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AN EFFICIENT SYNTHESIS OF 3-SUBSTITUTED 3*H*-ISOBENZOFURAN-1-YLIDENAMINES BY THE REACTION OF 2-CYANOBENZALDEHYDES WITH ORGANOLITHIUMS AND THEIR CONVERSION INTO ISOBENZOFURAN-1(3*H*)-ONES

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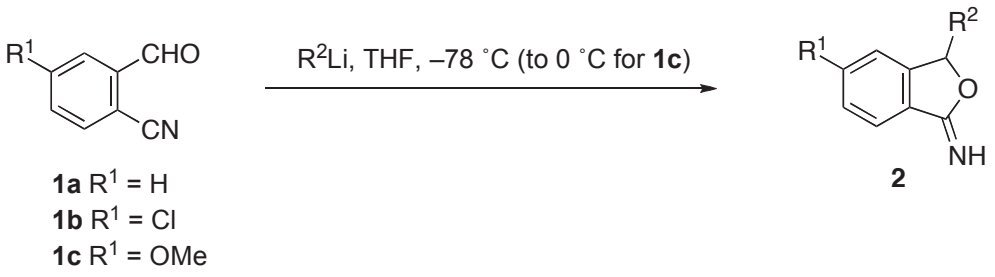
Abstract – A new and efficient synthesis of 3-substituted 3*H*-isobenzofuran-1-ylidenamines by the reaction of 2-cyanobenzaldehydes with nucleophiles, such as organolithiums or lithium enolates of *t*-butyl acetate and *N*,*N*-dimethylacetamide, is reported. Some of these products were converted into the corresponding 3-substituted isobenzofuran-1(3*H*)-ones (phthalides) upon treatment with hydrochloric acid in satisfactory yields.

There have been only a few reports on the preparation of 3*H*-isobenzofuran-1-ylidenamine derivatives in the literature. The synthesis of 3,3-disubstituted derivatives by the reaction of 2-lithiobenzonitrile with ketones has been reported by Parham and Jones in 1976.[1] In 1984 Kovtunenko and coworkers reported the synthesis of 3-phenyl-3*H*-isobenzofuran-1-ylidenamine by the hydride reduction of 2-benzoylbenzonitrile.[2] Van der Eycken and coworkers also reported the synthesis of 3-nonsubstituted 3*H*-isobenzofuran-1-ylidenamines by the hydride reduction of 2-cyanobenzaldehydes.[3] Recently, formation of this skeleton in the reaction of 1-isocyano-2-lithiobenzene with aldehydes as special cases has been reported by Alexander and de Meijere.[4] We report here an efficient one-pot method to synthesize 3-substituted 3*H*-isobenzofuran-1-ylidenamines by the reaction of 2-cyanobenzaldehydes with nucleophiles, such as organolithiums or lithium enolates of *t*-butyl acetate and *N*,*N*-dimethylacetamide. The conversion of some of these 3*H*-isobenzofuran-1-ylidenamines into the corresponding 3-substituted phthalides by acid hydrolysis is also reported. The biological activities[5] of phthalide derivatives have attracted the attention of many synthetic chemists.[6]

The synthesis of 3-alkyl(or aryl)-3*H*-isobenzofuran-1-ylidenamines (**2**) from 2-cyanobenzaldehydes (**1**) and organolithiums is outlined in Scheme 1. Thus, treatment of **1** with organolithiums was conducted in

THF to give **2**. An organolithium adds to the carbonyl carbon of **1** to generate a lithium alkoxide intermediate, which then attacks intramolecularly on the cyano carbon to yield lithium 3*H*-isobenzofuran-1-ylidenamide intermediate. This addition/ring closure sequence between 2-cyanobenzaldehydes (**1a**, **b**) and organolithiums proceeded smoothly at –78 ˚C to give, after usual workup and subsequent purification by column chromatography on silica gel, the desired 3*H*-isobenzofuran-1-ylidenamines (**2a-e**) in generally moderate-to-fair yields, as can be seen from Table 1, Entries 1-5. 2-Cyano-5-methoxybenzaldehyde (**1c**) was first treated with 4-methoxyphenyllithium under the same conditions as described above, but only a small amount of the corresponding 3*H*-isobenzofuran-1-ylidenamine (**2f**) was detected along with a considerable amount of 2-[hydroxy(4-methoxyphenyl)methyl]benzonitrile by ^{1}H NMR analyses of the mixture after aqueous workup. This is most likely due to the lower reactivity of the nitrile function in compound **1c**. TLC monitoring of the reaction also revealed that while the addition of 4-methoxyphenyl anion to the carbonyl function proceeded immediately at this temperature, ring closure by the addition of the resulting alkoxide to the cyano function was very sluggish. The production of **2f** in a somewhat lower yield compared to those of **2a-e**, however, was achieved by raising the reaction temperature to 0 ˚C (Entry 6). Attempts to obtain the respective 3*H*-isobenzofuran-1-ylidenamines from 2-cyano-4,5-methylenedioxybenzaldehyde and organolithiums resulted in an almost quantitative recovery of the starting materials. Presumably this result indicates that the methylenedioxy substituent considerably decreases the reactivity toward organolithiums.



1a R^1 = H
1b R^1 = Cl
1c R^1 = OMe

Scheme 1

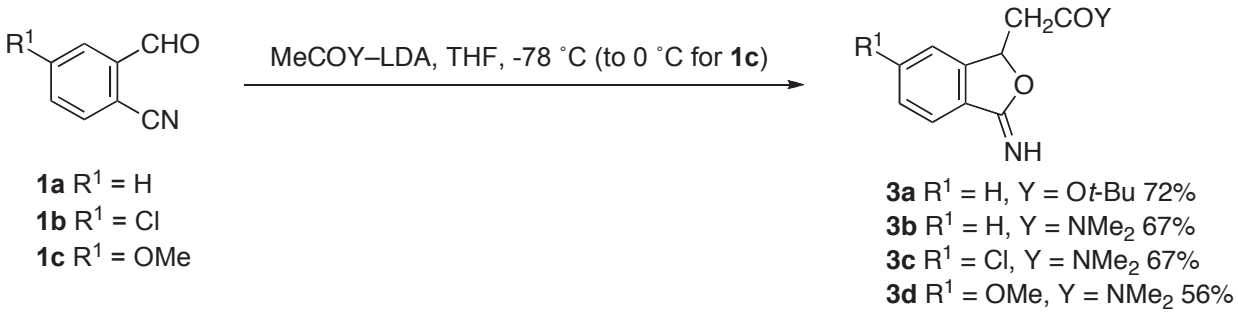
Table 1. Preparation of 3*H*-isobenzofuran-1-ylidenamines (**2**)

Entry	**1**	R^2 in R^2Li	**2** (Yield /%)[a]
1	**1a** (R^1 = H)	Ph	**2a** (58)
2	**1a**	*n*-Bu	**2b** (42)
3	**1a**	*t*-Bu	**2c** (36)
4	**1b** (R^1 = Cl)	Ph	**2d** (56)
5	**1b**	*p*-Tol	**2e** (52)
6	**1c** (R^1 = OMe)	4-$MeOC_6H_4$	**2f** (42)

[a] Isolated yields.

It should be noted that the use of Grignard reagents, such as ethylmagnesium bromide and phenylmagnesium bromide, in place of organolithiums proved to result in the formation of complex mixtures of products, containing those probably arising from the addition of Grignard reagents to the cyano carbon. The reaction of 2-benzoylbenzonitrile with phenyllithium gave a similar result. 2-Acetylbenzonitrile also did not work well due to deprotonation of α-hydrogen with organolithiums.

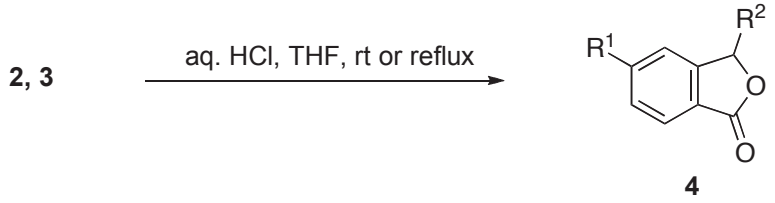
Compounds (**1a**) and (**1b**) were then allowed to react with lithium enolates of *t*-butyl acetate and *N*,*N*-dimethylacetamide under the conditions as described above for the preparation of 3-substituted 3*H*-isobenzofuran-1-ylidenamines (**2a-e**) to give the corresponding 2-(3-imino-1,3-dihydroisobenzofuran-1-yl)acetic acid derivatives (**3a-c**) in relatively good yields as shown in Scheme 2. The reaction of **1c** with lithium enolate of *N*,*N*-dimethylacetamide giving **3d** also required raising the reaction temperature to 0 ˚C and 2-cyano-4,5-methylenedioxybenzaldehyde did not give the desired product as well. It should be noted that the stereochemistry of the imino moiety of each of the products **2** and **3** is not clear yet.



1a R^1 = H
1b R^1 = Cl
1c R^1 = OMe

3a R^1 = H, Y = O*t*-Bu 72%
3b R^1 = H, Y = NMe_2 67%
3c R^1 = Cl, Y = NMe_2 67%
3d R^1 = OMe, Y = NMe_2 56%

Scheme 2



4

Scheme 3

Table 2. Preparation of isobenzofuran-1(3*H*)-ones **4**

Entry	**2** or **3**	Temp	Time	**4** (Yield /%)[a]
1	**2a**	rt	overnight	**4a** (78)
2	**2e**	rt	overnight	**4b** (70)
3	**2f**	reflux	4 h	**4c** (68)
4	**3c**	rt	overnight	**4d** (74)
5	**3d**	reflux	4 h	**4e** (53)

[a] Isolated yields.

Some of 3*H*-isobenzofuran-1-ylidenamine derivatives thus obtained were then hydrolyzed under acidic conditions to give the corresponding phthalide derivatives. Thus, treatment of **2a**, **2e**, and **3c** with 10 % hydrochloric acid in THF at room temperature overnight gave the corresponding phthalide derivatives (**4a**), (**4b**)**,** and (**4d**), respectively, in relatively good yields (Entries 1, 2, and 4). Hydrolysis of compounds **2f** and **3d**, which have a methoxy group at the 5-position, under the same conditions proved difficult. The higher temperature was required to accomplish hydrolysis of these compounds. Thus, heating solutions of **2f** and **3d** in THF containing 10 % hydrochloric acid at reflux temperature for 4 h provided the corresponding phthalide derivatives (**4c**) and (**4e**), respectively, in moderate-to-fair yields (Entries 3 and 5).

In conclusion, we have demonstrated that 3-substituted 3*H*-isobenzofuran-1-ylidenamines can be produced via addition of organolithiums or lithium enolates of *t*-butyl acetate and *N*,*N*-dimethylacetamide to the carbonyl carbon of 2-cyanobenzaldehydes, followed, in the same pot, by intramolecular attack of the resulting alkoxides on the cyano carbon. Acid treatment of some of these 3*H*-isobenzofuran-1-ylidenamines hydrolyzed the imino function to yield the corresponding isobenzofuran-1(3*H*)-one derivatives. As the synthetic method reported in this paper starts with readily available compounds and is operationally simple, it may find some value in organic synthesis.

EXPERIMENTAL

The melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were determined with a Shimadzu FTIR-8300 spectrophotometer. The ^{1}H NMR spectra were determined in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 MHz. The ^{13}C NMR spectra were determined in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz. Low- and high-resolution MS spectra (EI, 70 eV) were measured by a JEOL JMS AX505 HA spectrometer. TLC was carried out on a Merck Kieselgel 60 PF_{254}. Column chromatography was performed using Merck Kieselgel 60 (0.063–0.200 mm). All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

Starting Materials. 5-Chloro-2-cyanobenzaldehyde (**1b**)[7,8] and 2-cyano-5-methoxybenzaldehyde (**1c**)[7] were prepared by the appropriate reported procedure. All other chemicals used in this study were commercially available.

Typical Procedure for the Preparation of 3-Substituted 3*H*-isobenzofuran-1-ylidenamines (2). 3-Phenyl-3*H*-isobenzofuran-1-ylidenamine (2a). To a stirred solution of **1a** (0.14 g, 1.0 mmol) in THF (2 mL) at –78 ˚C was added PhLi (1.08 M in cyclohexane; 1.0 mmol); the mixture was stirred for 15 min at the same temperature before saturated aqueous NH_4Cl (10 mL) was added in order to quench the reaction. The organic materials were extracted with AcOEt three times (5 mL each), and the combined

extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated by evaporation. The residue was purified by column chromatography on silica gel (1:3 AcOEt–$CHCl_3$) to give **2a** (0.12 g, 58%); colorless needles; mp 121–123 °C (Et_2O) (lit.,[1] mp 120–121 °C); IR (KBr) 3298, 3284, 1686, 1614 cm^{-1}; ^1H NMR δ 6.38 (s, 1H), 7.22 (d, *J* = 7.8 Hz, 1H), 7.26–7.28 (m, 3H), 7.34–7.40 (m, 3H), 7.50 (dd, *J* = 7.8, 7.3 Hz, 1H), 7.54 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1H), 7.93 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR δ 84.81, 122.46, 123.87, 126.96 (2C), 128.88 (2C), 128.95, 129.06, 132.31, 137.93, 147.17; MS *m/z* 209 (M^+, 100).

3-Butyl-3*H*-isobenzofuran-1-ylidenamine (2b): a beige oil; R_f 0.29 (1:3 AcOEt–$CHCl_3$); IR (neat) 3295, 3233, 1683, 1616 cm^{-1}; ^1H NMR δ 0.92 (t, *J* = 7.3 Hz, 3H), 1.31–1.52 (m, 4H), 1.72–1.79 (m, 1H), 1.96–2.03 (m, 1H), 5.47 (dd, *J* = 7.8, 4.1 Hz, 1H), 7.26 (br, 1H), 7.26 (d, *J* = 7.8 Hz, 1H), 7.47 (dd, *J* = 7.8, 7.3 Hz, 1H), 7.56 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1H), 7.77 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR δ 13.88, 22.49, 26.85, 34.94, 83.30, 121.35 (2C), 123.81, 128.59, 128.99, 131.92, 147.48; MS *m/z* 189 (M^+, 100). Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.06; H, 7.86; N, 7.48.

3-(1,1-Dimethylethyl)-3*H*-isobenzofuran-1-ylidenamine (2c): a pale-yellow oil; R_f 0.40 (1:1 AcOEt–$CHCl_3$); IR (neat) 3296, 3219, 1683, 1615 cm^{-1}; ^1H NMR δ 1.00 (s, 9H), 5.12 (s, 1H), 7.26 (br s, 1H), 7.44 (d, *J* = 7.3 Hz, 1H), 7.46 (t, *J* = 7.3 Hz, 1H), 7.52 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR δ 25.39, 36.00, 90.55, 123.01 (2C), 123.77, 128.58, 128.98, 131.43, 145.35; MS *m/z* 189 (M^+, 100). Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 75.87; H, 8.27; N, 7.67.

5-Chloro-3-phenyl-3*H*-isobenzofuran-1-ylidenamine (2d): a pale-yellow solid; mp 103–105 °C (hexane); IR (KBr) 3277, 3230, 1676, 1605 cm^{-1}; ^1H NMR δ 6.34 (s, 1H), 7.20 (d, *J* = 1.8 Hz, 1H), 7.25–7.27 (m, 3H), 7.39–7.41 (m, 3H), 7.46 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.86 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR δ 84.25, 122.82, 125.18, 126.87 (2C), 129.05, 129.34, 129.70, 132.53, 137.23, 138.75, 148.85; MS *m/z* 243 (M^+, 100). Anal. Calcd for $C_{14}H_{10}ClNO$: C, 69.00; H, 4.14; N, 5.75. Found: C, 68.98; H, 4.23; N, 5.68.

5-Chloro-3-(4-methylphenyl)-3*H*-isobenzofuran-1-ylidenamine (2e): a pale-yellow solid; mp 110–112 °C (hexane–THF); IR (KBr) 3277, 1682, 1609 cm^{-1}; ^1H NMR δ 2.36 (s, 3H), 6.30 (s, 1H), 7.13 (d, *J* = 7.8 Hz, 2H), 7.20 (d, *J* = 7.8 Hz, 2H), 7.29–7.33 (m, 2H), 7.45 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.86 (br d, *J* = 8.2 Hz, 1H); ^{13}C NMR δ 21.20, 84.20, 122.78, 126.94 (2C), 129.68, 134.20, 135.71, 138.66, 139.39, 141.71, 142.99, 148.97; MS *m/z* 257 (M^+, 100). Anal. Calcd for $C_{15}H_{12}ClNO$: C, 69.91; H, 4.69; N, 5.43. Found: C, 69.91; H, 4.70; N, 5.26.

5-Methoxy-3-(4-methoxylphenyl)-3*H*-isobenzofuran-1-ylidenamine (2f): a colorless oil; R_f 0.28 (AcOEt); IR (neat) 3293, 1682, 1611 cm^{-1}; ^1H NMR δ 3.80 (s, 3H), 3.81 (s, 3H), 6.27 (s, 1H), 6.62 (d, *J* = 2.3 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 2H), 7.01 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.18 (d, *J* = 8.2 Hz, 2H), 7.26 (br s, 1H), 7.82 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR δ 55.33, 55.66, 84.23, 106.47, 114.28, 116.28, 125.16, 125.62,

128.76, 129.92, 130.89, 149.64, 160.27, 163.37; MS *m/z* 269 (M^+, 100). Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.22; H, 5.64; N, 5.19.

Typical Procedure for the Preparation of 2-(3-Imino-1,3-dihydroisobenzofuran-1-yl)acetic Acid Derivatives (3). 1,1-Dimethylethyl 2-(3-Imino-1,3-dihydroisobenzofuran-1-yl)acetate (3a). To a stirred solution of LDA (1.0 mmol), which was generated by the standard method, in THF (6 mL) at –78 ˚C was added dropwise 1,1-dimethylethyl acetate (0.12 g, 1.0 mmol). After 15 min a solution of 2-cyanobenzaldehyde (**1a**) (0.14 g, 1.0 mmol) in THF (2 mL) was added and stirring was continued for an additional 15 min before saturated aqueous NH_4Cl (10 mL) was added. The organic materials were extracted with AcOEt twice (10 mL each), and the combined extracts were washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel to afford **3a** (0.18 g, 72%) as a pale-yellow oil; R_f 0.32 (1:2 THF–hexane); IR (neat) 3296, 1730, 1688 cm^{-1}; ^1H NMR δ 1.45 (s, 9H), 2.78 (dd, *J* = 16.0, 6.4 Hz, 1H), 2.80 (dd, *J* = 16.0, 6.4 Hz, 1H), 5.82 (t, *J* = 6.4 Hz, 1H), 7.26 (br , 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.49 (t, *J* = 7.3 Hz, 1H), 7.56 (ddd, *J* = 7.8, 7.3, 0.9 Hz, 1H), 7.86 (br d, *J* = 7.3 Hz, 1H); ^{13}C NMR δ 28.00, 41.33, 79.27, 81.69, 121.59, 123.94, 125.50, 129.04 (2C), 132.15, 146.29, 168.83; MS *m/z* 247 (M^+, 1.2), 192 (15), 146 (100). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.95; H, 6.82; N, 5.64.

***N,N*-Dimethyl-2-(3-imino-1,3-dihydroisobenzofuran-1-yl)acetamide (3b):** a pale-yellow oil; R_f 0.27 (1:6 MeOH–C_6H_6); IR (neat) 3256, 1682, 1643 cm^{-1}; ^1H NMR δ 2.73 (dd, *J* = 16.0, 6.4 Hz, 1H), 2.99 (s, 3H), 3.00 (dd, *J* = 16.0, 6.8 Hz, 1H), 3.03 (s, 3H), 6.03 (dd, *J* = 6.8, 6.4 Hz, 1H), 7.26 (br, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.50 (dd, *J* = 7.8, 7.3 Hz, 1H), 7.55 (td, *J* = 7.3, 0.9 Hz, 1H), 7.86 (br d, *J* = 7.3 Hz, 1H); ^{13}C NMR δ 35.46, 37.27, 39.41, 80.09, 122.34, 123.77 (2C), 128.29, 128.96, 132.18, 147.01, 168.91; MS *m/z* 219 (M+1, 47), 218 (M^+, 100). Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.06; H, 6.50; N, 12.80.

2-(6-Chloro-3-imino-1,3-dihydroisobenzofuran-1-yl)-*N,N*-dimethylacetamide (3c): a pale-yellow oil; R_f 0.29 (1:6 MeOH–C_6H_6); IR (neat) 3258, 1688, 1643 cm^{-1}; ^1H NMR δ 2.69 (dd, *J* = 16.0, 6.9 Hz, 1H), 2.99 (s, 3H), 3.01 (dd, *J* = 16.0, 6.9 Hz, 1H), 3.03 (s, 3H), 5.98 (t, *J* = 6.9 Hz, 1H), 7.26 (br, 1H), 7.45 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.55 (d, *J* = 1.8 Hz, 1H), 7.79 (br d, *J* = 8.2 Hz, 1H); MS *m/z* (%) 253 (M+1, 12), 252 (M^+, 7.7), 180 (100). HR-MS Calcd for $C_{12}H_{13}ClN_2O_2$: M, 252.0666. Found: *m/z* 252.0651.

2-(3-Imino-6-methoxy-1,3-dihydroisobenzofuran-1-yl)-*N,N*-dimethylacetamide (3d): a colorless oil; R_f 0.28 (1:6 MeOH–C_6H_6); IR (neat) 3284, 1682, 1640 cm^{-1}; ^1H NMR δ 2.69 (dd, *J* = 16.0, 6.4 Hz, 1H), 2.98 (dd, *J* = 16.0, 7.3 Hz, 1H), 2.99 (s, 3H), 3.03 (s, 3H), 3.86 (s, 3H), 5.95 (dd, *J* = 7.3, 6.4 Hz, 1H), 6.98–7.01 (m, 2H), 7.36 (br, 1H), 7.74 (br d, *J* = 7.3 Hz, 1H); ^{13}C NMR δ 35.47, 37.31, 39.46, 55.70, 79.57, 99.90, 106.49, 116.24, 125.13, 128.31, 149.47, 163.26, 169.00; MS *m/z* 249 (M+1, 48), 248 (M^+, 100). Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.87; H, 6.69; N, 11.29.

General Procedure for the Preparation of 3-Substituted Isobenzofuran-1(3*H*)-ones 4. A solution of **3**

(0.5 mmol) in THF (3 mL) and 10% aqueous HCl (1.5 mL) was stirred for the time at the temperature indicated in Table 2. The mixture was then treated with saturated aqueous $NaHCO_3$ (10 mL) and the organic materials were extracted with AcOEt three times (5 mL each). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, concentrated by evaporation. The residual solid was recrystallized to give pure **4**.

3-Phenylisobenzofuran-1(3*H*)-one (4a): a white solid; mp 113–115˚C ($CHCl_3$) (lit.,[9] 114–115 ˚C). The spectral data for this product were identical to those reported previously.[10]

5-Chloro-3-(4-methylphenyl)isobenzofuran-1(3*H*)-one (4b): a pale-yellow solid; mp 164–166 ˚C ($CHCl_3$); IR (KBr) 1751 cm^{-1}; ^1H NMR δ 2.37 (s, 3H), 6.33 (s, 1H), 7.14 (d, *J* = 7.8 Hz, 2H), 7.20 (d, *J* = 7.8 Hz, 2H), 7.30 (s, 1H), 7.52 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.88 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR δ 21.22, 82.15, 123.27, 124.19, 126.78, 126.94, 129.78, 130.11, 132.67, 139.67, 141.02, 151.44, 169.37; MS *m/z* 258 (M^+, 100). Anal. Calcd for $C_{15}H_{11}ClO_2$: C, 69.64; H, 4.29. Found: C, 69.48; H, 4.46.

5-Methoxy-3-(4-methoxyphenyl)isobenzofuran-1(3*H*)-one (4c):[11] a pale-yellow solid; mp 99–101 ˚C (hexane–CH_2Cl_2); IR (KBr) 1751, 1620, 1609 cm^{-1}; ^1H NMR δ 3.82 (s, 3H), 3.88 (s, 3H), 6.63 (s, 1H), 6.94 (d, *J* = 1.8 Hz, 1H), 7.03 (d, *J* = 8.7 Hz, 2H), 7.22 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.28 (d, *J* = 8.7 Hz, 2H), 7.88 (d, *J* = 8.2 Hz, 1H).

2-(6-Chloro-3-oxo-1,3-dihydroisobenzofuran-1-yl)-*N*,*N*-dimethylacetamide (4d): a pale-yellow solid; mp 165–167 ˚C ($CHCl_3$); IR (KBr) 1759, 1636 cm^{-1}; ^1H NMR δ 2.68 (dd, *J* = 16.0, 8.2 Hz, 1H), 2.99 (s, 3H), 3.03 (s, 3H), 3.17 (dd, *J* = 16.0, 5.0 Hz, 1H), 6.00 (dd, 8.2, 5.0 Hz, 1H), 7.51 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.73 (d, *J* = 1.8 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR δ 35.44, 37.21, 38.63, 77.72, 124.07, 124.33, 126.67, 130.13, 133.01, 140.98, 151.57, 168.28; MS *m/z* 253 (M^+, 100). Anal. Calcd for $C_{12}H_{12}ClNO_3$: C, 56.81; H, 4.77; N, 5.52. Found: C, 56.90; H, 4.80; N, 5.41.

2-(6-Methoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-*N*,*N*-dimethylacetamide (4e): a pale-yellow solid; mp 119–121˚C (hexane–CH_2Cl_2); IR (KBr) 1759, 1645 cm^{-1}; ^1H NMR δ 2.68 (dd, *J* = 16.0, 7.8 Hz, 1H), 2.99 (s, 3H), 3.02 (s, 3H), 3.12 (dd, *J* = 16.0, 6.0 Hz, 1H), 3.89 (s, 3H), 5.95 (dd, *J* = 7.8, 6.0 Hz, 1H), 7.03 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.12 (d, *J* = 2.3 Hz, 1H), 7.79 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR δ 35.44, 37.32, 38.88, 55.83, 77.60, 106.98, 116.94, 117.98, 127.00, 152.78, 164.81, 168.70, 169.91. MS *m/z* 249 (M^+, 100). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.63; H, 6.09; N, 5.52.

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