A Convenient Synthesis of 2,3-Dihydro-3-methylidene-1*H*-isoindol-1-ones by Reaction of 2-Formylbenzonitriles with Dimethyloxosulfonium Methylide

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A facile method for the synthesis of 2,3-dihydro-3-methylidene-1*H*-isoindol-1-one and its derivatives carrying substituent(s) at C(5) and/or C(6) has been developed. The reaction of 2-formylbenzonitrile (**1a**) with dimethyloxosulfonium methylide, generated by the treatment of trimethylsulfoxonium iodide with NaH in DMSO/THF at 0°, resulted in the formation of 2,3-dihydro-3-methylidene-1*H*-isoindol-1-one (**2a**) in 77% yield. Similarly, six 2-formylbenzonitriles carrying substituent(s) at C(4) and/or C(5), *i.e.*, **1b**–**1g**, also gave the corresponding expected products **2b**–**2g** in comparable yields.

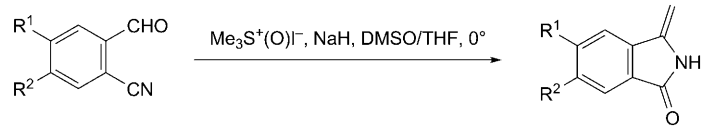
Introduction. – The use of dimethyloxosulfonium methylide, generated from trimethylsulfoxonium iodide and an appropriate base, for the preparation of epoxides from carbonyl compounds has already been described in the literature [1]. In this article, we describe the results of our study on the reaction of 2-formylbenzonitriles with this sulfur ylide. We have found that the reaction provides a convenient method to prepare 2,3-dihydro-3-methylidene-1*H*-isoindol-1-ones. Some molecules including 3-alkyl- or 3-arylmethylideneisoindol-1-one moiety have been shown to possess considerable medicinal versatility [2][1]). The development of synthetic protocols for the preparation of this class of heterocycles from readily available starting materials has, consequently, attracted the attention of several groups recently [3]. However, there are a few reports on the methods applicable to the preparation of 2,3-dihydro-3-methylidene-1*H*-isoindol-1-ones [3a][3f][3g][4]. For example, the construction of this skeleton by treating 1-(2-bromophenyl)ethanones with titanium–isocyanate complex prepared from $TiCl_4$ under atmospheric pressure of molecular N_2 and CO in the presence of a Pd catalyst has been achieved by *Uozumi*, *Mori*, and *Shibasaki* [3a]. *Meyer* and *Cossy* have synthesized 2-(2-bromophenyl)- and 2-allyl-2,3-dihydro-3-methylidene-1*H*-isoindol-1-ones by a Pd-catalyzed cyclization of the corresponding *N*-ethynyl-2-iodobenzamides [3f].

Results and Discussion. – We initiated our investigation by reacting 2-formylbenzonitrile (**1a**) with dimethyloxosulfonium methylide. Thus, trimethylsulfoxonium iodide was treated with NaH in DMSO/THF 1:1 (*v*/*v*) at 0° to generate the corresponding sulfur ylide. To this solution was added **1a**, which was consumed within 5 min. After usual workup and subsequent purification of the crude product by column

[1]) See also pertinent references cited in [3d] and [3f].

chromatography on silica gel, 2,3-dihydro-3-methylidene-1*H*-isoindol-1-one (**2a**) was isolated as the sole product in relatively good yield, as shown in *Scheme 1*. The structure of the product was determined by comparison of its spectral (IR and ^{1}H-NMR) data with those reported in [3a]. No trace of 2-(oxiran-2-yl)benzonitrile (**4**) was isolated.

Scheme 1



	R^1	R^2
1a	H	H
1b	H	Cl
1c	Cl	H
1d	H	MeO
1e	MeO	H
1f	MeO	MeO
1g	$-OCH_2O-$	

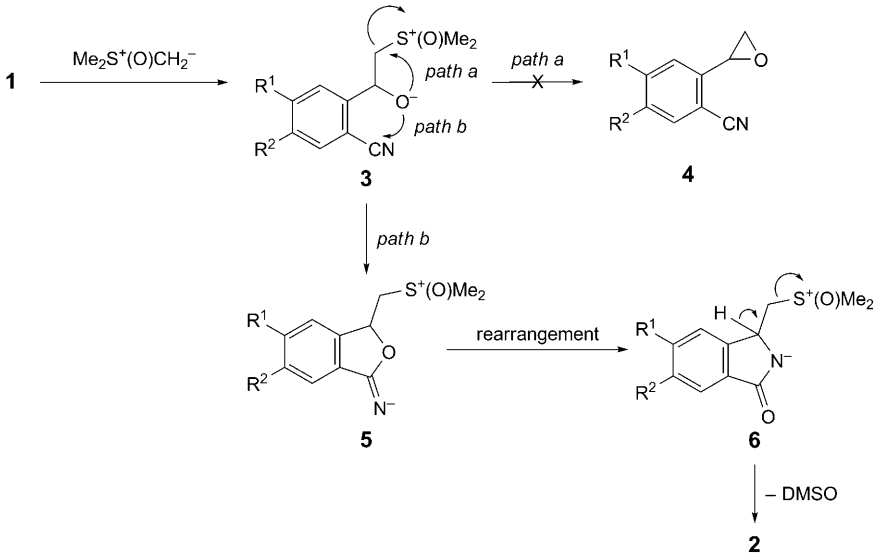
	R^1	R^2	Yield [%]
2a	H	H	77
2b	H	Cl	75
2c	Cl	H	72
2d	H	MeO	63
2e	MeO	H	78
2f	MeO	MeO	68
2g	$-OCH_2O-$		75

To explore the generality of this reaction, six other substituted 2-formylbenzonitriles **1b**–**1g** were prepared from the respective 2-bromobenzaldehydes according to the procedure developed by *Astles et al.* [5]. Using these starting materials, the corresponding substituted 2,3-dihydro-3-methylidene-1*H*-isoindol-1-ones **2b**–**2g** could be obtained under the conditions described above in comparable yields to that of **2a**. These results are also summarized in *Scheme 1*. All products were easily purified by column chromatography on silica gel or recrystallization.

A probable pathway leading to the formation of 2,3-dihydro-3-methylidene-1*H*-isoindol-1-ones **2** from 2-formylbenzonitriles **1** is illustrated in *Scheme 2*. Thus, dimethyloxosulfonium methylide adds to the C=O C-atom of **1** to give the adduct **3**. Formation of 2-(oxiran-2-yl)benzonitrile **4** by the intramolecular attack of the alkoxide of **3** at the C-atom adjacent to the oxosulfonium S-atom (*Path a*) does not occur. Instead, the alkoxide of **3** attacks intramolecularly the C-atom of the C≡N group (*Path b*) to generate the imino anion intermediate **5**. The latter rearranges to the lactam anion intermediate **6**, from which elimination of dimethyl sulfoxide, accompanied by H-atom transfer, gives rise to **2**. Similar rearrangement reactions have been reported previously [6].

In summary, we have developed a convenient method for preparing 2,3-dihydro-3-methylidene-1*H*-isoindol-1-ones, which are difficult to prepare by previous methods, by the reaction of 2-formylbenzonitriles with dimethyloxosulfonium methylide, generated from trimethylsulfoxonium iodide with NaH. Since the method employs readily available starting materials and is operationally very simple, it may be of value in organic synthesis.

Scheme 2



Experimental Part

General. All of the org. solvents used in this study were dried over appropriate drying agents and distilled prior to use. 2-Formylbenzonitriles **1d** [5], **1e** [5], **1f** [7], **1g** [8], and 2-bromo-4-chlorobenzaldehyde [9] were prepared by previously reported methods. TLC: *Merck Kieselgel 60 PF_{254}*. Column chromatography (CC): *Merck Kieselgel 60* (SiO_2; 0.063–0.200 mm). M.p.: *Laboratory Devices MEL-TEMP II* melting-point apparatus; uncorrected. IR Spectra: *Shimadzu FTIR-8300* spectrophotometer; in KBr disks. ^{1}H-NMR Spectra: *JEOL ECP500* FT NMR spectrometer operating at 500 MHz; in $CDCl_3$ with TMS as an internal reference. ^{13}C-NMR Spectra: *JEOL ECP500* FT NMR spectrometer operating at 125 MHz; with TMS as an internal reference. EI-MS (70 eV): *JEOL JMS AX505 HA* spectrometer.

2-Formylbenzonitriles **1b** *and* **1c**. These compounds were prepared from the respective 2-bromobenzaldehydes according to the procedure reported for the preparation of **1d** [5].

5-Chloro-2-formylbenzonitrile (**1b**). Yield 55%. White solid. M.p. 108–110° (from hexane/$CHCl_3$). IR: 2228, 1703. ^{1}H-NMR: 7.76 (*dd*, *J* = 8.2, 2.3, 1 H); 7.82 (*d*, *J* = 2.3, 1 H); 8.01 (*d*, *J* = 8.2, 1 H); 10.32 (*s*, 1 H). Anal. calc. for C_8H_4ClNO: C 58.03, H 2.43, N 8.46; found: C 58.12, H 2.42, N 8.32.

4-Chloro-2-formylbenzonitrile (**1c**). Yield 53%. White solid. M.p. 98–100° (from hexane/$CHCl_3$). IR: 2228, 1705. ^{1}H-NMR: 7.65 (*dd*, *J* = 8.2, 2.3, 1 H); 7.72 (*d*, *J* = 8.2, 1 H); 7.95 (*d*, *J* = 2.3, 1 H); 10.25 (*s*, 1 H). Anal. calc. for C_8H_4ClNO: C 58.03, H 2.43, N 8.46; found: C 58.13, H 2.53, N 8.32.

*2,3-Dihydro-3-methylidene-1*H*-isoindol-1-one* (**2a**; *Typical Procedure*). To a stirred suspension of $Me_3S^+(O)I^-$ (0.18 g, 0.82 mmol) in DMSO/THF 1:1 (3 ml) at 0° was added NaH (60% in oil; 33 mg, 0.82 mmol) in one portion. After the evolution of H_2 gas had ceased, a soln. of 2-formylbenzonitrile (**1a**) (0.11 g, 0.68 mmol) in DMSO/THF 1:1 (2 ml) was added dropwise. After 5 min, H_2O (10 ml) was added, and the org. materials were extracted with AcOEt (3 × 10 ml). The combined extracts were washed with H_2O (3 × 10 ml) and then brine (10 ml), and dried (Na_2SO_4). Evaporation of the solvent gave a residual solid, which was purified by CC (SiO_2; THF/hexane 1:3) to afford **2a** (91 mg, 76%). Pale-yellow solid. M.p. 240–243° (from hexane/CH_2Cl_2). The IR and ^{1}H-NMR data for this product were identical to those reported in [3a]. ^{13}C-NMR: 90.42; 120.25; 123.34; 129.52; 129.98; 132.25; 137.12; 139.81; 168.77. MS: 145 (100, M^+).

*6-Chloro-2,3-dihydro-3-methylidene-1*H*-isoindol-1-one* (**2b**). Beige solid. M.p. 143° (dec.; from hexane/CH_2Cl_2). IR: 3177, 1717, 1645, 1605. ^{1}H-NMR: 4.98 (*d*, *J* = 2.3, 1 H); 5.19 (*d*, *J* = 2.3, 1 H); 7.58

(*dd*, *J* = 8.2, 1.8, 1 H); 7.64 (*d*, *J* = 8.2, 1 H); 7.82 (*d*, *J* = 1.8, 1 H); 7.95 (br. *s*, 1 H). ^{13}C-NMR ($CDCl_3$): 91.54; 121.59; 123.48; 131.57; 132.46; 135.27; 135.78; 139.05; 167.56. MS: 179 (100, M^+). Anal. calc. for C_9H_6ClNO: C 60.19, H 3.37, N 7.80; found: C 60.08, H 3.49, N 7.72.

*5-Chloro-2,3-dihydro-3-methylidene-1*H-*isoindol-1-one* (**2c**). Pale-yellow solid. M.p. 186° (dec.; from hexane/CH_2Cl_2). IR: 3177, 1738, 1715, 1660, 1611. ^{1}H-NMR: 4.98 (*d*, *J* = 2.3, 1 H); 5.19 (*d*, *J* = 2.3, 1 H); 7.50 (*dd*, *J* = 8.2, 1.8, 1 H); 7.68 (*d*, *J* = 1.8, 1 H); 7.70 (br. *s*, 1 H); 7.78 (*d*, *J* = 8.2, 1 H). ^{13}C-NMR ((D_6)DMSO): 92.38; 121.20; 124.48; 128.74; 129.85; 137.36; 138.79; 139.30; 166.86. MS: 179 (100, M^+). Anal. calc. for C_9H_6ClNO: C 60.19, H 3.37, N 7.80; found: C 60.02, H 3.41, N 7.71.

*2,3-Dihydro-6-methoxy-3-methylidene-1*H-*isoindol-1-one* (**2d**). Pale-yellow needles. M.p. 115° (dec.; from hexane/CH_2Cl_2). IR: 3171, 1709, 1697, 1646, 1620. ^{1}H-NMR: 3.89 (*s*, 3 H); 4.88 (*d*, *J* = 1.8, 1 H); 5.08 (*d*, *J* = 1.8, 1 H); 7.16 (*dd*, *J* = 8.2, 2.3, 1 H); 7.32 (*d*, *J* = 2.3, 1 H); 7.60 (*d*, *J* = 8.2, 1 H); 8.11 (br. *s*, 1 H). ^{13}C-NMR ($CDCl_3$): 55.76; 89.49; 105.76; 120.66; 121.53; 129.87; 131.69; 139.64; 161.20; 168.93. MS: 175 (100, M^+). Anal. calc. for $C_{10}H_9NO_2$: C 68.56, H 5.18, N 8.00; found: C 68.54, H 5.14, N 7.96.

*2,3-Dihydro-5-methoxy-3-methylidene-1*H-*isoindol-1-one* (**2e**). Colorless crystals. M.p. 165° (dec.; from hexane/$CHCl_3$). IR: 3215, 1697, 1655, 1609. ^{1}H-NMR: 3.94 (*s*, 3 H); 4.90 (*d*, *J* = 1.8, 1 H); 5.14 (*d*, *J* = 1.8, 1 H); 7.05 (*dd*, *J* = 8.2, 2.3, 1 H); 7.15 (*d*, *J* = 2.3, 1 H); 7.60 (br. *s*, 1 H); 7.75 (*d*, *J* = 8.2, 1 H). ^{13}C-NMR ($CDCl_3$): 55.73; 90.00; 104.45; 116.60; 122.78; 124.78; 139.40; 139.86; 163.47; 168.67. MS: 175 (100, M^+). Anal. calc. for $C_{10}H_9NO_2$: C 68.56, H 5.18, N 8.00; found: C 68.33, H 5.30, N 7.90.

*2,3-Dihydro-5,6-dimethoxy-3-methylidene-1*H-*isoindol-1-one* (**2f**). Beige solid. M.p. 207° (dec.; from hexane/CH_2Cl_2). IR: 3179, 1724, 1686, 1672, 1609. ^{1}H-NMR: 3.96 (*s*, 3 H); 4.00 (*s*, 3 H); 4.87 (*d*, *J* = 2.3, 1 H); 5.07 (*d*, *J* = 2.3, 1 H); 7.12 (*s*, 1 H); 7.29 (*s*, 1 H); 7.69 (br. *s*, 1 H). ^{13}C-NMR ($CDCl_3$): 56.31 (two overlapped C-atoms); 89.34; 102.12; 104.58; 122.92; 130.99; 139.92; 151.12; 153.24; 168.95. MS: 205 (100, M^+). Anal. calc. for $C_{11}H_{11}NO_3$: C 64.38, H 5.40, N 6.83; found: C 64.29, H 5.56, N 6.79.

*6,7-Dihydro-7-methylidene-5*H-*[1,3]dioxolo[4,5-*f*]isoindol-5-one* (**2g**). Beige solid. M.p. 238° (dec.; from hexane/THF). IR: 3192, 1701, 1672, 1651, 1614. ^{1}H-NMR: 4.84 (*d*, *J* = 2.3, 1 H); 5.02 (*d*, *J* = 2.3, 1 H); 6.09 (*s*, 2 H); 7.06 (*s*, 1 H); 7.19 (*s*, 1 H); 7.52 (br. *s*, 1 H). ^{13}C-NMR ((D_6)DMSO): 89.70; 100.92; 101.79; 102.26; 124.89; 132.68; 140.20; 149.17; 151.40; 167.16. MS: 189 (100, M^+). Anal. calc. for $C_{10}H_7NO_3$: C 63.49, H 3.73, N 7.40; found: C 63.20, H 3.90, N 7.56.

We acknowledge Mrs. *Miyuki Tanmatsu* for determining mass spectra and performing combustion analyses.

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Received January 26, 2010