o*-ethynylbenzamide, in sulfuric acid in the presence of mercuric sulfate, afforded 3-substituted isocoumarins. The palladium-catalyzed reaction of *o*-halobenzoic acid derivatives with terminal acetylenes to obtain the starting materials for the cyclization is also described.

Keywords——isocoumarin; ethyl *o*-ethynylbenzoate; *o*-ethynylbenzonitrile; *o*-ethynylbenzamide; acetylene; palladium-catalyzed reaction; mercuric sulfate

In 1977, Korte *et al.* reported the cyclization of *o*-allylbenzoic acid derivatives (prepared by condensation of the corresponding *o*-halobenzoic acid derivatives with an appropriate π-allyl complex) to isocoumarins.[2] An advantage of this method is considered to be the wide availability of *o*-halobenzoic acid derivatives employed as starting materials. Prior to this work, isocoumarins were commonly synthesized by the intramolecular cyclization of ethyl *o*-acylmethylbenzoates[3a] or *o*-acylmethylbenzonitriles,[3b] whose synthesis is troublesome in some cases. Thus, Korte's method is useful, even though formation of the final products involves oxidation.

Meanwhile, the hydration of phenylethynyl-substituted N-heteroaromatics such as quinoline, isoquinoline, and pyrimidine, has been reported not to give phenylacetyl derivatives, but to yield the benzoylmethyl derivatives in general.[4] From these results, it is conceivable that the hydration of ethynylbenzene derivatives containing an ethoxycarbonyl or a cyano group at the *ortho* position, and subsequent intramolecular condensation between the resulting acylmethyl group and the carboxyl groups would give isocoumarins. The present paper deals with the palladium-catalyzed reaction of *o*-halobenzoic acid derivatives with terminal acetylenes, and its application to the synthesis of isocoumarins.

Firstly, the palladium-catalyzed reaction of *o*-halobenzoic acid derivatives with several terminal acetylenes, including trimethylsilylacetylene (TMSA) was investigated. Reaction of ethyl *o*-bromobenzoate (**1**) with phenylacetylene in the presence of dichlorobis(triphenylphosphine)palladium gave ethyl *o*-phenylethynylbenzoate (**3a**) in good yield. Similarly, the reactions of 1-hexyne and TMSA with **1** proceeded smoothly to give ethyl *o*-(1-hexynyl)- (**3b**) and *o*-(trimethylsilylethynyl)benzoate (**3d**), respectively. In reaction with 1-propyne, however, **1** does not show enough reactivity at room temperature. Thus the synthesis of the desired ethyl *o*-(1-propynyl)benzoate (**3c**) was accomplished by the reaction of ethyl *o*-iodobenzoate (**5**) with 1-propyne at room temperature. Reaction of these terminal acetylenes with *o*-halobenzonitriles (**2** and **6**) also gave the corresponding ethynylbenzonitriles (**4a**—**d**) in satisfactory yields, as expected.

Furthermore, the reaction of *o*-bromo-*N*,*N*-dimethylbenzamide (**7**) with phenylacetylene gave the corresponding phenylethynylbenzamide (**9**). On the other hand, *N*-methyl-*o*-phenylethynylbenzamide (**8**) was prepared from *o*-iodo-*N*-methylbenzamide (**10**), since the reaction of *o*-bromo-*N*-methylbenzamide with phenylacetylene failed to give **8**.

In addition to the above compounds, *o*-phenylethynylbenzamide (**11a**) was synthesized by the partial hydrolysis of **4a**, and *o*-phenylethynylbenzoic acid (**12**) was prepared by the saponification of **3a**.

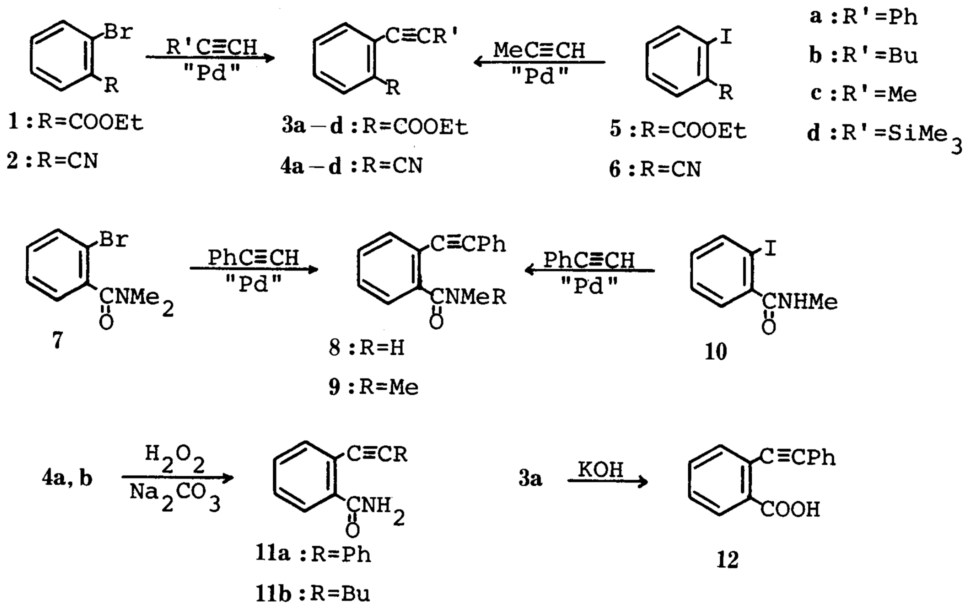

Chart 1

Secondly, the cyclization of the ethynylbenzoic acid derivatives to isocoumarins was investigated. When **3a** was heated with mercuric sulfate in dilute sulfuric acid, 3-phenylisocoumarin (**13a**) was obtained as expected. Similarly, 3-butylisocoumarin (**13b**) and 3-methylisocoumarin (**13c**) were obtained in satisfactory yields through this route. The same products (**13a**—**c**) were alternatively synthesized by the hydration of **4a**—**c** under the same conditions as above.

Although the yields of **13a**—**c** from **4a**—**c** were inferior to those from **3a**—**c**, the use of *o*-halobenzonitriles was preferable for the synthesis of unsubstituted isocoumarin (**13d**). Namely, the hydration of **3d** in the presence of mercuric sulfate resulted in the formation of ethyl *o*-acetylbenzoate (**15**), giving no cyclized product, and the reaction of **3d** with sodium ethoxide in ethanol gave a mixture of many products instead of the desired compound (**16**). In contrast, the reaction of **4d** with sodium ethoxide afforded *o*-(2-ethoxyethenyl)benzonitrile (**14**) which cyclized to **13d** on treatment with hydrobromic acid.

It is known[5)] that the hydration of ethynyl-*N*-heteroaromatics in the presence of mercuric sulfate gives the acetyl compounds instead of formylmethyl compounds. Thus, the formation of **15** in the above cases seems reasonable.

In order to compare the behavior of primary, secondary, and tertiary carbamoyl groups with that of cyano and ethoxycarbonyl groups in the isocoumarin cyclization, further experiments were carried out as described below. When *o*-phenylethynylbenzamide (**11a**) was heated in sulfuric acid in the presence of mercuric sulfate, 3-benzylidenephthalide (**17a**) was unexpectedly isolated together with **13a**. In the case of *o*-(1-hexynyl)benzamide (**11b**), though **13b** was obtained as a main product, the formation of the same type of phthalide (**17b**) was also observed. On the other hand, *N*,*N*-dimethyl-*o*-phenylethynylbenzamide (**9**) and *N*-

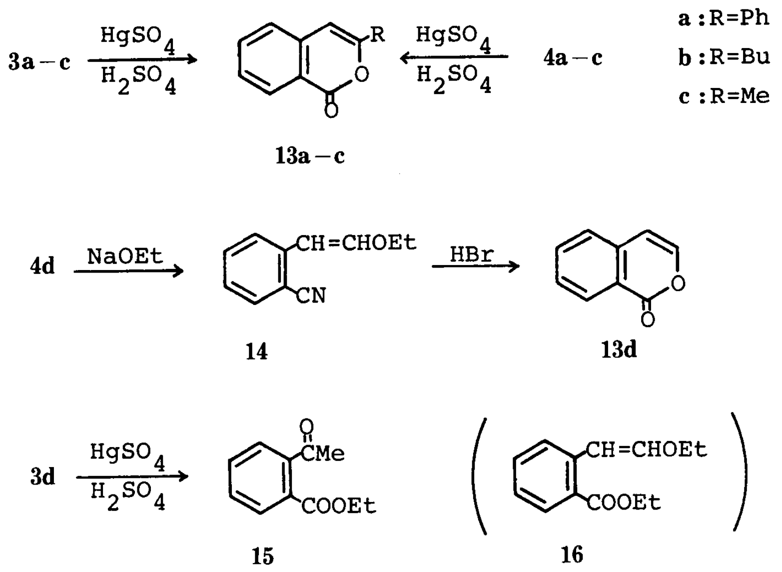

Chart 2

methyl-*o*-phenylethynylbenzamide (**8**) both cyclized to **13a** without forming **17a**. It is of interest that the formation of the phthalide (**17a**, **b**) due to reverse hydration to the ethynyl groups was observed only in the case of the primary benzamide derivatives, but the reason for this is not clear.

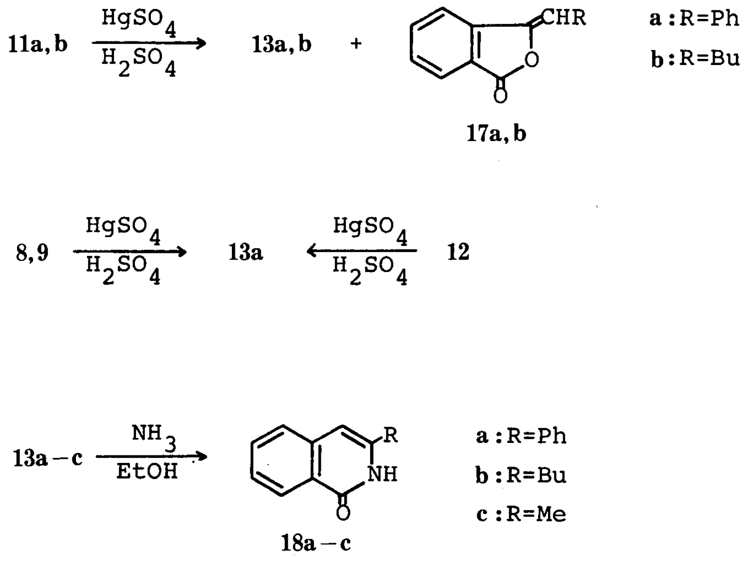

Chart 3

When *o*-phenylethynylbenzoic acid (**12**) was heated under the same conditions as above, **13a** was obtained in only 18% yield, which is the lowest cyclization yield in the present investigation. Thus, the free *o*-ethynylbenzoic acids were presumed not to be real reaction intermediates in all cases.

Finally, it should be mentioned that the isocoumarins (**13a**—**c**) were easily transformed into 3-substituted isoquinolones (**18a**—**c**) by treatment with ethanolic ammonia in a sealed tube. *o*-Phenylethynylbenzamide (**11a**) did not cyclize to **18a** under alkaline conditions, although this type of cyclization of 4,6-dimethyl-3-phenylethynyl-2-pyridinecarboxamide is known to give 2,4-dimethyl-6-phenyl-1,7-naphthyridin-8-one.[6)]

Experimental

All melting points and boiling points are uncorrected. Infrared (IR) spectra were measured with a JASCO IRA-1 spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken at 60 MHz with a JEOL JMN-PMX 60 spectrometer. Chemical shifts are expressed in δ (ppm) values. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad.

Synthesis of *o*-Ethynylbenzoic Acid Derivatives: General Procedure A——A mixture of an *o*-halobenzoic acid (10 mmol), an acetylene (12 mmol), $Pd(PPh_3)_2Cl_2$ (160 mg), CuI (80 mg), and Et_3N (2 ml)[7] was heated in a sealed tube at 120 °C for an appropriate time as shown in Table I. The reaction mixture was diluted with H_2O and extracted with ether. The residue obtained from the ethereal extract was purified by SiO_2 column chromatography using hexane–C_6H_6 (2 : 1) and then by distillation under reduced pressure or by recrystallization.

General Procedure B——Propyne [generated from 1,2-dibromopropane (20.2 g, 100 mmol) with KOH (18 g, 320 mmol) in BuOH (40 ml)] was introduced into a mixture of an *o*-iodobenzoic acid (10 mmol), $Pd(PPh_3)_2Cl_2$ (160 mg), CuI (80 mg), and Et_3N (50 ml), contained in a three necked flask fitted with a dry-ice condenser. After being stirred at room temperature for 6 h, the mixture was concentrated to dryness under reduced pressure. The residue was worked-up according to general procedure A.

TABLE I. *o*-Ethynylbenzoic Acid Derivatives from *o*-Halobenzoic Acid Derivatives

No.	Reaction time (h)	Yield (%)	bp (mmHg)[a] [mp] (°C)	IR ($CHCl_3$) cm^{-1}	^{1}H-NMR (CCl_4) δ (ppm)
3a	6	95	175 (3)	2210 1720	1.35 (3H, t, J=7.0 Hz), 4.35 (2H, q, J=7.0 Hz) 7.2—7.7 (8H, m), 7.8—8.1 (1H, m)
3b	6	70	140 (3)	2200 1720	0.95 (3H, t, J=7.0 Hz), 1.37 (3H, t, J=7.0 Hz) 1.2—1.9 (4H, m), 2.37 (2H, t, J=7.0 Hz) 4.20 (2H, q, J=7.0 Hz), 7.0—7.8 (4H, m)
3c	6	93	140 (3)	2230 1710	1.33 (3H, t, J=7.0 Hz), 2.03 (3H, s) 4.27 (2H, q, J=7.0 Hz), 7.1—7.5 (3H, m) 7.7—7.9 (1H, m)
3d	1	98	140 (3)	2170 1710	0.26 (9H, s), 1.37 (3H, t, J=7.0 Hz) 4.33 (2H, q, J=7.0 Hz), 7.1—8.0 (4H, m)
4a	20	86	175 (4)	2210 2220	7.2—7.8 (9H, m)
4b	16	77	140 (3)	2220	0.96 (3H, t, J=7.0 Hz), 1.2—1.9 (4H, m) 2.50 (2H, t, J=7.0 Hz), 7.0—7.6 (4H, m)
4c	6	100	140 (4)	2220	2.15 (3H, s), 7.2—7.7 (4H, m)
8[b]	18	43	[105—107]	3410 2200 1655	3.07 (3H, d, J=5.0 Hz), 7.1—8.2 (10H, m)
9[b]	46	20	170 (3)	2200 1630	2.77 (3H, s), 3.05 (3H, s), 7.0—7.7 (9H, m)

a) Bath temperature. *b*) The ^{1}H-NMR spectra of **8** and **9** were measured in $CDCl_3$.

TABLE II. Analytical Data for *o*-Ethynylbenzoic Acid Derivatives

No.	Formula	Analysis (%)					
		Calcd			Found		
		C	H	N	C	H	N
3a	$C_{17}H_{14}O_2$	81.58	5.64		81.84	5.73	
3b	$C_{15}H_{19}O_2$	78.23	7.88		77.94	7.61	
3c	$C_{12}H_{12}O_2$	76.57	6.43		76.44	6.45	
4a	$C_{15}H_9N$	88.64	4.46	6.89	89.06	4.49	6.58
4b	$C_{13}H_{13}N$	85.21	7.15	7.64	85.16	7.35	7.52
4c	$C_{10}H_7N$	85.08	5.00	9.92	85.51	5.00	9.80
8	$C_{16}H_{13}NO$	81.68	5.57	5.95	81.40	5.36	5.84
9	$C_{17}H_{15}NO$	81.90	6.06	5.62	81.86	5.95	5.58

Table III. Isocoumarins from *o*-Ethynylbenzoic Acid Derivatives

Product No.	Starting compd.	Yield (%)	mp (°C)	IR ($CHCl_3$) cm^{-1}	^1H-NMR ($CDCl_3$) δ (ppm)
13a	**3a**	97	87—88[a)]	1730	6.90 (1H, s), 7.3—7.9 (8H, m), 8.1—8.4 (1H, m)
	4a	76			
	8	68			
	9	27			
	12	18			
13b	**3b**	92	45—48[b)]	1730	0.98 (3H, t, J=7.0 Hz), 1.2—2.0 (4H, m) 2.50 (2H, t, J=7.0 Hz), 6.03 (1H, s), 7.1—7.7 (3H, m)
	4b	64			
13c	**3c**	95	67—68[c)]	1730	2.20 (3H, s), 6.10 (1H, s), 7.1—7.7 (3H, m) 8.0—8.3 (1H, m)
	5c	65			

a) Lit.[8)] mp 90—91 °C. *b*) Lit.[9)] mp 44—45 °C. *c*) Lit.[10)] mp 73 °C.

***o*-Phenylethynylbenzamide (11a)**——A mixture of *o*-phenylethynylbenzonitrile (**4a**) (1.0 g, 5 mmol), 3 N Na_2CO_3 (30 ml), 15% H_2O_2 (30 ml), and acetone (30 ml) was stirred at room temperature for 24 h. After removal of the solvent, the residue was diluted with H_2O and extracted with $CHCl_3$. The crude product obtained from the extract was recrystallized from AcOEt to give colorless needles, mp 155—157 °C. Yield 980 mg (89%). IR ($CHCl_3$) cm^{-1}: 3510, 3380, 2200, 1670. ^1H-NMR ($CDCl_3$): 6.6 (2H, br s), 7.1—7.7 (8H, m), 7.9—8.2 (1H, m). *Anal.* Calcd for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.28; H, 4.75; N, 6.14.

***o*-(1-Hexynyl)benzamide (11b)**——A mixture of *o*-(1-hexynyl)benzonitrile (**4b**) (1.65 g, 9 mmol), 3 N Na_2CO_3 (50 ml), 15% H_2O_2 (50 ml), and acetone (50 ml) was stirred at room temperature for 24 h. After removal of the solvent, the residue was diluted with H_2O and extracted with $CHCl_3$. The crude product obtained from the $CHCl_3$ extract was recrystallized from cyclohexane to give colorless needles, mp 105—107 °C. Yield 1.2 g (67%). IR ($CHCl_3$) cm^{-1}: 3500, 3360, 2200, 1665. ^1H-NMR ($CDCl_3$): 0.96 (3H, t, J=7.0 Hz), 1.2—2.0 (4H, m), 2.47 (2H, t, J=7.0 Hz), 6.6 (2H, br s), 7.3—7.8 (3H, m), 7.9—8.2 (1H, m). *Anal.* Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.86; H, 7.27; N, 6.82.

***o*-Phenylethynylbenzoic Acid (12)**——A mixture of ethyl *o*-phenylethynylbenzoate (**3a**) (1.25 g, 5 mmol), KOH (500 mg, 9 mmol), and 50% aq. EtOH (20 ml) was refluxed for 6 h. After removal of the solvent, the residue was diluted with H_2O and washed with $CHCl_3$. The aqueous layer was acidified with 3 N HCl and extracted with $CHCl_3$. The $CHCl_3$ extract was purified by SiO_2 column chromatography using $CHCl_3$–ether (9 : 1) as an eluent. The product obtained from the $CHCl_3$–ether (9 : 1) eluate was recrystallized from hexane–$CHCl_3$ to give colorless prisms, mp 126—127 °C. Yield 900 mg (80%). IR ($CHCl_3$) cm^{-1}: 2200, 1700. ^1H-NMR ($CDCl_3$): 7.2—8.1 (9H, m), 11.5 (1H, br s). *Anal.* Calcd for $C_{15}H_{10}O$: C, 81.06; H, 4.54. Found: C, 80.87; H, 4.43.

Synthesis of 3-Substituted Isocoumarins: General Procedure C——A mixture of an *o*-ethynylbenzoic acid (4 mmol), $HgSO_4$ (4 mmol), conc. H_2SO_4 (8 mmol), and 80% aq. acetone (50 ml) was refluxed for 48 h. After removal of the solvent, the residue was diluted with H_2O and extracted with $CHCl_3$. The product obtained from the $CHCl_3$ extract was purified by SiO_2 column chromatography using hexane–ether (9 : 1) as an eluent and by subsequent recrystallization from hexane or hexane–ether to give colorless needles or plates.

Isocoumarin (13d)——A mixture of *o*-(2-ethoxyethenyl)benzonitrile (**14**)[6)] (340 mg, 2 mmol), and 48% HBr (15 ml) was stirred at room temperature for 84 h. The reaction mixture was diluted with H_2O and extracted with ether. The crude product obtained from the ethereal extract was distilled under reduced pressure to give a colorless liquid, bp 130 °C (3 mmHg), which was solidified at room temperature, mp 44—46 °C (lit.[11)] mp 45—46 °C). Yield 70 mg (24%). IR ($CHCl_3$) cm^{-1}: 1730. ^1H-NMR ($CDCl_3$): 6.45 (1H, d, J=6.0 Hz), 7.1—7.8 (4H, m), 8.2—8.4 (1H, m).

Ethyl *o*-Acetylbenzoate (15)——The crude product was obtained according to general procedure C from ethyl *o*-(trimethylsilylethynyl)benzoate (**3d**) (980 mg, 4 mmol), and was distilled under reduced pressure to give a colorless liquid, bp 120 °C (3 mmHg) (lit.[12)] bp 279 °C). Yield 470 mg (62%). ^1H-NMR (CCl_4): 1.33 (3H, t, J=7.0 Hz), 2.40 (3H, s), 4.28 (2H, q, J=7.0 Hz), 7.2—7.9 (4H, m).

Reaction of 11a with $HgSO_4$–H_2SO_4——The crude product was obtained according to general procedure C from **11a** (880 mg, 4 mmol), and was purified by SiO_2 column chromatography using hexane–C_6H_6 (3 : 1) as an eluent. The first eluate gave 3-benzylidenephthalide (**17a**) (lit.[13)] mp 100—101 °C) as colorless needles (mp 95—97 °C), which were recrystallized from hexane. Yield 380 mg (43%). IR ($CHCl_3$) cm^{-1}: 1770. ^1H-NMR ($CDCl_3$): 6.32 (1H, s), 7.2—8.0 (9H, m). The second eluate gave colorless needles (**13a**). Yield 250 mg (28%).

Reaction of 11b with $HgSO_4$–H_2SO_4——The crude product was obtained according to general procedure C from **11b** (800 mg, 4 mmol), and was purified by SiO_2 column chromatography using hexane–C_6H_6 (4 : 1) as an eluent.

The first eluate gave 3-pentylidenephthalide (**17b**) (lit.[14] bp 158—160 °C (4 mmHg)) as a colorless liquid (bp 150 °C (3 mmHg)). Yield 130 mg (16%). IR ($CHCl_3$) cm^{-1}: 1775. ^1H-NMR (CCl_4): 0.7—2.7 (9H, m), 5.50 (1H, t, J=8.0 Hz), 7.1—8.3 (4H, m). The second eluate gave colorless plates (**13b**). Yield 360 mg (45%).

Synthesis of Isoquinolone (18): General Procedure D——An EtOH solution of an isocoumarin (2 mmol) was saturated with NH_3 gas, and the mixture was heated in a sealed tube at 130 °C for 4 h. After removal of the EtOH, the residue was recrystallized.

3-Phenyl-1(2*H*)-isoquinolone (**18a**): Colorless needles (EtOH), mp 198—200 °C (lit.[15] mp 197 °C). Yield 91%. IR ($CHCl_3$) cm^{-1}: 3380, 1650. ^1H-NMR ($CDCl_3$): 6.75 (1H, s), 7.3—7.9 (8H, m), 8.3—8.6 (1H, m), 10.7 (1H, br s).

3-Butyl-1(2*H*)-isoquinolone (**18b**): Colorless prisms (hexane–acetone), mp 140—142 °C (lit.[15] mp 139—140 °C). Yield 89%. IR ($CHCl_3$) cm^{-1}: 3400, 1660. ^1H-NMR ($CDCl_3$): 0.96 (3H, t, J=7.0 Hz), 1.2—2.2 (4H, m), 2.66 (2H, t, J=7.0 Hz), 6.30 (1H, s), 7.3—7.9 (3H, m), 8.3—8.6 (1H, m), 11.9 (1H, br s).

3-Methyl-1(2*H*)-isoquinolone (**18c**): Colorless needles (hexane–acetone), mp 210—212 °C (lit.[16] mp 211 °C). Yield 75%. IR ($CHCl_3$) cm^{-1}: 3380, 1650. ^1H-NMR ($CDCl_3$): 2.30 (3H, s), 6.20 (1H, s), 7.3—7.7 (3H, m), 8.3—8.6 (1H, m), 11.8 (1H, br s).

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