One-Pot Synthesis of 3-Alkoxy-2,3-dihydro-1*H*-isoindol-1-ones by the Reactions of 2-(Azidomethyl)benzoates with NaH

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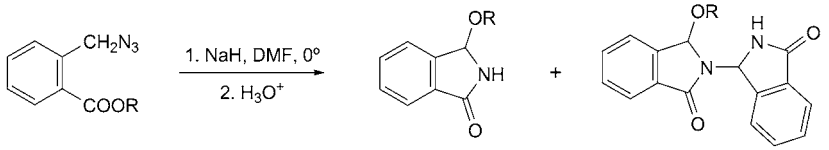
A new and facile method for the general preparation of 3-alkoxy-2,3-dihydro-1*H*-isoindol-1-ones has been developed. Thus, the reaction of 2-(azidomethyl)benzoates with NaH affords, after workup with H_2O, 3-alkoxy-2,3-dihydro-1*H*-isoindol-1-ones **2**. 2-Substituted 3-alkoxy-2,3-dihydro-1*H*-isoindol-1-ones **4** can be obtained by adding alkyl halides prior to workup with H_2O.

Introduction. – Recently, 3-alkoxy-2,3-dihydro-1*H*-isoindol-1-ones are attracting much attention, because this structure is present in a large number of molecules of pharmaceutical and biological interest [1]. Utilization of a 3-alkoxy-2,3-dihydro-1*H*-isoindol-1-one derivative as a precursor for the synthesis of an isoindoloisoquinoline derivative has also been demonstrated [2]. Accordingly, some new methods for the preparation of these derivatives have recently been developed [3], though the method by the reaction of 2-cyanobenzaldehyde with alcohols was reported by *Sato et al.* [4]. For example, a synthesis of 3-alkoxy-2-alkyl-2,3-dihydro-1*H*-isoindol-1-ones by the reaction of 2-alkylphthalimides with *Grignard* reagents followed by the addition of alkyl halides has been reported by *Jayawardena et al.* [3a], and *Dennis et al.* have reported a synthesis of 3-alkoxy-2-aryl-2,3-dihydro-1*H*-isoindol-1-ones by the reaction of 2-arylphthalimides with Et_2Zn followed by the treatment with an alcohol under acidic conditions [3b]. We therefore embarked on the research on developing a novel and facile methodology for the preparation of 3-alkoxy-2,3-dihydro-1*H*-isoindol-1-ones **2**. In this article, we describe a one-pot synthesis of **2** and 3-alkoxy-2-alkyl-2,3-dihydro-1*H*-isoindol-1-ones **4** from 2-(azidomethyl)benzoates **1**.

Results and Discussion. – *Scheme 1* illustrates the initial attempts at preparing 3-alkoxy-2,3-dihydro-1*H*-isoindol-1-ones **2a** and **2b** from 2-(azidomethyl)benzoates **1a** and **1b**, respectively. Treatment of methyl 2-(azidomethyl)benzoate (**1a**) with NaH in DMF at 0° resulted in immediate consumption of the starting material to give the desired 3-methoxy-2,3-dihydro-1*H*-isoindol-1-one (**2a**) in 24% yield along with 3′-methoxy-1*H*-1,2′-biisoindole-1′,3(2*H*,3′*H*)-dione (**3a**; 26%). The reaction of ethyl 2-(azidomethyl)benzoate (**1b**) under the same conditions also led to the isolation of 19% of 3-ethoxy-2,3-dihydro-1*H*-isoindol-1-one (**2b**) along with 3′-ethoxy-1*H*-1,2′-biisoindole-1′,3(2*H*,3′*H*)-dione (**3b**; 21%), as anticipated.

We then conducted the treatment of **1a** and **1b** in THF in place of DMF. Fortunately, exclusive formation of **2a** and **2b** was achieved in satisfactory yields as

Scheme 1



1a R = Me
1b R = Et

2a R = Me (24%)
2b R = Et (19%)

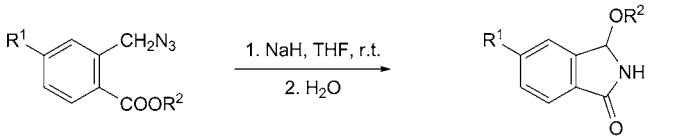
3a R = Me (26%)
3b R = Et (21%)

illustrated in *Scheme 2*. The starting materials were consumed gradually at room temperature, and the desired products were obtained after workup with H_2O followed by purification using column chromatography on SiO_2. Methyl 2-(azidomethyl)-4-chlorobenzoate (**1c**) was similarly treated with NaH. Unfortunately, however, the corresponding desired product 5-chloro-2,3-dihydro-3-methoxy-1*H*-isoindol-1-one (**2c**) could be isolated from a rather complex reaction mixture of products only in lower yield than those of **2a** and **2b**, though the reason for this is unclear yet.

Thereafter, we tried to introduce a substituent to the 2-position of the products. Thus, after treatment of **1** with NaH in THF as described above, alkyl halides were added prior to workup with H_2O to afford 3-alkoxy-2-alkyl-2,3-dihydro-1*H*-isoindol-1-ones **4**, as shown in *Scheme 3*. The yields of the products were compiled in the *Table*. These results indicate that the *N*-alkylation of the intermediate from **1a** (*Entries 1–5*) took place cleanlier than that from **1b** (*Entries 6–10*). This is probably due to the difference of the steric bulkiness between MeO and EtO substituents. We found that a non-activated haloalkane, such as BuBr, could work well to give the corresponding product **4b**, but in somewhat diminished yield (*Entry 2*). *Entries 11* and *12* indicate a considerable decrease in the yields of the products from **1c**. This is predictable from the low yield of **2c**.

The formation of **4** from **1** is thought to proceed as shown in *Scheme 4*. Treatment of **1** with NaH generates the corresponding benzyl anion intermediates **5**, which upon

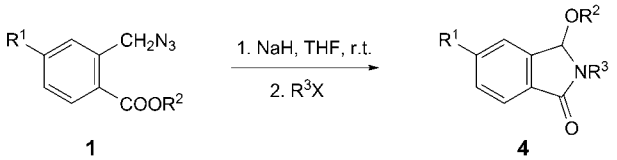
Scheme 2



1a R^1 = H, R^2 = Me
1b R^1 = H, R^2 = Et
1c R^1 = Cl, R^2 = Me

2a R^1 = H, R^2 = Me (74%)
2b R^1 = H, R^2 = Et (67%)
2c R^1 = Cl, R^2 = Me (47%)

Scheme 3



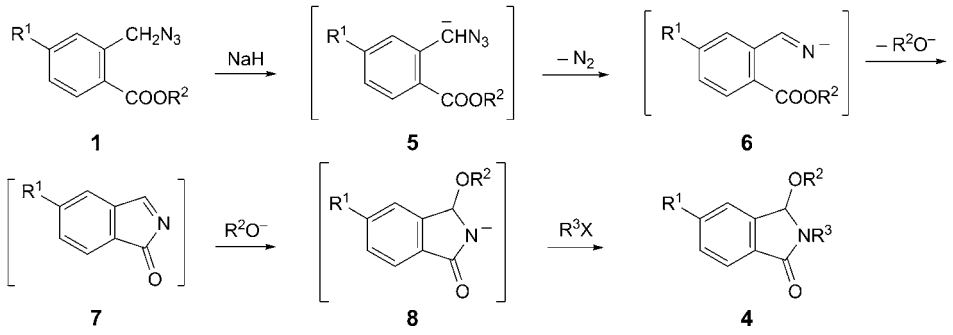
1 **4**

Table. *Preparation of 2-Substituted 3-Alkoxy-2,3-dihydro-1*H*-isoindol-1-ones* **4**

Entry	**1**	R^3X	**4**	Yield [%][a])
1	**1a** (R^1 = H, R^2 = Me)	MeI	**4a**	60
2	**1a**	BuBr	**4b**	53
3	**1a**	BnBr	**4c**	60
4	**1a**	*t*-BuOCOCH$_2$Br	**4d**	67
5	**1a**	NCCH$_2$Br	**4e**	62
6	**1b** (R^1 = H, R^2 = Et)	MeI	**4f**	43
7	**1b**	BnBr	**4g**	43
8	**1b**	BnOCH$_2$Cl	**4h**	37
9	**1b**	*t*-BuOCOCH$_2$Br	**4i**	48
10	**1b**	NCCH$_2$Br	**4j**	39
11	**1c** (R^1 = Cl, R^2 = Me)	MeI	**4k**	33
12	**1c**	*t*-BuOCOCH$_2$Br	**4l**	32

[a]) Yield of isolated product.

Scheme 4



continuous denitrogenation provides the benzylidenaminide anion intermediate **6**. Intramolecular nucleophilic addition/elimination reaction of **6** gives 1*H*-isoindol-1-one intermediate **7**. An alkoxide, eliminated from **6**, attacks at the 3-position of **7** to give 1-oxo-1*H*-isoindol-2-yl anion intermediate **8**, of which alkylation with alkyl halides leads to **4**.

In conclusion, we have demonstrated that the one-pot sequence from 2-(azidomethyl)benzoates provides a new and efficient approach to 3-alkoxy-2,3-dihydro-1*H*-isoindol-1-ones. Although the yields of products are not so high, the present synthesis may be valuable in organic synthesis because of the good availability of the starting materials, and mild and operationally simple reaction conditions.

Experimental Part

General. All chemicals used in this study were commercially available. All org. solvents used in this work 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: *PerkinElmer Spectrum65* FT-IR spectrophotometer; $\tilde{\nu}$ in

cm^{-1}. ^{1}H-NMR Spectra: *Bruker Biospin AVANCE II 600* FT-NMR spectrometer or *JEOL ECP500* FT-NMR spectrometer (at 600 or 500 MHz, resp.); δ in ppm rel. to Me_4Si as internal standard in $CDCl_3$, J in Hz. ^{13}C-NMR Spectra: *Bruker Biospin AVANCE II 600* FT-NMR spectrometer or *JEOL ECP500* FT-NMR spectrometer (at 150 or 125 MHz, resp.); δ in ppm rel. to Me_4Si as internal standard in $CDCl_3$. HR-MS (DART, pos.): *Thermo Scientific Exactive* spectrometer; in *m*/*z*.

Methyl 2-(azidomethyl)benzoate (**1a**) [5], *ethyl 2-(azidomethyl)benzoate* (**1b**) [6], and *methyl 2-(bromomethyl)-4-chlorobenzoate* [7] were prepared according to the appropriate reported procedures.

Methyl 2-(Azidomethyl)-4-chlorobenzoate (**1c**) was prepared from methyl 2-(bromomethyl)-4-chlorobenzoate [7] and NaN_3 as described previously for the preparation of **1a** [5]. Yield: 86%. White solid. M.p. 42–43° (pentane). IR (KBr): 2118, 1730. ^{1}H-NMR (500 MHz): 3.92 (*s*, 3 H); 4.84 (*s*, 2 H); 7.37 (*dd*, J = 8.6, 2.3, 1 H); 7.53 (*d*, J = 2.3, 1 H); 7.97 (*d*, J = 8.6, 1 H). Anal. calc. for $C_9H_8ClN_3O_2$ (225.63): C 47.91, H 3.57, N 18.62; found: C 47.87, H 3.64, N 18.59.

Reaction Procedure of Methyl 2-(Azidomethyl)benzoate (**1a**) *with NaH in DMF.* To a stirred suspension of NaH (60% in mineral oil; 31 mg, 0.78 mmol) in DMF (2 ml) at 0° was added dropwise a soln. of **1a** (0.15 g, 0.78 mmol) in DMF (2 ml). After 2 h, a sat. aq. NH_4Cl (20 ml) soln. was added, and the mixture was extracted with AcOEt (3 × 10 ml). The combined extracts were washed with H_2O (2 × 15 ml) and brine (10 ml), dried (Na_2SO_4), and concentrated by evaporation. The residue was separated by CC (SiO_2; AcOEt/hexane 1:1) to afford **2a** (31 mg, 24%) and **3a** (30 mg, 26%).

*2,3-Dihydro-3-methoxy-1*H*-isoindol-1-one* (**2a**) [4][8]. Pale-yellow solid. M.p. 99–101° (hexane/CH_2Cl_2) ([4]: 100°). IR (KBr): 3226, 1708, 1681. ^{1}H-NMR (500 MHz): 3.22 (*s*, 3 H); 5.99 (*s*, 1 H); 7.54 (br., 1 H); 7.55 (*t*, J = 7.6, 1 H); 7.57 (*d*, J = 7.6, 1 H); 7.63 (*t*, J = 7.6, 1 H); 7.85 (*d*, J = 7.6, 1 H). ^{13}C-NMR (125 MHz): 51.6; 84.4; 123.6; 123.7; 129.9; 132.1; 132.6; 142.7; 170.5.

*3′-Methoxy-1*H*-1,2′-biisoindole-1′,3(2*H*,3′*H*)-dione* (**3a**). White solid. M.p. 150–151° (hexane/$CHCl_3$). IR (KBr): 3275, 1706, 1615. ^{1}H-NMR (500 MHz): 3.20 (*s*, 3 H); 6.01 (*s*, 1 H); 6.95 (*s*, 1 H); 7.40 (br., 1 H); 7.42 (*d*, J = 7.6, 1 H); 7.52–7.56 (*m*, 2 H); 7.59–7.62 (*m*, 3 H); 7.86 (*d*, J = 7.6, 1 H); 7.87 (*d*, J = 7.6, 1 H). ^{13}C-NMR (125 MHz): 50.3; 61.9; 84.6; 123.6; 123.6; 123.8; 123.9; 129.4; 129.9; 130.1; 131.4; 132.1; 133.0; 141.0; 143.6; 168.8; 170.6. HR-MS: 295.1081 ($[M+H]^+$, $C_{17}H_{15}N_2O_3^+$; calc. 295.1082). Anal. calc. for $C_{17}H_{14}N_2O_3$ (294.30): C 69.38, H 4.79, N 9.52; found: C 69.31, H 5.01, N 9.32.

Reaction of Ethyl 2-(Azidomethyl)benzoate (**1b**) *with NaH in DMF.* Compound **1b** (0.20 g, 0.97 mmol) was treated with an equiv. of NaH, worked up, and purified as described above for the reaction of **1a** with NaH to afford **2b** (33 mg, 19%) and **3b** (35 mg, 21%).

*3-Ethoxy-2,3-dihydro-1*H*-isoindol-1-one* (**2b**) [4][9]. Pale-yellow solid. M.p. 103–104° (hexane/CH_2Cl_2) ([4]: 105°). IR (KBr): 3190, 1715, 1702. ^{1}H-NMR (500 MHz): 1.22 (*t*, J = 7.6, 3 H); 3.35–3.41 (*m*, 1 H); 3.54–3.60 (*m*, 1 H); 5.98 (*s*, 1 H); 7.44 (br., 1 H); 7.54 (*t*, J = 7.6, 1 H); 7.58 (*d*, J = 7.6, 1 H); 7.62 (*t*, J = 7.6, 1 H); 7.84 (*d*, J = 7.6, 1 H). ^{13}C-NMR (125 MHz): 15.3; 60.7; 83.9; 123.6; 123.7; 129.8; 131.9; 132.5; 143.3; 170.3.

*3′-Ethoxy-1*H*-1,2′-biisoindole-1′,3(2*H*,3′*H*)-dione* (**3b**). Pale-yellow solid. M.p. 183–184° (hexane/CH_2Cl_2). IR (KBr): 3195, 1709, 1615. ^{1}H-NMR (500 MHz): 0.47 (*t*, J = 6.9, 3 H); 2.69–2.75 (*m*, 1 H); 2.89–2.95 (*m*, 1 H); 6.02 (*s*, 1 H); 6.96 (*s*, 1 H); 7.42 (*d*, J = 7.6, 1 H); 7.49–7.54 (*m*, 2 H); 7.56–7.61 (*m*, 4 H); 7.83 (*d*, J = 8.4, 1 H); 7.50 (*d*, J = 8.4, 1 H). ^{13}C-NMR (125 MHz): 14.1; 59.5; 61.8; 84.4; 123.5; 123.6; 123.7; 123.8; 129.3; 129.9; 131.1; 131.5; 132.2; 132.8; 141.7; 144.1; 168.4; 170.7. HR-MS: 309.1233 ($[M+H]^+$, $C_{18}H_{17}N_2O_3^+$; calc. 309.1239). Anal. calc. for $C_{18}H_{16}N_2O_3$ (308.33): C 70.12, H 5.23, N 9.09; found: C 70.01, H 5.29, N 9.06.

Reaction Procedure of 2-(Azidomethyl)benzoates **1** *with NaH in THF.* To a stirred suspension of NaH (60% in mineral oil; 31 mg, 0.78 mmol) in THF (1.5 ml) at 0° was added dropwise a soln. of **1** (0.78 mmol) in THF (1.5 ml). The temp. was raised to r.t., and stirring was continued until complete consumption of the starting materials was confirmed by TLC analyses on SiO_2 (AcOEt/hexane 1:2) (*ca.* 5 h for **1a**, 8 h for **1b**, and 1 h for **1c**). A sat. aq. NH_4Cl (20 ml) soln. was added, and the mixture was extracted with AcOEt (3 × 10 ml). The combined extracts were washed with brine (10 ml), dried (Na_2SO_4), and concentrated by evaporation. The residual solid was purified by recrystallization to afford **2**.

*5-Chloro-2,3-dihydro-3-methoxy-1*H*-isoindol-1-one* (**2c**). Pale-yellow solid. M.p. 168–169° (hexane/CH_2Cl_2). IR (KBr): 3218, 1740, 1616. ^{1}H-NMR (500 MHz): 3.20 (*s*, 3 H); 5.95 (*s*, 1 H); 6.75 (br., 1 H);

7.52 (*dd*, *J* = 8.0, 1.7, 1 H); 7.55 (*d*, *J* = 1.7, 1 H); 7.77 (*d*, *J* = 8.0, 1 H). ^{13}C-NMR (125 MHz): 52.0; 83.9; 124.3; 124.9; 130.5; 130.5; 139.2; 144.5; 169.3. HR-MS: 198.0317 ($[M+H]^+$, $C_9H_9ClNO_2^+$; calc. 198.0322). Anal. calc. for $C_9H_8ClNO_2$ (197.62): C 54.70, H 4.08, N 7.09; found: C 54.41, H 4.17, N 7.08.

*2,3-Dihydro-3-methoxy-2-methyl-1*H-*isoindol-1-one* (**4a**) [10] (*Representative Procedure*). Compound **1a** (0.15 g, 0.78 mmol) was treated with NaH (60% in mineral oil; 31 mg, 0.78 mmol) in THF (3 ml) as described above. After complete consumption of **1a** had been confirmed by TLC analyses on SiO_2 (AcOEt/hexane 1:2), MeI (0.11 g, 0.78 mmol) was added, and stirring was continued overnight. The resulting mixture was worked up, and the crude product was purified as described above for the reactions in DMF to afford **4a** (83 mg, 60%). Yellow oil. R_f (AcOEt/hexane 1:1) 0.39. IR (neat): 1708, 1617. ^{1}H-NMR (500 MHz): 2.90 (*s*, 3 H); 3.10 (*s*, 3 H); 5.78 (*s*, 1 H); 7.53 (*t*, *J* = 7.6, 1 H); 7.54 (*d*, *J* = 7.6, 1 H); 7.59 (*td*, *J* = 7.6, 1.5, 1 H); 7.84 (*d*, *J* = 7.6, 1 H). ^{13}C-NMR (125 MHz): 26.4; 49.1; 87.9; 123.3; 123.4; 129.9; 131.9; 133.1; 140.1; 167.5.

*2-Butyl-2,3-dihydro-3-methoxy-1*H-*isoindol-1-one* (**4b**) [11]. Pale-yellow oil. R_f (AcOEt/hexane 1:4) 0.22. IR (neat): 1708, 1617. ^{1}H-NMR (600 MHz): 0.96 (*t*, *J* = 7.4, 3 H); 1.36–1.42 (*m*, 2 H); 1.62–1.68 (*m*, 2 H); 2.88 (*s*, 3 H); 3.20–3.25 (*m*, 1 H); 3.79–3.83 (*m*, 1 H); 5.89 (*s*, 1 H); 7.51–7.54 (*m*, 2 H); 7.58 (*td*, *J* = 7.4, 1.1, 1 H); 7.83 (*dd*, *J* = 7.4, 1.1, 1 H). ^{13}C-NMR (150 MHz): 13.8; 20.3; 30.2; 39.2; 49.1; 86.2; 123.4; 123.4; 129.9; 131.9; 133.3; 140.3; 167.7.

*2,3-Dihydro-3-methoxy-2-(phenylmethyl)-1*H-*isoindol-1-one* (**4c**) [11]. Colorless oil. R_f (AcOEt/hexane 1:3) 0.33. IR (neat): 1707, 1617. ^{1}H-NMR (500 MHz): 2.89 (*s*, 3 H); 4.21 (*d*, *J* = 14.5, 1 H); 5.20 (*d*, *J* = 14.5, 1 H); 5.72 (*s*, 1 H); 7.28 (*d*, *J* = 7.6, 1 H); 7.33 (*t*, *J* = 7.6, 2 H); 7.37 (*d*, *J* = 7.6, 2 H); 7.49 (*d*, *J* = 6.9, 1 H); 7.53 (*dd*, *J* = 7.6, 6.9, 1 H); 7.58 (*t*, *J* = 6.9, 1 H); 7.88 (*d*, *J* = 6.9, 1 H). ^{13}C-NMR (125 MHz): 43.0; 49.3; 85.5; 123.5; 123.7; 127.6; 128.6; 128.7; 129.9; 131.1; 132.8; 136.7; 140.3; 167.5.

*1,1-Dimethylethyl 2-(1,3-Dihydro-1-methoxy-3-oxo-2*H-*isoindole-2-yl)acetate* (**4d**). Yellow oil. R_f (AcOEt/hexane 1:2) 0.48. IR (neat): 1741, 1716, 1617. ^{1}H-NMR (600 MHz): 1.47 (*s*, 9 H); 2.92 (*s*, 3 H); 3.83 (*d*, *J* = 17.5, 1 H); 4.56 (*d*, *J* = 17.5, 1 H); 6.05 (*s*, 1 H); 7.54 (*t*, *J* = 7.4, 1 H); 7.56 (*d*, *J* = 6.9, 1 H); 7.61 (*ddd*, *J* = 7.4, 6.9, 1.0, 1 H); 7.87 (*d*, *J* = 7.4, 1 H). ^{13}C-NMR (150 MHz): 28.1; 41.3; 49.5; 82.3; 86.7; 123.6; 123.8; 130.0; 132.3; 132.5; 140.7; 167.8; 168.0. HR-MS: 278.1387 ($[M+H]^+$, $C_{15}H_{20}NO_4^+$; calc. 278.1392). Anal. calc. for $C_{15}H_{19}NO_4$ (277.32): C 64.97, H 6.91, N 5.05; found: C 64.95, H 7.06, N 5.81.

*2-(1,3-Dihydro-1-methoxy-3-oxo-2*H-*isoindol-2-yl)acetonitrile* (**4e**). Pale-yellow oil. R_f (AcOEt/hexane 1:4) 0.17. IR (neat): 2257, 1718, 1617. ^{1}H-NMR (600 MHz): 3.00 (*s*, 3 H); 4.32 (*d*, *J* = 17.5, 1 H); 4.66 (*d*, *J* = 17.5, 1 H); 6.01 (*s*, 1 H); 7.59 (*t*, *J* = 7.5, 1 H); 7.60 (*d*, *J* = 7.5, 1 H); 7.68 (*td*, *J* = 7.5, 1.0, 1 H); 7.89 (*d*, *J* = 7.5, 1 H). ^{13}C-NMR (150 MHz): 27.8; 50.1; 86.6; 114.7; 123.9; 124.2; 130.5; 131.3; 133.2; 140.1; 166.8. HR-MS: 203.0810 ($[M+H]^+$, $C_{11}H_{11}N_2O_2^+$; calc. 203.0820). Anal. calc. for $C_{11}H_{10}N_2O_2$ (202.21): C 65.34, H 4.98, N 13.85; found: C 65.29, H 5.03, N 13.65.

*3-Ethoxy-2,3-dihydro-2-methyl-1*H-*isoindol-1-one* (**4f**). Colorless oil. R_f (AcOEt/hexane 1:2) 0.30. IR (neat): 1709, 1617. ^{1}H-NMR (600 MHz): 0.98 (*t*, *J* = 6.9, 3 H); 2.82–2.88 (*m*, 1 H); 2.94 (*s*, 3 H); 2.98–3.04 (*m*, 1 H); 5.60 (*s*, 1 H); 7.34 (*td*, *J* = 7.3, 1.2, 1 H); 7.37 (*d*, *J* = 6.8, 1 H); 7.41 (*ddd*, *J* = 7.3, 6.8, 1.0, 1 H); 7.66 (*d*, *J* = 7.3, 1 H). ^{13}C-NMR (150 MHz): 15.1; 26.5; 57.6; 87.7; 123.2; 123.3; 129.8; 131.9; 132.7; 140.9; 167.7. HR-MS: 192.1018 ($[M+H]^+$, $C_{11}H_{14}NO_2^+$; calc. 192.1024). Anal. calc. for $C_{11}H_{13}NO_2$ (191.23): C 69.09, H 6.85, N 7.32; found: C 69.05, H 6.76, N 7.14.

*3-Ethoxy-2,3-dihydro-2-(phenylmethyl)-1*H-*isoindol-1-one* (**4g**). Pale-yellow needles. M.p. 72–75° (hexane). IR (KBr): 1698, 1616. ^{1}H-NMR (600 MHz): 1.09 (*t*, *J* = 6.9, 3 H); 2.97–3.02 (*m*, 1 H); 3.12–3.17 (*m*, 1 H); 4.28 (*d*, *J* = 16.7, 1 H); 5.15 (*d*, *J* = 16.7, 1 H); 5.71 (*s*, 1 H); 7.27 (*tt*, *J* = 7.3, 1.3, 1 H); 7.32 (*t*, *J* = 7.3, 2 H); 7.38 (*dd*, *J* = 7.3, 1.3, 2 H); 7.49 (*d*, *J* = 7.3, 1 H); 7.51 (*td*, *J* = 7.3, 1.1, 1 H); 7.56 (*td*, *J* = 7.3, 1.1, 1 H); 7.86 (*d*, *J* = 7.3, 1 H). ^{13}C-NMR (150 MHz): 15.1; 43.3; 58.0; 85.5; 123.4; 123.6; 127.6; 128.6; 128.7; 129.8; 132.0; 132.8; 137.0; 141.2; 167.4. HR-MS: 268.1331 ($[M+H]^+$, $C_{17}H_{18}NO_2^+$; calc. 268.1337). Anal. calc. for $C_{17}H_{17}NO_2$ (267.32): C 76.38, H 6.41, N 5.24; found: C 76.31, H 6.40, N 5.17.

*3-Ethoxy-2,3-dihydro-2-[(phenylmethoxy)methyl]-1*H-*isoindol-1-one* (**4h**).Yellow oil. R_f (AcOEt/hexane 1:5) 0.23. IR (neat): 1715, 1616. ^{1}H-NMR (500 MHz): 1.14 (*t*, *J* = 6.9, 3 H); 3.11–3.17 (*m*, 1 H); 3.25–3.29 (*m*, 1 H); 4.60 (*s*, 2 H); 4.86 (*d*, *J* = 10.9, 1 H); 5.34 (*d*, *J* = 10.9, 1 H); 6.04 (*s*, 1 H); 7.18–7.37 (*m*, 5 H); 7.48–7.58 (*m*, 3 H); 7.86 (*d*, *J* = 7.4, 1 H). ^{13}C-NMR (125 MHz): 15.1; 59.0; 69.2; 70.8; 85.3; 123.6; 124.0; 126.9; 127.7; 127.7; 128.3; 129.9; 132.7; 137.8; 141.7; 168.2. HR-MS: 298.1437 ($[M+H]^+$,

$C_{18}H_{20}NO_3^+$; calc. 298.1443). Anal. calc. for $C_{18}H_{19}NO_3$ (297.35): C 72.71, H 6.44, N 4.71; found: C 72.73, H 6.61, N 4.78.

*1,1-Dimethylethyl 2-(1-Ethoxy-1,3-dihydro-3-oxo-2*H*-isoindol-2-yl)acetate* (**4i**). Colorless needles. M.p. 86–87° (hexane/Et_2O). IR (KBr): 1741, 1702, 1616. ^{1}H-NMR (600 MHz): 1.14 (*t*, *J* = 7.1, 3 H); 1.47 (*s*, 9 H), 3.03–3.08 (*m*, 1 H); 3.19–3.24 (*m*, 1 H); 3.86 (*d*, *J* = 17.6, 1 H); 4.55 (*d*, *J* = 17.6, 1 H); 6.04 (*s*, 1 H); 7.52 (*td*, *J* = 7.4, 1.0, 1 H); 7.56 (*d*, *J* = 7.4, 1 H); 7.60 (*td*, *J* = 7.4, 1.0, 1 H); 7.85 (*d*, *J* = 7.4, 1 H). ^{13}C-NMR (150 MHz): 15.2; 28.1; 41.4; 58.1; 82.3; 86.5; 123.5; 123.8; 129.8; 132.2; 132.3; 141.4; 167.7; 168.0. HR-MS: 292.1535 ($[M+H]^+$, $C_{16}H_{22}NO_4^+$; calc. 292.1549). Anal. calc. for $C_{16}H_{21}NO_4$ (291.34): C 65.96, H 7.27, N 4.81; found: C 65.88, H 7.25, N 4.77.

*(1-Ethoxy-1,3-dihydro-3-oxo-2*H*-isoindol-2-yl)acetonitrile* (**4j**). Yellow oil. R_f (AcOEt/hexane 1:3) 0.21. IR (neat): 2250, 1716, 1616. ^{1}H-NMR (500 MHz): 1.04 (*t*, *J* = 6.9, 3 H); 2.95–3.03 (*m*, 1 H); 3.09–3.14 (*m*, 1 H); 4.17 (*d*, *J* = 17.8, 1 H); 4.48 (*d*, *J* = 17.8, 1 H); 5.83 (*s*, 1 H); 7.39–7.45 (*m*, 2 H); 7.50 (*t*, *J* = 7.4, 1 H); 7.70 (*d*, *J* = 7.4, 1 H). ^{13}C-NMR (125 MHz): 14.9; 27.8; 59.0; 86.3; 114.7; 123.7; 124.1; 130.3; 131.0; 133.1; 140.8; 166.7. HR-MS: 217.0969 ($[M+H]^+$, $C_{12}H_{13}N_2O_2^+$; calc. 217.0977). Anal. calc. for $C_{12}H_{12}N_2O_2$ (216.24): C 66.65, H 5.59, N 12.96; found: C 66.61, H 5.55, N 12.80.

*5-Chloro-2,3-dihydro-3-methoxy-2-methyl-1*H*-isoindol-1-one* (**4k**). White solid. M.p. 97–98° (hexane). IR (KBr): 1710, 1613. ^{1}H-NMR (500 MHz): 2.93 (*s*, 3 H); 3.08 (*s*, 3 H); 5.74 (*s*, 1 H); 7.50 (*dd*, *J* = 8.0, 1.7, 1 H); 7.53 (*d*, *J* = 1.7, 1 H); 7.76 (*d*, *J* = 8.0, 1 H). ^{13}C-NMR (125 MHz): 26.5; 49.4; 87.4; 123.8; 124.5; 130.4; 131.5; 138.4; 142.0; 166.6. HR-MS: 212.0473 ($[M+H]^+$, $C_{10}H_{11}ClNO_2^+$; calc. 212.0478). Anal. calc. for $C_{10}H_{10}ClNO_2$ (211.64): C 56.75, H 4.76, N 6.62; found: C 65.74, H 4.73, N 6.50.

*1,1-Dimethylethyl 2-(5-Chloro-1,3-dihydro-3-methoxy-1-oxo-2*H*-isoindol-2-yl)acetate* (**4l**). Pale-yellow solid. M.p. 82–83° (hexane/CH_2Cl_2). IR (KBr): 1750, 1713, 1613. ^{1}H-NMR (500 MHz): 1.47 (*s*, 9 H); 2.95 (*s*, 3 H); 3.81 (*d*, *J* = 17.2, 1 H); 4.53 (*d*, *J* = 17.2, 1 H); 6.02 (*s*, 1 H); 7.52 (*dd*, *J* = 8.0, 1.7, 1 H); 7.55 (*d*, *J* = 1.7, 1 H); 7.79 (*d*, *J* = 8.0, 1 H). ^{13}C-NMR (125 MHz): 28.1; 41.3; 49.8; 82.5; 86.2; 124.0; 125.0; 130.5; 130.9; 138.9; 142.4; 166.7; 167.7. HR-MS: 312.0997 ($[M+H]^+$, $C_{15}H_{19}ClNO_4^+$; calc. 312.1002). Anal. calc. for $C_{15}H_{18}ClNO_4$ (311.76): C 57.79, H 5.82, N 4.49; found: C 57.50, H 5.79, N 4.34.

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