Generation of Aryl(2-lithiophenyl)methanone *O*-Methyl Oximes and Their Use for the Synthesis of *N*-(3-Alkyl-1-aryl- or 1,3-diaryl-1*H*-isoindol-1-yl)-*O*-methylhydroxylamines *via* the Reaction with Nitriles

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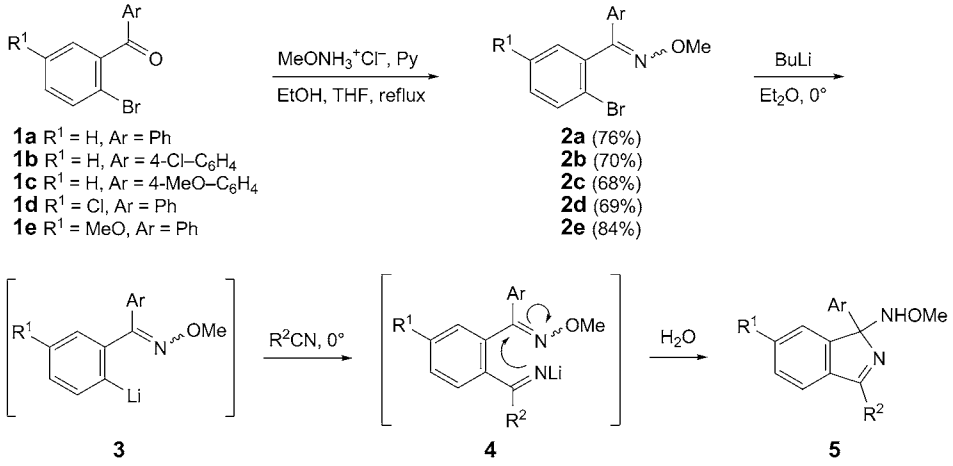
An efficient two-step procedure for the preparation of a new type of 1*H*-isoindoles, *i.e.*, *N*-(3-alkyl-1-aryl- or 1,3-diaryl-1*H*-isoindol-1-yl)-*O*-methylhydroxylamines **5**, from readily available aryl(2-bromophenyl)methanones **1** has been developed. Aryl(2-bromophenyl)methanone *O*-methyloximes **2**, derived from the corresponding ketones, were treated with BuLi in Et_2O at 0° to generate novel lithium compounds, aryl(2-lithiophenyl)methanone *O*-methyloximes **3**, which were allowed to react with nitriles to give the desired products **5** in moderate-to-fair yields.

Introduction. – In this article, we report a convenient approach to the synthesis of a new type of 1*H*-isoindole derivatives, *i.e.*, *N*-(3-alkyl-1-aryl- or 1,3-diaryl-1*H*-isoindol-1-yl)-*O*-methylhydroxylamines **5**, from readily available aryl(2-bromophenyl)methanones **1**. We found that corresponding *O*-methyloximes **2**, derived from **1**, are treated with BuLi to generate aryl(2-lithiophenyl)methanone *O*-methyloximes **3**, which are allowed to react with nitriles to give the desired 1*H*-isoindole derivatives **5**. Because a number of molecules with the 1*H*-isoindole structure are known to possess a variety of biological activities [1][2], several synthetic approaches to 1,1-disubstituted 1*H*-isoindole derivatives have been developed [1][3]. However, to the best of our knowledge, there has been only one previous report on the synthesis of 1*H*-isoindole with an amino substituent at C(1) [4]. Thus, synthesis of 1,3-bis(1,1-dimethylethyl)-1*H*-isoindol-1-amine has been achieved by treatment of a V^{III}–benzyne complex, $CpV(\eta^2\text{-}C_6H_4)(Me_3P)_2$, with *t*-BuNC, followed by acid hydrolysis of the resulting isoindolenine-substituted V^{III}–imido complex, $CpV[NC(t\text{-}Bu)N{=}C(t\text{-}Bu)C_6H_4](Me_3P)_2$.

Results and Discussion. – *N*-(3-Alkyl-1-aryl- or 1,3-diaryl-1*H*-isoindol-1-yl)-*O*-methylhydroxylamines **5** were obtained by the two-step sequence from aryl(2-bromophenyl)methanones **1** as outlined in *Scheme 1*. Treatment of **1** with $MeONH_3^+Cl^-$ in the presence of C_5H_5N in refluxing EtOH/THF gave aryl(2-bromophenyl)methanone *O*-methyloximes **2** in satisfactory yields. Compounds **2a**, **2c**, and **2e** were obtained as mixtures of stereoisomers, while stereoisomers of compound **2b** were separable, and only (*E*)-**2d** was obtained. Although the configurations of the stereoisomers could not be determined unambiguously, we

Scheme 1



tentatively assigned them based on the concept that the less crowded, thermodynamically more stable stereoisomer must be produced predominantly. A mixture of isomers was used in the next reaction in each case except **2d**.

Initially, we tried to achieve Br/Li exchange between (2-bromophenyl)phenylmethanone *O*-methyloxime (**2a**) and BuLi in THF at $-78°$ to generate (2-lithiophenyl)-phenylmethanone *O*-methyloxime (**3a**). However, none of the desired product **5a** was observed in the mixture after addition of PhCN, followed by usual workup. Subsequently, we found that the generation of **3** could be accomplished by treating **2** with BuLi in Et_2O at 0°. After generation of **3**, nitriles were added at the same temperature. The addition of the carbanion to the nitrile C-atom, followed by cyclization through attack of the resulting imido anion in intermediate **4** on the methoxyimino C-atom proceeded smoothly. After aqueous workup, followed by purification of the crude products by recrystallization (in general), the desired products **5** were obtained in generally moderate-to-fair yields, as compiled in the *Table*. The results indicate that 2-methylpropanenitrile carrying an α-H-atom is also usable in this sequence, and that the corresponding 3-(1-methylethyl) derivatives **5f**, **5h**, and **5l** are obtained in yields comparable to those obtained with aromatic nitriles (*Entries 6*, *8*, and *12*, resp.). Unfortunately, however, propanenitrile proved to be unusable in this reaction; a considerably complex mixture of products was obtained from the reaction with **3a**.

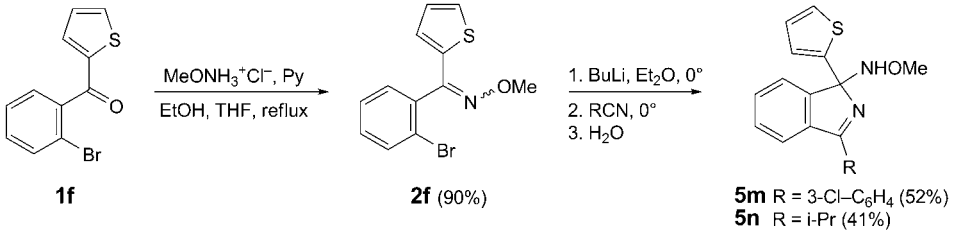
Next, we turned our attention to the synthesis of 1-hetaryl derivatives to demonstrate the scope of the present method. As shown in *Scheme 2*, (2-bromophenyl)(thiophen-2-yl)methanone *O*-methyloxime (**2f**), which is accessible by condensation of (2-bromophenyl)(thiophen-2-yl)methanone (**1f**) with *O*-methylhydroxylamine, furnished *N*-[1-(thiophen-2-yl)-1*H*-isoindol-1-yl]-*O*-methylhydroxylamines **5m** and **5n** under the same reaction conditions as described above. The yield of **2f** was excellent, but the yields of the conversion of **2f** into **5m** and **5n** were somewhat lower than those obtained with **2a**–**2e**.

Table. *Preparation of* N-(*1,3-Disubstituted 1*H-*Isoindol-1-yl)*-O-*methylhydroxylamines* **5**

Entry	Compound **2**	R^2	Product	Yield[a]) [%]
1	**2a** (R^1 = H, Ar = Ph)	Ph	**5a**	66
2	**2a**	4-Me–C_6H_4	**5b**	62
3	**2a**	3-Cl–C_6H_4	**5c**	59
4	**2a**	4-Cl–C_6H_4	**5d**	55
5	**2a**	4-MeO–C_6H_4	**5e**	61
6	**2a**	i-Pr	**5f**	60
7	**2b** (R^1 = H, Ar = 4-Cl–C_6H_4)	4-Cl–C_6H_4	**5g**	57
8	**2c** (R^1 = H, Ar = 4-MeO–C_6H_4)	i-Pr	**5h**	64
9	**2d** (R^1 = Cl, Ar = Ph)	4-Cl–C_6H_4	**5i**	59
10	**2e** (R^1 = MeO, Ar = Ph)	3-Me–C_6H_4	**5j**	64
11	**2e**	4-Cl–C_6H_4	**5k**	61
12	**2e**	i-Pr	**5l**	66

[a]) Yields of isolated products.

Scheme 2



1f **2f** (90%) **5m** R = 3-Cl–C_6H_4 (52%) **5n** R = i-Pr (41%)

In summary, a convenient procedure to synthesize a new type of 1*H*-isoindoles, *N*-(3-alkyl-1-aryl- or 1,3-diaryl-1*H*-isoindol-1-yl)-*O*-methylhydroxylamines **5**, based on the reaction of new lithium compounds, *i.e.*, aryl(2-lithiophenyl)methanone *O*-methyloximes **3**, with nitriles has been developed. The ready availability of the starting materials and simplicity of the operations render the present method attractive.

Experimental Part

General. All of the 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}. ^{1}H- and ^{13}C-NMR spectra: *JEOL ECP500* or *JEOL LA400* FT NMR spectrometer (500 or 400 and 125 or 100 MHz, resp.); δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. HR-MS (DART, pos.): *Thermo Scientific Exactive* spectrometer; in *m*/*z*.

Synthesis of Diarylmethanones **1**. *(2-Bromophenyl)(4-chlorophenyl)methanone* (**1b**) [5], *(2-bromophenyl)(4-methoxyphenyl)methanone* (**1c**) [6], *(2-bromo-5-chlorophenyl)(phenyl)methanone* (**1d**) [7], and *(2-bromo-5-methoxyphenyl)(phenyl)methanone* (**1e**) [8] were prepared according to the literature methods. BuLi was supplied by *Asia Lithium Corporation*. All other chemicals used were commercially available.

(2-Bromophenyl)(thiophen-2-yl)methanol [9] was prepared by treating 2-bromobenzaldehyde with (thiophen-2-yl)lithium as described in [5]. Yield: 99%. Pale-yellow oil. R_f (AcOEt/hexane 1:10) 0.33. IR (neat): 3367. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.52 (*d*, *J* = 4.0, 1 H); 6.41 (*d*, *J* = 4.0, 1 H); 6.92–6.95 (*m*, 2 H); 7.18 (*td*, *J* = 7.4, 1.7, 1 H); 7.27 (*dd*, *J* = 4.6, 1.1, 1 H); 7.38 (*ddd*, *J* = 8.0, 7.4, 1.1, 1 H); 7.54 (*dd*, *J* = 8.0, 1.1, 1 H); 7.71 (*dd*, *J* = 8.0, 1.7, 1 H). Anal. calc. for $C_{11}H_9BrOS$ (269.16): C 49.09, H 3.37; found: C 49.12, H 3.52.

(2-Bromophenyl)(thiophen-2-yl)methanone (**1f**) [10] was prepared by the pyridinium chlorochromate (PCC) oxidation of the above alcohol as described in [11]. Yield: 91%. Pale-yellow oil. R_f (AcOEt/hexane 1:12) 0.35. IR (neat): 1650. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.13 (*dd*, *J* = 5.1, 1.1, 1 H); 7.34–7.44 (*m*, 4 H); 7.66 (*d*, *J* = 8.6, 1 H); 7.77 (*dd*, *J* = 5.1, 1.1, 1 H). Anal. calc. for $C_{11}H_7BrOS$ (267.14): C 49.46, H 2.64; found: C 49.46, H 2.65.

Syntheses of Diarylmethanone Oximes **2**. *Representative Procedure: 1-(2-Bromophenyl)*-N-*methoxy-1-phenylmethanimine* (= *(2-Bromophenyl)phenylmethanone* O-*Methyloxime*; **2a**). To a soln. of $MeONH_3^+Cl^-$ (0.30 g, 3.5 mmol) in EtOH (2 ml) and pyridine (2 ml) was added a soln. of **1a** (0.37 g, 1.8 mmol) in THF (2 ml). The mixture was heated at reflux for 8 h under stirring. After cooling, aq. sat. $NaHCO_3$ soln. (10 ml) was added, and the mixture was extracted with Et_2O (2 × 10 ml). The combined extracts were washed with brine (10 ml), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by CC (SiO_2; Et_2O/hexane 1:10) to give **2a** (0.32 g, 76%). A mixture of stereoisomers (*E*)/(*Z*) *ca.* 9:1). White solid. M.p. 118–121°. IR (KBr): 1602, 1052. ^{1}H-NMR (500 MHz, $CDCl_3$): 3.99 (*s*, 2.7 H); 4.04 (*s*, 0.3 H); 7.17 (*dd*, *J* = 8.0, 1.1, 0.9 H); 7.27–7.42 (*m*, 5 H); 7.45–7.55 (*m*, 2.1 H); 7.58 (*d*, *J* = 8.0, 0.1 H); 7.67 (*d*, *J* = 8.0, 0.9 H). Anal. calc. for $C_{14}H_{12}BrNO$ (290.16): C 57.95, H 4.17, N 4.83; found: C 57.90, H 4.18, N 4.70.

1-(2-Bromophenyl)-1-(4-chlorophenyl)-N-*methoxymethanimine* (= *(2-Bromophenyl)(4-chlorophenyl)methanone* O-*Methyloxime*; **2b**).

Data of (*E*)-**2b**. Yield: 57%. Pale-yellow oil. R_f (Et_2O/hexane 1:10) 0.37. IR (neat): 1603, 1052. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.98 (*s*, 3 H); 7.15 (*dd*, *J* = 7.8, 2.0, 1 H); 7.29–7.32 (*m*, 3 H); 7.39–7.42 (*m*, 3 H); 7.67 (*d*, *J* = 7.8, 1 H). Anal. calc. for $C_{14}H_{11}BrClNO$ (324.60): C 51.80, H 3.42, N 4.32; found: C 51.81, H 3.71, N 4.23.

Data of (*Z*)-**2b**. Yield: 13%. Pale-yellow oil. R_f (Et_2O/hexane 1:10) 0.30. IR (neat): 1589, 1037. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.04 (*s*, 3 H); 7.28 (*dd*, *J* = 7.8, 6.9, 1 H); 7.33 (*d*, *J* = 8.8, 2 H); 7.39 (*dd*, *J* = 7.8, 6.9, 1 H); 7.45 (*d*, *J* = 7.8, 1 H), 7.49 (*d*, *J* = 8.8, 2 H); 7.59 (*d*, *J* = 7.8, 1 H). Anal. calc. for $C_{14}H_{11}BrClNO$ (324.60): C 51.80, H 3.42, N 4.32; found: C 51.81, H 3.39, N 4.20.

1-(2-Bromophenyl)-N-*methoxy-1-(4-methoxyphenyl)methanimine* (= *(2-Bromophenyl)(4-methoxyphenyl)methanone* O-*Methyloxime*; **2c**). A mixture of stereoisomers (*E*)/(*Z*) *ca.* 9:1). Colorless oil. An anal. specimen of each isomer was obtained by CC (SiO_2).

Data of (*E*)-**2c**. Colorless oil. R_f (THF/hexane 1:15) 0.39. IR (neat): 1607, 1052. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.81 (*s*, 3 H); 3.96 (*s*, 3 H); 6.85 (*d*, *J* = 8.8, 2 H); 7.16 (*dd*, *J* = 7.8, 2.2, 1 H); 7.28 (*td*, *J* = 7.8, 2.0, 1 H); 7.38–7.42 (*m*, 3 H); 7.66 (*d*, *J* = 7.8, 1 H). Anal. calc. for $C_{15}H_{14}BrNO_2$ (320.18): C 56.27, H 4.41, N 4.37; found: C 55.97, H 4.45, N 4.45.

Data of (*Z*)-**2c**. Colorless oil. R_f (THF/hexane 1:15) 0.34. IR (neat): 1604, 1037. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.82 (*s*, 3 H); 4.04 (*s*, 3 H); 6.87 (*d*, *J* = 8.8, 2 H); 7.26 (*t*, *J* = 7.8, 1 H); 7.36 (*t*, *J* = 7.8, 1 H); 7.43 (*dd*, *J* = 7.8, 2.0, 1 H); 7.53 (*d*, *J* = 8.8, 2 H); 7.58 (*d*, *J* = 7.8, 1 H). Anal. calc. for $C_{15}H_{14}BrNO_2$ (320.18): C 56.27, H 4.41, N 4.37; found: C 56.14, H 4.45, N 4.30.

*(*E*)-1-(2-Bromo-5-chlorophenyl)*-N-*methoxy-1-phenylmethanimine* (= *(*E*)-(2-Bromo-5-chlorophenyl)phenylmethanone* O-*Methyloxime*; **2d**). Colorless oil. R_f (THF/hexane 1:40) 0.47. IR (neat): 1593, 1054. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.99 (*s*, 3 H); 7.16 (*d*, *J* = 2.9, 1 H); 7.26 (*dd*, *J* = 7.8, 2.9, 1 H); 7.33–7.40 (*m*, 3 H); 7.46 (*dd*, *J* = 7.8, 2.0, 2 H); 7.59 (*d*, *J* = 7.8, 1 H). Anal. calc. for $C_{14}H_{11}BrClNO$ (324.60): C 51.80, H 3.42, N 4.32; found: C 51.77, H 3.59, N 4.18.

1-(2-Bromo-5-methoxyphenyl)-N-*methoxy-1-phenylmethanimine* (= *(2-Bromo-5-methoxyphenyl)-phenylmethanone* O-*Methyloxime*; **2e**; mixture of stereoisomers, (*E*)/(*Z*) *ca.* 9:1). Colorless oil. An anal. specimen of each isomer was obtained by CC (SiO_2).

Data of (*E*)-**2e**. White solid. M.p. 62–64° (hexane/THF). R_f (THF/hexane 1:40) 0.43. IR (KBr): 1587, 1054. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.78 (*s*, 3 H); 3.99 (*s*, 3 H); 6.70 (*d*, *J* = 2.9, 1 H); 6.84 (*dd*,

$J = 8.8, 2.9, 1$ H); 7.31–7.36 (m, 3 H); 7.49 (dd, $J = 7.8, 2.0, 2$ H); 7.54 (d, $J = 8.8, 1$ H). Anal. calc. for $C_{15}H_{14}BrNO_2$ (320.18): C 56.27, H 4.41, N 4.37; found: C 56.23, H 4.49, N 4.36.

Data of (*Z*)-**2e**. White solid. M.p. 87–89° (hexane/THF). R_f (THF/hexane 1:40) 0.38. IR (KBr): 1578, 1036. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.82 (s, 3 H); 4.04 (s, 3 H); 6.82 (dd, $J = 8.8, 2.9, 1$ H); 7.00 (d, $J = 2.9, 1$ H); 7.35–7.37 (m, 3 H); 7.45 (d, $J = 8.8, 1$ H); 7.55–7.57 (m, 2 H). Anal. calc. for $C_{15}H_{14}BrNO_2$ (320.18): C 56.27, H 4.41, N 4.37; found: C 56.00, H 4.45, N 4.08.

1-(2-Bromophenyl)-N-*methoxy-1-(thiophen-2-yl)methanimine* (=*(2-Bromophenyl)(thiophen-2-yl)-methanone* O-*Methyloxime*; **2f**, a mixture of stereoisomers (*E*)/(*Z*) *ca.* 7:3). White solid. An anal. specimen of each isomer was obtained by CC (SiO_2).

Data of (*E*)-**2f**. White solid. M.p. 51–55° (hexane/THF). R_f (THF/hexane 1:30) 0.43. IR (KBr): 1575, 1051. ^{1}H-NMR (500 MHz, $CDCl_3$): 4.18 (s, 3 H); 6.88 (dd, $J = 4.0, 1.1, 1$ H); 7.00 (dd, $J = 5.2, 4.0, 1$ H); 7.31 (td, $J = 7.4, 1.7, 1$ H); 7.40 (td, $J = 7.4, 1.1, 1$ H); 7.44 (dd, $J = 7.4, 1.7, 1$ H); 7.57 (dd, $J = 5.2, 1.1, 1$ H); 7.66 (d, $J = 7.4, 1$ H). Anal. calc. for $C_{12}H_{10}BrNOS$ (296.18): C 48.66, H 3.40, N 4.73; found: C 48.41, H 3.22, N 4.82.

Data of (*Z*)-**2f**. White solid. M.p. 79–81° (hexane/THF). R_f (THF/hexane 1:30) 0.37. IR (KBr): 1564, 1046. ^{1}H-NMR (500 MHz, $CDCl_3$): 3.96 (s, 3 H); 6.70 (d, $J = 4.0, 1$ H); 6.94 (dd, $J = 5.2, 4.0, 1$ H); 7.24 (dd, $J = 7.4, 1.7, 1$ H); 7.29 (ddd, $J = 8.0, 7.4, 1.7, 1$ H); 7.32 (d, $J = 5.2, 1$ H); 7.40 (t, $J = 7.4, 1$ H); 7.67 (d, $J = 8.0, 1$ H).

*Synthesis of (1*H-*Isoindol-1-yl)hydroxylamines* **5**. *Representative Procedure:* N-*Methoxy-1,3-diphenyl-1*H-*isoindol-1-amine* (=N-*(1,3-Diphenyl-1*H-*isoindol-1-yl)*-O-*methylhydroxylamine*; **5a**). To a stirred soln. of **2a** (0.29 g, 1.0 mmol) in Et_2O (4 ml) at 0° was added, dropwise BuLi (1.6M in hexane; 1.0 mmol). After 5 min, PhCN (0.10 g, 1.0 mmol) was added, and stirring was continued at the same temp. for an additional 15 min, before sat. aq. NH_4Cl soln. (10 ml) was added. The mixture was extracted with AcOEt (3×10 ml), and the combined extracts were washed with brine (10 ml) and dried (Na_2SO_4). After evaporation of the solvent, the residual solid was recrystallized from hexane/Et_2O to afford **5a** (0.21 g, 66%). Colorless needles. M.p. 118–121°. IR (KBr): 3185, 1603. ^{1}H-NMR (500 MHz, $CDCl_3$): 3.38 (s, 3 H); 6.43 (s, 1 H); 7.28–7.34 (m, 3 H); 7.40–7.43 (m, 2 H); 7.54–7.55 (m, 3 H); 7.70–7.75 (m, 4 H); 8.06–8.08 (m, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 63.17; 94.67; 123.03; 124.03; 126.57; 128.33; 128.41; 128.54; 128.55; 128.64; 128.84; 130.55; 134.02; 137.79; 138.29; 153.06; 171.55. HR-MS: 315.1495 ($[M+H]^+$, $C_{21}H_{19}N_2O^+$; calc. 315.1497). Anal. calc. for $C_{21}H_{18}N_2O$ (314.38): C 80.23, H 5.77, N 8.91; found: C 79.94, H 5.87, N 8.83.

N-*Methoxy-3-(4-methylphenyl)-1-phenyl-1*H-*isoindol-1-amine* (=O-*Methyl*-N-*[3-(4-methylphenyl)-1-phenyl-1*H-*isoindol-1-yl]hydroxylamine*; **5b**). White solid. M.p. 136–138° (hexane/Et_2O). IR (KBr): 3225, 1614, 1601. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.46 (s, 3 H); 3.38 (s, 3 H); 6.41 (s, 1 H); 7.23–7.41 (m, 7 H); 7.69–7.74 (m, 4 H); 7.98 (d, $J = 8.2$, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 21.53; 63.16; 94.52; 123.05; 123.97; 126.56; 128.26; 128.37; 128.48; 128.51; 128.74; 129.32; 131.23; 137.90; 138.45; 140.78; 153.05; 171.35. HR-MS: 329.1650 ($[M+H]^+$, $C_{22}H_{21}N_2O^+$; calc. 329.1654). Anal. calc. for $C_{22}H_{20}N_2O$ (328.41): C 80.46, H 6.14, N 8.53; found: C 80.19, H 6.30, N 8.56.

3-(3-Chlorophenyl)-N-*methoxy-1-phenyl-1*H-*isoindol-1-amine* (=N-*[3-(3-Chlorophenyl)-1-phenyl-1*H-*isoindol-1-yl]*-O-*methylhydroxylamine*; **5c**). Pale-yellow solid. M.p. 112–114° (hexane/Et_2O). IR (KBr): 3179, 1601. ^{1}H-NMR (500 MHz, $CDCl_3$): 3.37 (s, 3 H); 6.43 (s, 1 H); 7.30–7.35 (m, 3 H); 7.43–7.44 (m, 2 H); 7.48 (t, $J = 8.0$, 1 H); 7.53 (dd, $J = 8.0, 1.1, 1$ H); 7.68–7.71 (m, 3 H); 7.75 (d, $J = 8.0$, 1 H); 7.95 (dd, $J = 8.0, 1.1, 1$ H); 8.07 (d, $J = 1.1$, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 63.20; 94.80; 122.78; 124.14; 126.50; 126.63; 128.21; 128.47; 128.61; 128.67; 129.08; 129.93; 130.61; 134.77; 135.65; 137.28; 137.87; 152.98; 170.32. HR-MS: 349.1096 ($[M+H]^+$, $C_{21}H_{18}ClN_2O^+$; calc. 349.1107). Anal. calc. for $C_{21}H_{17}ClN_2O$ (348.83): C 72.31, H 4.91, N 8.03; found: C 72.13, H 5.07, N 7.81.

3-(4-Chlorophenyl)-N-*methoxy-1-phenyl-1*H-*isoindol-1-amine* (=N-*[3-(4-Chlorophenyl)-1-phenyl-1*H-*isoindol-1-yl]*-O-*methylhydroxylamine*; **5d**). White solid. M.p. 88–92° (hexane/Et_2O). IR (KBr): 3161, 1597. ^{1}H-NMR (500 MHz, $CDCl_3$): 3.37 (s, 3 H); 6.42 (s, 1 H); 7.23–7.25 (m, 1 H); 7.30–7.36 (m, 3 H); 7.42–7.44 (m, 2 H); 7.52 (d, $J = 8.6$, 2 H); 7.67–7.69 (m, 2 H); 7.74–7.76 (m, 1 H); 8.02 (d, $J = 8.6$, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 63.16; 94.71; 122.76; 124.11; 127.09; 128.02; 128.20; 128.42; 128.62; 128.91; 128.99; 132.37; 136.69; 137.38; 137.98; 152.98; 170.42. HR-MS: 349.1094 ($[M+H]^+$,

$C_{21}H_{18}ClN_2O^+$; calc. 349.1107). Anal. calc. for $C_{21}H_{17}ClN_2O$ (348.83): C 72.31, H 4.91, N 8.03; found: C 72.24, H 5.04, N 8.01.

N-*Methoxy-3-(4-methoxyphenyl)-1-phenyl-1*H-*isoindol-1-amine* (= N-*[3-(4-Methoxyphenyl)-1-phenyl-1*H-*isoindol-1-yl]*-O-*methylhydroxylamine*; **5e**). Isolated by CC (SiO_2). Pale-yellow amorphous powder. R_f (THF/hexane 1:4) 0.23. IR (neat): 3179, 1610. ^{1}H-NMR (500 MHz, (D_6)DMSO): 3.24 (*s*, 3 H); 3.86 (*s*, 3 H); 7.14 (*d*, *J* = 8.7, 2 H); 7.25–7.31 (*m*, 3 H); 7.42–7.46 (*m*, 2 H); 7.58 (*dd*, *J* = 8.0, 1.8, 2 H); 7.73–7.75 (*m*, 1 H); 7.79–7.81 (*m*, 1 H); 8.04 (*d*, *J* = 8.6, 2 H); 9.14 (br. *s*, 1 H). ^{13}C-NMR (125 MHz, (D_6)DMSO): 55.40; 62.34; 94.29; 114.25; 122.78; 123.89; 126.27; 126.61; 127.94; 128.14; 128.51; 128.60; 129.89; 137.22; 139.14; 153.68; 161.21; 168.58. HR-MS: 345.1599 ($[M+H]^+$, $C_{22}H_{21}N_2O_2^+$; calc. 345.1603). Anal. calc. for $C_{22}H_{20}N_2O_2$ (344.41): C 76.72, H 5.85, N 8.13; found: C 76.64, H 5.94, N 8.00.

N-*Methoxy-3-(1-methylethyl)-1-phenyl-1*H-*isoindol-1-amine* (= O-*Methyl*-N-*[3-(1-methylethyl)-1-phenyl-1*H-*isoindol-1-yl]hydroxylamine*; **5f**). Pale-yellow solid. M.p. 106–109° (hexane). IR (KBr): 3177, 1610. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.47 (*d*, *J* = 6.9, 3 H); 1.48 (*d*, *J* = 6.9, 3 H); 3.29 (*sept.*, *J* = 6.9, 1 H); 3.35 (*s*, 3 H); 6.28 (*s*, 1 H); 7.26–7.38 (*m*, 5 H); 7.49 (*d*, *J* = 6.9, 1 H); 7.62–7.64 (*m*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 20.27; 20.53; 30.04; 63.14; 94.25; 121.35; 123.55; 126.31; 128.10; 128.28; 128.33; 128.67; 138.05; 138.56; 152.46; 179.33. HR-MS: 281.1629 ($[M+H]^+$, $C_{18}H_{21}N_2O^+$; calc. 281.1654). Anal. calc. for $C_{18}H_{20}N_2O$ (280.36): C 77.11, H 7.19, N 9.99; found: C 77.06, H 7.26, N 9.92.

1,3-Bis(4-chlorophenyl)-N-*methoxy-1*H-*isoindol-1-amine* (= N-*[1,3-Bis(4-chlorophenyl)-1*H-*isoindol-1-yl]*-O-*methylhydroxylamine*; **5g**). White solid. M.p. 123–125° (hexane/CH_2Cl_2). IR (KBr): 3214, 1597. ^{1}H-NMR (500 MHz, $CDCl_3$): 3.38 (*s*, 3 H); 6.33 (*s*, 1 H); 7.29 (*d*, *J* = 8.6, 2 H); 7.43–7.45 (*m*, 2 H); 7.53 (*d*, *J* = 8.6, 2 H); 7.63 (*d*, *J* = 8.6, 2 H); 7.69–7.71 (*m*, 2 H); 8.01 (*d*, *J* = 8.6, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 63.20; 94.20; 122.93; 124.01; 127.98; 128.57; 128.86; 128.98; 129.19; 129.84; 132.20; 134.32; 136.69; 136.89; 137.27; 152.60; 170.81. HR-MS: 383.0708 ($[M+H]^+$, $C_{21}H_{17}Cl_2N_2O^+$; calc. 383.0718). Anal. calc. for $C_{21}H_{16}Cl_2N_2O$ (383.27): C 65.81, H 4.21, N 7.31; found: C 65.76, H 4.28, N 7.45.

N-*Methoxy-1-(4-methoxyphenyl)-3-(1-methylethyl)-1*H-*isoindol-1-amine* (= N-*[1-(4-methoxyphenyl)-3-(1-methylethyl)-1*H-*isoindol-1-yl]*-O-*methylhydroxylamine*; **5h**). White solid. M.p. 138–140° (hexane/CH_2Cl_2). IR (KBr): 3167, 1610. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.45 (*d*, *J* = 6.9, 3 H); 1.46 (*d*, *J* = 6.9, 3 H); 3.27 (*sept.*, *J* = 6.9, 1 H); 3.33 (*s*, 3 H); 3.76 (*s*, 3 H); 6.24 (*s*, 1 H); 6.82 (*d*, *J* = 8.6, 2 H); 7.34–7.37 (*m*, 2 H); 7.48 (*dd*, *J* = 6.9, 2.3, 1 H); 7.57 (*d*, *J* = 8.6, 2 H); 7.64 (*dd*, *J* = 6.9, 2.3, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 17.02; 17.26; 32.83; 55.37; 62.89; 96.30; 113.95; 122.64; 123.36; 126.78; 128.17; 128.24; 129.94; 139.28; 151.72; 161.97; 169.97. HR-MS: 311.1743 ($[M+H]^+$, $C_{19}H_{23}N_2O_2^+$; calc. 311.1759). Anal. calc. for $C_{19}H_{22}N_2O_2$ (310.39): C 73.52, H 7.14, N 9.03; found: C 73.32, H 7.18, N 8.80.

6-Chloro-3-(4-chlorophenyl)-N-*methoxy-1-phenyl-1*H-*isoindol-1-amine* (= N-*[6-Chloro-3-(4-chlorophenyl)-1-phenyl-1*H-*isoindol-1-yl]*-O-*methylhydroxylamine*; **5i**). White solid. M.p. 136–139° (hexane/CH_2Cl_2). IR (KBr): 3185, 1597. ^{1}H-NMR (500 MHz, $CDCl_3$): 3.38 (*s*, 3 H); 6.42 (*s*, 1 H); 7.33–7.35 (*m*, 3 H); 7.40 (*dd*, *J* = 8.0, 1.7, 1 H); 7.52 (*d*, *J* = 8.6, 2 H); 7.59 (*d*, *J* = 8.6, 2 H); 7.64 (*dd*, *J* = 8.0, 1.7, 1 H); 7.70 (*d*, *J* = 1.7, 1 H); 7.99 (*d*, *J* = 8.6, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 63.26; 94.51; 123.51; 124.60; 126.38; 128.61; 128.73; 128.97; 129.04; 129.78; 131.96; 135.87; 135.90; 137.00; 137.33; 155.18; 169.60. HR-MS: 383.0705 ($[M+H]^+$, $C_{21}H_{17}Cl_2N_2O^+$; calc. 383.0718). Anal. calc. for $C_{21}H_{16}Cl_2N_2O$ (383.27): C 65.81, H 4.21, N 7.31; found: C 65.53, H 4.24, N 7.10.

N,*6-Dimethoxy-3-(3-methylphenyl)-1-phenyl-1*H-*isoindol-1-amine* (= N-*[6-Methoxy-3-(3-methylphenyl)-1-phenyl-1*H-*isoindol-1-yl]*-O-*methylhydroxylamine*; **5j**). White solid. M.p. 103–104° (hexane/CH_2Cl_2). IR (KBr): 3174, 1613, 1599. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.54 (*s*, 3 H); 3.42 (*s*, 3 H); 3.91 (*s*, 3 H); 6.40 (*s*, 1 H); 6.94 (*dd*, *J* = 8.6, 2.3, 1 H); 7.23 (*d*, *J* = 2.3, 1 H); 7.29–7.35 (*m*, 4 H); 7.42 (*t*, *J* = 7.4, 1 H); 7.63 (*d*, *J* = 8.6, 1 H); 7.68 (*dd*, *J* = 7.2, 1.1, 2 H); 7.82 (*d*, *J* = 8.0, 1 H); 7.88 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 21.43; 55.66; 63.15; 93.95; 110.06; 114.07; 123.96; 125.53; 126.44; 128.23; 128.42; 129.07 (2 overlapped Cs); 130.87; 131.25; 134.04; 138.44; 138.56; 155.61; 160.76; 171.29. HR-MS: 359.1750 ($[M+H]^+$, $C_{23}H_{23}N_2O_2^+$; calc. 359.1759). Anal. calc. for $C_{23}H_{22}N_2O_2$ (358.43): C 77.07, H 6.19, N 7.82; found: C 77.00, H 6.25, N 7.56.

3-(4-Chlorophenyl)-N,*6-dimethoxy-1-phenyl-1*H-*isoindol-1-amine* (= N-*[3-(4-Chlorophenyl)-6-methoxy-1-phenyl-1*H-*isoindol-1-yl]*-O-*methylhydroxylamine*; **5k**). White solid. M.p. 147–149° (hexane/AcOEt). IR (KBr): 3142, 1607. ^{1}H-NMR (500 MHz, $CDCl_3$): 3.41 (*s*, 3 H); 3.87 (*s*, 3 H); 6.39 (*s*, 1 H);

6.92 (*dd*, *J* = 8.8, 2.0, 1 H); 7.25 (*d*, *J* = 2.0, 1 H); 7.29 – 7.33 (*m*, 3 H); 7.50 (*d*, *J* = 7.8, 2 H); 7.58 (*d*, *J* = 8.8, 1 H); 7.66 (*dd*, *J* = 7.8, 2.0, 2 H); 8.00 (*d*, *J* = 7.8, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 55.67; 63.17; 94.07; 110.24; 114.17; 123.68; 126.42; 128.36; 128.47; 128.88; 129.82; 130.41; 132.55; 136.58; 138.25; 155.63; 160.90; 170.03. HR-MS: 379.1198 ($[M+H]^+$, $C_{22}H_{20}ClN_2O_2^+$; calc. 379.1213). Anal. calc. for $C_{22}H_{19}ClN_2O_2$ (378.85): C 69.75, H 5.05, N 7.39; found: C 69.52, H 5.19, N 7.30.

N*,6-Dimethoxy-3-(1-methylethyl)-1-phenyl-1*H*-isoindol-1-amine* (= N-*[6-Methoxy-3-(1-methylethyl)-1-phenyl-1*H*-isoindol-1-yl]*-O-*methylhydroxylamine*; **5l**). White solid. M.p. 105 – 107° (hexane/CH_2Cl_2). IR (KBr): 3133, 1614. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.448 (*d*, *J* = 6.9, 3 H); 1.451 (*d*, *J* = 6.9, 3 H), 3.24 (*sept.*, *J* = 6.9, 1 H); 3.39 (*s*, 3 H); 3.83 (*s*, 3 H); 6.26 (*s*, 1 H); 6.87 (*dd*, *J* = 8.6, 2.3, 1 H); 7.14 (*d*, *J* = 2.3, 1 H); 7.28 – 7.31 (*m*, 3 H); 7.39 (*d*, *J* = 8.6, 1 H); 7.60 (*d*, *J* = 6.9, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 20.32; 20.59; 30.10; 55.60; 63.11; 93.69; 109.69; 113.91; 122.18; 126.26; 128.04; 128.30; 131.17; 138.79; 155.01; 160.66; 178.98. HR-MS: 311.1749 ($[M+H]^+$, $C_{19}H_{23}N_2O_2^+$; calc. 311.1759). Anal. calc. for $C_{19}H_{22}N_2O_2$ (310.39): C 73.52, H 7.14, N 9.03; found: C 73.36, H 7.18, N 8.97.

*3-(3-Chlorophenyl)-*N*-methoxy-1-(thiophen-2-yl)-1*H*-isoindol-1-amine* (= N-*[3-(3-Chlorophenyl)-1-(thiophen-2-yl)-1*H*-isoindol-1-yl]*-O-*methylhydroxylamine*; **5m**). White solid. M.p. 90 – 92° (hexane/CH_2Cl_2). IR (KBr): 3157, 1606. ^{1}H-NMR (500 MHz, $CDCl_3$): 3.36 (*s*, 3 H); 6.40 (*s*, 1 H); 6.96 (*dd*, *J* = 5.2, 3.4, 1 H); 7.23 (*dd*, *J* = 3.4, 1.1, 1 H); 7.27 (*dd*, *J* = 5.2, 1.1, 1 H); 7.45 – 7.53 (*m*, 4 H); 7.70 (*dd*, *J* = 6.9, 1.7, 1 H); 7.88 (*dd*, *J* = 6.9, 1.7, 1 H); 7.92 (*d*, *J* = 7.4, 1 H); 8.04 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 63.30; 92.99; 122.96; 123.95; 125.75; 125.77; 126.64; 126.68; 128.67; 129.00; 129.30; 129.95; 130.75; 134.78; 135.42; 137.20; 140.19; 152.31; 170.46. HR-MS: 355.0660 ($[M+H]^+$, $C_{19}H_{16}ClN_2OS^+$; calc. 355.0672). Anal. calc. for $C_{19}H_{15}ClN_2OS$ (354.85): C 64.31, H 4.26, N 7.89; found: C 64.26, H 4.19, N 7.86.

N-*Methoxy-3-(1-methylethyl)-1-(thiophen-2-yl)-1*H*-isoindol-1-amine* (= O-*Methyl*-N-*[3-(1-methylethyl)-1-(thiophen-2-yl)-1*H*-isoindol-1-yl]hydroxylamine*; **5n**). White solid. M.p. 97 – 99° (hexane/CH_2Cl_2). IR (KBr): 3157, 1607. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.43 (*d*, *J* = 6.9, 3 H); 1.46 (*d*, *J* = 6.9, 3 H); 3.23 – 3.28 (*m*, 1 H); 3.35 (*s*, 3 H); 6.27 (*s*, 1 H); 6.92 (*dd*, *J* = 4.6, 4.0, 1 H); 7.17 (*d*, *J* = 4.0, 1 H); 7.21 (*d*, *J* = 4.6, 1 H); 7.39 – 7.40 (*m*, 2 H); 7.49 (*dd*, *J* = 8.0, 2.8, 1 H); 7.76 (*dd*, *J* = 8.0, 2.8, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 20.17; 20.37; 29.97; 63.22; 92.64; 121.53; 123.39; 125.24; 125.31; 126.51; 128.61; 128.89; 137.87; 141.11; 151.81; 179.68. HR-MS: 287.1214 ($[M+H]^+$, $C_{16}H_{19}N_2OS^+$; calc. 287.1218). Anal. calc. for $C_{16}H_{18}N_2OS$ (286.39): C 67.10, H 6.33, N 9.78; found: C 67.04, H 6.44, N 9.62.

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