FULL PAPER

A Convenient Synthesis of 1-Alkoxy-2-alkyl-1,2-dihydroisoquinoline-3,4-diones Utilizing the Reaction of 2-(Dialkoxymethyl)phenyllithiums with Dimethyl Oxalate

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A new and convenient method for the preparation of 1,2-dihydroisoquinoline-3,4-diones with alkoxy and alkyl groups at the 4- and 3-positions, respectively, using an easily operated three-step sequence starting from 2-(dialkoxymethyl)phenyl bromides has been developed. Thus, the starting materials are treated with BuLi to generate 2-(dialkoxymethyl)phenyllithiums, which are allowed to react with $(COOMe)_2$ to give methyl 2-(dialkoxymethyl)phenyl-2-oxoacetates. These are then transformed into the corresponding secondary amides by the reaction with primary amines. Treatment of these keto amides with a catalytic amount of $TsOH \cdot H_2O$ affords the desired products. In order to demonstrate the synthetic utility of these products, transformation of one of them into the corresponding isoquinoline-1,3,4(2*H*)-trione derivative by the oxidation with PCC was achieved.

Introduction. – Some biologically active compounds including the 1,2-dihydroisoquinoline-3,4-dione structure have been isolated from nature [1]. However, only a few methods for the synthesis of 1,2-dihydroisoquinoline-3,4-dione derivatives have been reported. A synthesis of 1,2-dihydro-1,6,7-trimethoxy-2-methylisoquinoline-3,4-dione by the oxidation of 1,2-dihydro-6,7-dimethoxy-2-methylisoquinolin-4(3*H*)-one with $NaIO_4$ has been reported by *Möhre* and *Rohn* [2]. *Quevedo et al.* have reported the formation of 1,2-dihydro-6,7-dimethoxyisoquinoline-3,4-dione by the reaction of 2-(3,4-dimethoxyphenyl)methanamine with $(COOH)_2$ in the presence of dicyclohexyl carbodiimide (DCC) [3]. On the other hand, we have recently reported that 2-(1,1-alkoxyalkyl)phenyllithiums, easily generated by the Br/Li exchange between 2-(1,1-alkoxyalkyl)phenyl bromides and BuLi, undergo reactions with various electrophiles to provide the corresponding precursors for the facile preparation of useful benzene-fused heterocyclic derivatives [4]. We envisaged that 1-alkoxy-2-alkyl-1,2-dihydroisoquinoline-3,4-diones **5** would be obtained by acid-catalyzed cyclization of *N*-alkyl-2-[2-(dialkoxymethyl)phenyl]-2-oxoacetamides **3**, which could be derived from the reaction of these lithium compounds with $(COOMe)_2$, followed by treatment of the resulting methyl 2-[2-(dialkoxymethyl)phenyl]-2-oxoacetates **2** with primary amines. In this article, we wish to demonstrate results of our study, which provide a novel and convenient access to this type of isoquinoline derivatives. Transformation of one of these products into an isoquinoline-1,3,4(2*H*)-trione derivative is also described. Isoquinoline-1,3,4(2*H*)-trione derivatives are biologically [5] as well as synthetically [6] important. This class of heterocycles has commonly been prepared by oxidation of 3,4-dihydroisoquinolin-1(2*H*)-ones [7], though the methods starting from 1*H*-indene-1,2,3-trione [8] or 2,2-dihydroxy-1*H*-indene-1,3(2*H*)-dione [9] have recently been reported.

Results and Discussion. – Our synthesis of **5** from 2-(dialkoxymethyl)phenyl bromides **1** was conducted according to the sequence outlined in *Scheme 1*. One of the compounds **1** was commercially available, and the others were easily prepared from the respective 2-bromobenzaldehydes as described in [10 – 12]. As the first step of our sequence, 2-(dialkoxymethyl)phenyllithiums were generated by the Br/Li exchange between **1** and BuLi in THF at $-78°$ and allowed to react with $(COOMe)_2$. The reactions performed well to result in the formation of the corresponding keto esters **2** in relatively good yields. The keto esters **2** were then transformed into keto amides **3**. This transformation was easily carried out by reacting **2** with primary amines in THF at room temperature. The yields were generally good as summarized in the *Table*.

These keto amides **3**, thus obtained, were subjected to the treatment with a catalytic amount of $TsOH \cdot H_2O$ in refluxing CH_2Cl_2. They rearranged to the desired products **5** *via* the diastereomeric intermediates **4**. The ^{1}H-NMR spectra of the solutions during the reactions revealed that they were mixtures of the starting materials **3**, the intermediates **4**, and the desired products **5**. Heating was continued until no signals due to the benzyl H-atoms of **3** and **4** were observed anymore (see the *Table*). After aqueous workup and the subsequent column chromatography over SiO_2, the desired products **5** were isolated in the yields compiled in the *Table*. They were moderate to good. The reaction times are summarized as well. As indicated by these results, the precursors derived from methyl [2-(diethoxymethyl)phenyl](oxo)acetate (**2b**; *e.g.*, **3e** and **3f**)

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Scheme 1

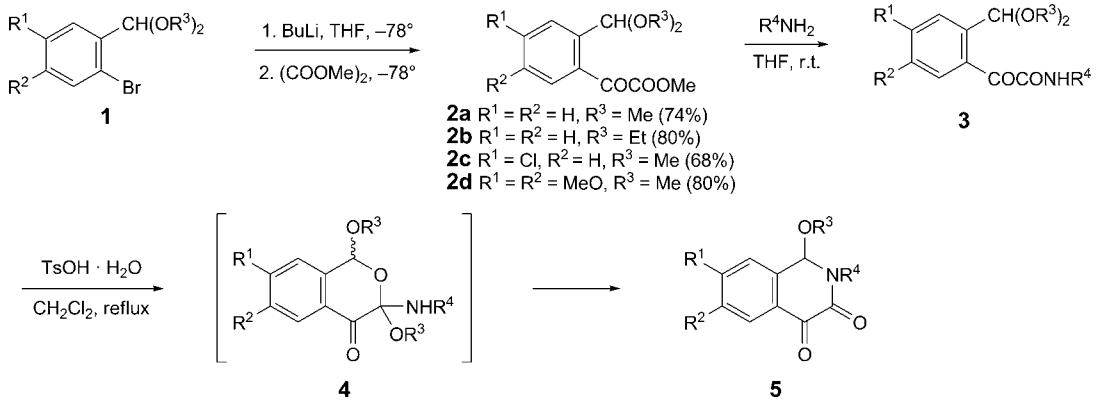


Table. *Preparation of 1,2-Dihydroisoquinoline-3,4-diones* **5**

Entry	**2**	R^4 in R^4NH_2	**3**	Yield [%][a])	**5**	Time [h]	Yield [%][a])
1	**2a** ($R^1 = R^2 = H$, $R^3 = Me$)	Me	**3a**	87	**5a**	24	86
2	**2a**	Pr	**3b**	80	**5b**	24	70
3	**2a**	Bn	**3c**	95	**5c**	24	69
4	**2a**	Cyclohexyl	**3d**	69	**5d**	48	48
5	**2b** ($R^1 = R^2 = H$, $R^3 = Et$)	$MeO–(CH_2)_2$	**3e**	79	**5e**	12	76
6	**2b**	$4\text{-}MeO–C_6H_4CH_2$	**3f**	84	**5f**	12	86
7	**2c** ($R^1 = Cl$, $R^2 = H$, $R^3 = Me$)	Me	**3g**	96	**5g**	72	47
8	**2d** ($R^1 = R^2 = MeO$, $R^3 = Me$)	Me	**3h**	77	**5h**	6	59
9	**2d**	Bu	**3i**	76	**5i**	6	57
10	**2d**	^{i}Bu	**3j**	95	**5j**	6	52

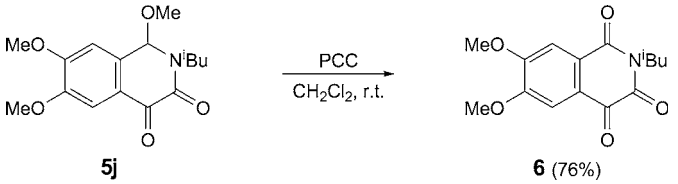
[a]) Yields of isolated products.

underwent rearrangement to the corresponding products **5e** and **5f** more smoothly than those derived from methyl [2-(dimethoxymethyl)phenyl](oxo)acetate (**2a**; *e.g.* **3a**–**3c**), though the yields were comparable (*Entries 1–3*, *5*, and *6*). This may be attributable to the release from the crowdedness of the *o*-diethoxymethyl moiety. The yield of the product **3d** carrying a rather bulky cyclohexyl substituent was only moderate (*Entry 4*). As can be seen from *Entry 7*, the precursor derived from methyl [4-chloro-2-(dimethoxymethyl)phenyl](oxo)acetate (**2c**; *e.g.* **3g**) took much time for the rearrangement, and the yield of the product was also only moderate. This may be ascribed to the smaller stability of the benzyl cation due to the chloro substituent on the benzene ring. On the other side, the rearrangement of **3h**–**3j** to **5h**–**5j** completed shortly. This may be rationalized by the stability of the benzyl cations due to the MeO substituents on the benzene ring. Unfortunately, however, the yields of the products **3h**–**3j** were moderate-to-fair, probably due to the lability of the products under reaction conditions.

In order to demonstrate the utility of 1-alkoxy-1,2-dihydroisoquinoline-3,4-dione derivatives **5** in synthesis, transformation of one of them into the corresponding isoquinoline-1,3,4(2*H*)-trione derivative was examined. Thus, PCC oxidation of **5j** in CH_2Cl_2 proceeded smoothly at room temperature, and the desired product **6** was obtained in good yield as shown in *Scheme 2*. The oxidation of cyclic acetals to the corresponding lactones with PCC has recently been reported [4d][13]

In conclusion, an efficient method for the preparation of 1-alkoxy-2-alkyl-1,2-dihydroisoquinoline-3,4-diones from 2-(dialkoxymethyl)phenyl bromides has been developed. The method commences with the reaction of 2-(dimethoxymethyl)phenyllithiums with dimethyl oxalate giving the corresponding methyl 2-[2-(dialkoxymethyl)-phenyl]-2-oxoacetates and these are converted into the

Scheme 2



desired products by a two-step sequence under mild conditions. Transformation of one of the products into the corresponding isoquinoline-1,3,4(2*H*)-trione derivative by oxidation with PCC under mild conditions has also been demonstrated. The present method may be of use in organic synthesis because of the ease of operations as well as the good availability of the starting materials, and it may offer the possibility to access compounds of potential biological interest.

Experimental Part

General. All org. solvents used in this study were dried over appropriate drying agents and distilled prior to use. TLC: *Merck* silica gel *60 PF_{254}*. Column chromatography (CC): *Wako Gel C-200E*. M.p.: *Laboratory Devices MEL-TEMP II* melting-point apparatus; uncorrected. IR Spectra: *Perkin Elmer Spectrum65* FT-IR spectrophotometer; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *JEOL ECP500* FT-NMR spectrometer (at 500 and 125 MHz, resp.), in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. HR-MS: *Thermo Scientific Exactive* (DART or ESI, pos.) or *JEOL JMS-T100GCV* (EI, TOF; 70 eV) spectrometer; in *m*/*z*. Elemental analyses: *Elementar Vario EL II* instrument.

1-Bromo-2-(dimethoxymethyl)benzene (**1a**) [10], *1-bromo-4-chloro-2-(dimethoxymethyl)benzene* (**1b**) [11], and *methyl 2-[2-(dimethoxymethyl)-4,5-dimethoxyphenyl]-2-oxoacetate* (**2d**) [4d] were prepared according to the appropriate reported procedures. BuLi was supplied by *Asia Lithium Corporation*. All other chemicals used in this study were commercially available.

Methyl 2-[2-(Dialkoxymethyl)phenyl]-2-oxoacetates **2** were prepared from 1-bromo-2-(dialkoxymethyl)benzenes and dimethyl oxalate as described for the preparation of **2d** [4d]. The physical, spectral, and analytical data for the new compounds follow.

Methyl [2-(Dimethoxymethyl)phenyl](oxo)acetate (**2a**). Yield: 62%. Pale-yellow solid. M.p. 44 – 45° (hexane/CH_2Cl_2). IR (KBr): 1736, 1711, 1600. ^1H-NMR: 3.25 (*s*, 6 H); 3.92 (*s*, 3 H); 5.66 (*s*, 1 H); 7.44 (*ddd*, *J* = 7.6, 6.1, 2.3, 1 H); 7.50 (*d*, *J* = 7.6, 1 H); 7.54 – 7.56 (*m*, 2 H). Anal. calc. for $C_{12}H_{14}O_5$ (238.24): C 60.50, H 5.92; found: C 60.28, H 5.95.

Methyl [2-(Diethoxymethyl)phenyl](oxo)acetate (**2b**). Yield: 80%. Pale-yellow oil. R_f (AcOEt/hexane 1:7) 0.29. IR (neat): 1737, 1713, 1601. ^1H-NMR: 1.21 (*t*, *J* = 6.9, 6 H); 3.45 – 3.51 (*m*, 2 H); 3.52 – 3.58 (*m*, 2 H); 3.92 (*s*, 3 H); 5.79 (*s*, 1 H); 7.43 (*td*, *J* = 7.6, 1.5, 1 H); 7.49 (*d*, *J* = 7.6, 1 H); 7.55 (*td*, *J* = 7.6, 1.6, 1 H); 7.60 (*d*, *J* = 7.6, 1 H). Anal. calc. for $C_{14}H_{18}O_5$ (266.29): C 63.15, H 6.81; found: C 63.12, H 7.04.

Methyl [4-Chloro-2-(dimethoxymethyl)phenyl](oxo)acetate (**2c**). Yield: 68%. White solid. M.p. 68 – 70° (hexane). IR (KBr): 1732, 1717. ^1H-NMR: 3.25 (*s*, 6 H); 3.93 (*s*, 3 H); 5.63 (*s*, 1 H); 7.42 (*dd*, *J* = 8.0, 1.7, 1 H); 7.46 (*d*, *J* = 8.0, 1 H); 7.55 (br. *s*, 1 H). Anal. calc. for $C_{12}H_{13}ClO_5$ (272.68): C 52.86, H 4.81; found: C 52.64, H 4.91.

2-[2-(Dimethoxymethyl)phenyl]-N-*methyl-2-oxoacetamide* (**3a**). *Representative Procedure.* To a stirred soln. of **2a** (0.31 g, 1.3 mmol) in THF (4 ml) was added $MeNH_2$ (9.8M in MeOH; 1.3 mmol). The mixture was stirred at the same temp. for 2 h. After evaporation of the solvent, the residue was purified by CC (SiO_2) to afford **3a** (0.27 g, 87%) as a white solid. M.p. 104 – 105° (hexane/CH_2Cl_2). IR (KBr): 3312, 1685, 1669, 1601. ^1H-NMR: 2.97 (*d*, *J* = 5.4, 3 H); 3.23 (*s*, 6 H); 5.78 (*s*, 1 H); 7.12 (br., 1 H); 7.41 – 7.43 (*m*, 2 H); 7.51 – 7.54 (*m*, 2 H). Anal. calc. for $C_{12}H_{15}NO_4$ (237.25): C 60.75, H 6.37, N 5.90; found: C 60.79, H 6.35, N 5.87.

2-[2-(Dimethoxymethyl)phenyl]-2-oxo-N-*propylacetamide* (**3b**). Pale-yellow oil. R_f (AcOEt/hexane 1:2) 0.22. IR (neat): 3331, 1678, 1601. ^1H-NMR: 0.99 (*t*, *J* = 7.4, 3 H); 1.60 – 1.68 (*m*, 2 H); 3.23 (*s*, 6 H); 3.32 – 3.36 (*m*, 2 H); 5.78 (*s*, 1 H); 7.13 (br., 1 H); 7.40 – 7.43 (*m*, 2 H); 7.50 – 7.54 (*m*, 2 H). HR-ESI-MS: 288.1205 ($[M + Na]^+$, $C_{14}H_{19}NNaO_4^+$; calc. 288.1212).

2-[2-(Dimethoxymethyl)phenyl]-2-oxo-N-*(phenylmethyl)acetamide* (**3c**). Pale-yellow oil. R_f (AcOEt/hexane 1:4) 0.28. IR (neat): 3332, 1679, 1601. ^1H-NMR: 3.20 (*s*, 6 H); 4.55 (*d*, *J* = 6.1, 2 H); 5.79 (*s*, 1 H); 7.29 – 7.38 (*m*, 5 H); 7.40 – 7.44 (*m*, 3 H); 7.50 – 7.55 (*m*, 2 H). Anal. calc. for $C_{18}H_{19}NO_4$ (313.35): C 68.99, H 6.11, N 4.47; found: C 60.79, H 6.35, N 4.46.

N-*Cyclohexyl-2-[2-(dimethoxymethyl)phenyl]-2-oxoacetamide* (**3d**). White solid. M.p. 79 – 81° (hexane). IR (KBr): 3312, 1678, 1603. ^1H-NMR: 1.22 – 1.32 (*m*, 3 H); 1.34 – 1.44 (*m*, 2 H); 1.64 – 1.66 (*m*, 1 H); 1.75 – 1.78 (*m*, 2 H); 1.97 – 1.99 (*m*, 2 H); 3.24 (*s*, 6 H); 3.78 – 3.79 (*m*, 1 H); 5.77 (*s*, 1 H); 7.01 (br. *s*, 1 H); 7.40 – 7.42 (*m*, 2 H), 7.50 – 7.52 (*m*, 2 H). HR-ESI-MS: 328.1518 ($[M + Na]^+$, $C_{17}H_{23}NNaO_4^+$; calc. 328.1525).

2-[2-(Diethoxymethyl)phenyl]-N-*(2-methoxyethyl)-2-oxoacetamide* (**3e**). Colorless oil. R_f (AcOEt/hexane 1:2) 0.34. IR (neat): 3336, 1683, 1600. ^1H-NMR: 1.19 (*t*, *J* = 6.9, 6 H); 3.39 (*s*, 3 H); 3.40 – 3.57 (*m*, 8 H); 5.89 (*s*, 1 H); 7.38 – 7.43 (*m*, 2 H); 7.45 (br., 1 H); 7.51 (*td*, *J* = 7.6, 1.5, 1 H); 7.58 (*d*, *J* = 7.6, 1 H). Anal. calc. for $C_{16}H_{23}NO_5$ (309.36): C 62.12, H 7.49, N 4.53; found: C 62.96, H 7.57, N 4.39.

2-[2-(Diethoxymethyl)phenyl]-N-*[(4-methoxyphenyl)methyl]-2-oxoacetamide* (**3f**). Pale-yellow oil. R_f (AcOEt/hexane 1:3) 0.34. IR (neat): 3371, 1679, 1613. ^1H-NMR: 1.15 (*t*, *J* = 6.9, 6 H); 3.42 – 3.54 (*m*, 4 H); 3.82 (*s*, 3 H); 4.47 (*d*, *J* = 5.4, 2 H); 5.92 (*s*, 1 H); 6.89 (*d*, *J* = 8.4, 2 H); 7.28 (*d*, *J* = 8.4, 2 H); 7.35 (br., 1 H); 7.40 (*t*, *J* = 7.6, 1 H); 7.42 (*d*, *J* = 7.6, 1 H); 7.52 (*td*, *J* = 7.6, 1.5, 1 H); 7.59 (*d*, *J* = 7.6, 1 H). Anal. calc. for $C_{21}H_{25}NO_5$ (371.43): C 67.91, H 6.78, N 3.77; found: C 67.61, H 6.85, N 3.70.

2-[4-Chloro-2-(dimethoxymethyl)phenyl]-N-*methyl-2-oxoacetamide* (**3g**). White solid. M.p. 100 – 102° (hexane/CH_2Cl_2). IR (KBr): 3329, 1690, 1670. ^1H-NMR: 2.96 (*d*, *J* = 5.2, 3 H); 3.23 (*s*, 6 H); 5.75 (*s*, 1 H); 7.08 (br., 1 H); 7.38 (br. *s*, 2 H); 7.55 (*s*, 1 H). Anal. calc. for $C_{12}H_{14}ClNO_4$ (271.70): C 53.05, H 5.19, N 5.16; found: C 53.06, H 5.21, N 5.13.

2-[2-(Dimethoxymethyl)-4,5-dimethoxyphenyl]-N-*methyl-2-oxoacetamide* (**3h**). White solid. M.p. 113 – 115° (hexane/CH_2Cl_2). IR (KBr) 3426, 1698, 1678. ^1H-NMR: 2.97 (*d*, *J* = 5.2, 3 H); 3.24 (*s*, 6 H); 3.90 (*s*, 3 H); 3.95 (*s*, 3 H); 5.78 (*s*, 1 H); 7.09 (*s*, 1 H); 7.10 (*s*, 1 H); 7.12 (br. *s*, 1 H). Anal. calc. for $C_{14}H_{19}NO_6$ (297.30): C 56.56, H 6.44, N 4.71; found: C 56.43, H 6.49, N 4.57.

N-*Butyl-2-[2-(dimethoxymethyl)-4,5-dimethoxyphenyl]-2-oxoacetamide* (**3i**). Yellow oil. R_f (AcOEt/CH_2Cl_2 1:10) 0.36. IR (neat): 3353, 1674, 1602. ^1H-NMR: 0.96 (*t*, *J* = 7.4, 3 H); 1.39 – 1.44 (*m*, 2 H); 1.57 – 1.61 (*m*, 2 H); 3.24 (*s*, 6 H); 3.37 (*q*, *J* = 6.9, 2 H); 3.90 (*s*, 3 H); 3.95 (*s*, 3 H); 5.78 (*s*, 1 H); 7.07 (br. *s*, 1 H); 7.09 (*s*, 1 H); 7.11 (*s*, 1 H). Anal. calc. for $C_{17}H_{25}NO_6$ (339.38): C 60.16, H 7.42, N 4.13; found: C 60.12, H 7.38, N 4.03.

2-[2-(Dimethoxymethyl)-4,5-dimethoxyphenyl]-N-*(2-methylpropyl)-2-oxoacetamide* (**3j**). Yellow oil. R_f (AcOEt/hexane 1:2) 0.37. IR (neat): 3354, 1676, 1602. ^1H-NMR: 0.99 (*d*, *J* = 6.9, 6 H); 1.84 – 1.92 (*m*, 1 H); 3.21 (*dd*, *J* = 6.9, 4.5, 2 H); 3.24 (*s*, 6 H); 3.90 (*s*, 3 H); 3.95 (*s*, 3 H); 5.78 (*s*, 1 H); 7.09 (*s*, 1 H); 7.12 (*s*, 1 H); 7.13 (br. *s*, 1 H). Anal. calc. for $C_{17}H_{25}NO_6$ (339.38): C 60.16, H 7.42, N 4.13; found: C 60.11, H 7.45, N 3.87.

1,2-Dihydro-1-methoxy-2-methylisoquinoline-3,4-dione (**5a**). *Representative Procedure.* A soln. of **3a** (0.26 g, 1.1 mmol) in CH_2Cl_2 (7 ml) containing $TsOH \cdot H_2O$ (11 mg, 0.055 mmol) was heated at reflux temp. until ^1H-NMR spectroscopy of the mixture revealed disappearance of the signals due to **3a** and the intermediate **4a** (about 1 d). After cooling to r.t., sat. aq. $NaHCO_3$ (15 ml) and then CH_2Cl_2 (10 ml) were added. The layers were separated and the aq. layer was extracted with CH_2Cl_2 (2 × 10 ml). The combined org. layers were washed with brine (15 ml), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by CC (SiO_2; AcOEt/hexane 1:1) to give **5a** (0.19 g, 86%). Pale-yellow solid. M.p. 100 – 102° (hexane/CH_2Cl_2). IR (KBr): 1706, 1674, 1604. ^1H-NMR: 2.92 (*s*, 3 H); 3.28 (*s*, 3 H); 5.95 (*s*, 1 H); 7.61 (*t*,

J = 7.6, 1 H); 7.62 (*d*, J = 7.6, 1 H); 7.79 (*td*, J = 7.6, 1.5, 1 H); 8.18 (*d*, J = 7.6, 1 H). ^{13}C-NMR: 32.17; 48.75; 85.66; 127.62; 127.75; 130.12; 130.91; 135.20; 136.99; 158.05; 176.62. HR-MS (DART): 206.0810 ([M + H]$^+$, $C_{11}H_{12}NO_3^+$; calc. 206.0817). Anal. calc. for $C_{11}H_{11}NO_3$ (205.21): C 64.38, H 5.40, N 6.83; found: C 64.29, H 5.30, N 6.98.

1,2-Dihydro-1-methoxy-2-propylisoquinoline-3,4-dione (**5b**). Pale-yellow solid. M.p. 138 – 140° (hexane/CH_2Cl_2). IR (neat): 1706, 1679, 1603. ^{1}H-NMR: 0.99 (*t*, J = 7.4, 3 H); 1.73 – 1.79 (*m*, 2 H); 2.90 (*s*, 3 H); 3.36 – 3.42 (*m*, 1 H); 3.89 – 3.95 (*m*, 1 H); 5.99 (*s*, 1 H); 7.58 – 7.61 (*m*, 2 H); 7.77 (*td*, J = 7.4, 1.1, 1 H); 8.16 (*dd*, J = 7.4, 2.3, 1 H). ^{13}C-NMR: 11.43; 20.30; 46.35; 48.90; 84.13; 127.54; 127.87; 130.05; 131.09; 135.08; 137.06; 157.83; 177.07. HR-EI-MS: 233.1056 (M^+, $C_{13}H_{15}NO_3^+$; calc. 233.1052). Anal. calc. for $C_{13}H_{15}NO_3$ (233.26): C 66.94, H 6.48, N 6.00; found: C 66.82, H 6.73, N 5.99.

1,2-Dihydro-1-methoxy-2-(phenylmethyl)isoquinoline-3,4-dione (**5c**). Pale-yellow solid. M.p. 122 – 123° (hexane/CH_2Cl_2). IR (KBr): 1705, 1681, 1602. ^{1}H-NMR: 2.91 (*s*, 3 H); 4.34 (*d*, J = 14.5, 1 H); 5.57 (*d*, J = 14.5, 1 H); 5.86 (*s*, 1 H), 7.27 – 7.36 (*m*, 3 H); 7.42 (*d*, J = 6.9, 2 H); 7.52 (*d*, J = 7.6, 1 H); 7.58 (*t*, J = 7.6, 1 H); 7.73 (*td*, J = 7.6, 1.5, 1 H); 8.17 (*d*, J = 7.6, 1 H). ^{13}C-NMR: 46.47; 48.89; 82.55; 127.60; 128.00; 128.08; 128.81; 129.11; 130.08; 130.95; 135.19; 135.50; 136.98; 157.87; 176.90. HR-ESI-MS: 282.1127 ([M + H]$^+$, $C_{17}H_{16}NO_3^+$; calc. 282.1130). Anal. calc. for $C_{17}H_{15}NO_3$ (281.31): C 72.58, H 5.37, N 4.98; found: C 72.45, H 5.45, N 4.89.

2-Cyclohexyl-1,2-dihydro-1-methoxyisoquinoline-3,4-dione (**5d**). Pale-yellow solid. M.p. 164 – 166° (hexane/CH_2Cl_2). IR (KBr): 1706, 1673, 1602. ^{1}H-NMR: 1.21 – 1.28 (*m*, 1 H); 1.38 – 1.48 (*m*, 2 H); 1.71 – 1.98 (*m*, 7 H); 2.88 (*s*, 3 H); 4.22 – 4.27 (*m*, 1 H); 6.03 (*s*, 1 H); 7.53 (*d*, J = 8.0, 1 H); 7.57 (*dd*, J = 8.0, 7.4, 1 H); 7.74 (*ddd*, J = 8.0, 7.4, 1.1, 1 H); 8.10 (*d*, J = 8.0, 1 H). ^{13}C-NMR: 25.47; 25.97; 26.01; 29.74; 30.34; 48.90; 56.72; 82.41; 127.42; 127.66; 129.90; 131.06; 134.92; 137.38; 158.02; 177.94. HR-EI-MS: 273.1375 (M^+, $C_{16}H_{19}NO_3^+$; calc. 273.1365). Anal. calc. for $C_{16}H_{19}NO_3$ (273.33): C 70.31, H 7.01, N 5.12; found: C 70.14, H 7.04, N 4.85.

1-Ethoxy-1,2-dihydro-2-(2-methoxyethyl)isoquinoline-3,4-dione (**5e**). Pale-yellow oil. R_f (AcOEt/hexane 1:1) 0.30. IR (KBr): 1706, 1682, 1603. ^{1}H-NMR: 1.10 (*t*, J = 6.9, 3 H); 2.93 – 2.98 (*m*, 1 H); 3.19 – 3.23 (*m*, 1 H); 3.33 (*s*, 3 H); 3.63 – 3.69 (*m*, 2 H); 3.74 – 3.80 (*m*, 1 H); 4.17 – 4.22 (*m*, 1 H); 6.20 (*s*, 1 H); 7.58 (*t*, J = 7.6, 1 H); 7.61 (*d*, J = 7.6, 1 H); 7.76 (*td*, J = 7.6, 1.5, 1 H); 8.16 (*d*, J = 7.6, 1 H). ^{13}C-NMR: 14.76; 43.53; 57.52; 58.91; 70.47; 84.88; 127.53; 127.85; 129.80; 130.78; 135.01; 138.08; 157.83; 177.10. HR-EI-MS: 263.1161 (M^+, $C_{14}H_{17}NO_4^+$; calc. 263.1158). Anal. calc. for $C_{14}H_{17}NO_4$ (263.29): C 63.87, H 6.51, N 5.32; found: C 63.83, H 6.59, N 5.07.

1-Ethoxy-1,2-dihydro-2-[(4-methoxyphenyl)methyl]isoquinoline-3,4-dione (**5f**). Pale-yellow oil. R_f (AcOEt/hexane 1:2) 0.25. IR (neat): 1705, 1679, 1603. ^{1}H-NMR: 1.09 (*t*, J = 6.9, 3 H); 2.89 – 2.95 (*m*, 1 H); 3.17 – 3.23 (*m*, 1 H); 3.79 (*s*, 3 H); 4.31 (*d*, J = 13.8, 1 H); 5.48 (*d*, J = 13.8, 1 H); 5.85 (*s*, 1 H); 6.87 (*d*, J = 8.4, 2 H); 7.37 (*d*, J = 8.4, 2 H); 7.53 (*d*, J = 8.4, 1 H); 7.56 (*dd*, J = 8.4, 7.6, 1 H); 7.72 (*dd*, J = 8.4, 7.6, 1 H); 8.14 (*d*, J = 8.4, 1 H). ^{13}C-NMR: 14.71; 46.34; 55.24; 57.23; 82.01; 114.07; 127.53; 127.65; 127.87; 129.89; 130.59; 130.67; 136.09; 137.73; 157.71; 159.33; 177.10. HR-MS (DART): 326.1388 ([M + H]$^+$, $C_{19}H_{20}NO_4^+$; calc. 326.1392). Anal. calc. for $C_{19}H_{19}NO_4$ (325.36): C 70.14, H 5.89, N 4.31; found: C 69.86, H 6.05, N 4.23.

7-Chloro-1,2-dihydro-1-methoxy-2-methylisoquinoline-3,4-dione (**5g**). Pale-yellow solid. M.p. 106 – 108° (hexane). IR (KBr): 1715, 1688. ^{1}H-NMR: 2.95 (*s*, 3 H); 3.26 (*s*, 3 H); 5.89 (*s*, 1 H); 7.57 (*dd*, J = 8.6, 1.7, 1 H); 7.60 (br. *s*, 1 H); 8.12 (*d*, J = 8.6, 1 H). ^{13}C-NMR: 32.20; 49.04; 85.20; 127.83; 129.30; 129.36; 130.85; 138.59; 142.18; 157.69; 175.62. HR-MS (DART): 240.0416 ([M + H]$^+$, $C_{11}H_{11}ClNO_3^+$; calc. 240.0427). Anal. calc. for $C_{11}H_{10}ClNO_3$ (239.66): C 55.13, H 4.21, N 5.84; found: C 55.05, H 4.25, N 5.78.

1,2-Dihydro-1,6,7-trimethoxy-2-methylisoquinoline-3,4-dione (**5h**). Yellow solid. M.p. 160 – 164° (dec.) ([2]: 164 – 166° (dec.). The spectral (IR and ^{1}H-NMR) data of this product were identical to those reported in [2].

2-Butyl-1,2-dihydro-1,6,7-trimethoxyisoquinoline-3,4-dione (**5i**). Yellow oil. R_f (AcOEt/hexane 2:1) 0.51. IR (neat): 1672. ^{1}H-NMR: 0.97 (*t*, J = 7.4, 3 H); 1.38 – 1.44 (*m*, 2 H); 1.67 – 1.73 (*m*, 2 H); 2.87 (*s*, 3 H); 3.35 – 3.41 (*m*, 1 H); 3.91 – 3.96 (*m*, 1 H); 3.98 (*s*, 3 H); 4.02 (*s*, 3 H); 5.93 (*s*, 1 H); 6.96 (*s*, 1 H); 7.53 (*s*, 1 H). ^{13}C-NMR: 13.80; 20.28; 29.02; 44.07; 48.25; 56.36; 56.50; 83.31; 107.73; 108.81; 124.97; 132.32; 150.57; 155.47; 157.86; 175.50. HR-MS (DART): 308.1491 ([M + H]$^+$, $C_{16}H_{22}NO_5^+$; calc. 308.1498). Anal. calc. for $C_{16}H_{21}NO_5$ (307.34): C 62.53, H 6.89, N 4.56; found: C 62.42, H 6.96, N 4.59.

1,2-Dihydro-1,6,7-trimethoxy-2-(2-methylpropyl)isoquinoline-3,4-dione (**5j**). White solid. M.p. 150 – 152° (hexane/AcOEt). IR (KBr): 1666. ^{1}H-NMR: 0.94 (*d*, J = 6.9, 3 H); 1.00 (*d*, J = 6.3, 3 H); 2.17 – 2.23 (*m*, 1 H); 2.87 (*s*, 3 H); 3.09 (*dd*, J = 13.2, 7.4, 1 H); 3.977 (*dd*, J = 13.2, 8.0, 1 H); 3.984 (*s*, 3 H); 4.02 (*s*, 3 H); 5.92 (*s*, 1 H); 6.95 (*s*, 1 H); 7.55 (*s*, 1 H). ^{13}C-NMR: 20.13; 20.36; 26.44; 48.30; 50.65; 56.35; 56.47; 83.67; 107.77; 108.96; 125.02; 132.21; 150.61; 155.44; 158.24; 175.50. HR-MS (DART): 308.1490 ([M + H]$^+$, $C_{16}H_{22}NO_5^+$; calc. 308.1498). Anal. calc. for $C_{16}H_{21}NO_5$ (307.34): C 62.53, H 6.89, N 4.56; found: C 62.47, H 6.83, N 4.52.

*6,7-Dimethoxy-2-(2-methylpropyl)isoquinoline-1,3,4(2*H*)-trione* (**6**). To a stirring mixture of **5j** (0.12 g, 0.38 mmol) and *Celite*® 545 (0.60 g) in CH_2Cl_2 (3 ml) at r.t. was added PCC (0.16 g, 0.76 mmol) in several portions. After 2 h, the mixture was filtered under reduced pressure and the filtrate was concentrated by evaporation. The residue was purified by CC (SiO_2; hexane/Et_2O 1:2) to afford **6** (85 mg, 76%). Yellow solid. M.p. 189 – 191° (hexane/Et_2O). IR (KBr): 1691, 1673. ^{1}H-NMR: 0.95 (*d*, J = 6.3, 6 H); 2.05 – 2.16 (*m*, 1 H); 3.90 (*d*, J = 6.9, 2 H); 4.04 (*s*, 3 H); 4.08 (*s*, 3 H); 7.58 (*s*, 1 H); 7.72 (*s*, 1 H). ^{13}C-NMR: 20.14; 27.26; 47.75; 56.71; 56.78; 108.22; 110.66; 124.91; 125.35; 153.85; 155.61; 157.69; 162.43; 173.44. HR-EI-MS: 291.1121 (M^+, $C_{15}H_{17}NO_5^+$; calc. 291.1107). Anal. calc. for $C_{15}H_{17}NO_5$ (291.30): C 61.85, H 5.88, N 4.81; found: C 61.58, H 5.61, N 4.75.

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