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A NEW ENTRY TO (E)-[3,3']BIBENZOFURANYLIDENE-2,2'-DIONES (ISOXINDIGOS)

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ABSTRACT - A one-pot synthesis of isoxindigos **4** is described via o-specific alkylation of dichloroaluminum phenolates **2** with trichloroacetaldehyde and subsequent basic alumina-promoted thermal conversion of 2-(2,2,2-trichloro-1-hydroxyethyl)phenol intermediates **3**.

Few years ago, we reported a high-yield and mild procedure for direct o-specific trichloro-hydroxyethylation of phenols with trichloroacetaldehyde (chloral) using aluminum trichloride at room temperature.[1] During the course of that study, production of an orange compound was observed as a minor component of the reaction mixture from 2-tert-butylphenol and chloral, to which (E)-[3,3']bibenzofuranylidene-7,7'-di-tert-butyl-2,2'-dione (7,7'-di-tert-butylisoxindigo) structure (**4b**) was assigned on the basis of X-ray crystal structure analysis.[2]

A recent paper dealing with the oxidative conversion of benzofuranylidenones into isoxindigos[3] prompted us to reinvestigate the reaction of phenol with chloral in order to develop a new viable entry into these relatively unexplored heterocycles.[4] We now wish to report the realization of this synthesis.

In the first study, 2-(2,2,2-trichloro-1-hydroxyethyl)-6-tert-butylphenol (**3b**), obtained in 98% yield by aluminum trichloride-promoted reaction of potassium 2-tert-butylphenoxide (**1b**) in toluene with anhydrous chloral at room temperature,[1] was refluxed in aprotic non polar solvents in the presence of basic alumina as a hydrochloric acid scavenger with the results shown in Table 1. Good yields (86%) of the corresponding isoxindigo derivative **4b** was obtained using decalin and an excess of basic alumina (Entry 1 in Table 1).

Table 1. Influence of conditions on conversion of **3b** into **4b**; reaction time, 4hr.

Entry	Solvent	HCl scavanger	Temp. °C	**3b** yield%
1	decalin	Al_2O_3-basic	190	86
2	decalin	none	190	8
3	mesitylene	Al_2O_3-basic	165	traces
4	toluene	Al_2O_3-basic	110	traces

Inspection of the data in Table 1 reveals that among tested nonpolar compounds only non-aromatic ones are the solvent of choice since carbinol **3b** easily incorporate aromatic solvents at high temperature giving variable yields of adducts with a not-well defined composition.†

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† The structure of 2-oxo-3-mesityl-7-tert-butyl-2,3-dihydrobenzofuran was tentatively assigned to the major compound obtained by refluxing **3b** in mesitylene in the presence of basic alumina.

Our success in the conversion of **3b** into isoxindigo **4b** with a simple thermal operation led to a second study in which the synthesis of compounds **4** was accomplished in a one-pot operation directly without isolation of carbinol intermediates.

The method consists of reacting preformed toluene sospension of phenoxydichloroaluminum **2**, obtained in situ from potassium phenolate **1** and aluminum trichloride, with chloral at room temperature, giving the carbinol **3**. Substitution of toluene with decalin, addition of an excess of basic alumina into the same flask, and refluxing of the mixture then allow to conversion of **3** into isoxindigos **4** which can often be at least partially separated by crystallization from an ethanol/toluene mixture.

The sequence so far described is given in the Scheme.

Preparative data of synthesized isoxindigos **4a–f** are collected in Table 2.

The structure of compounds **4a–f** were confirmed by analytical and spectral data (Table 3), namely an intense band at about 1770 cm^{-1} (typical for lactone structure) in

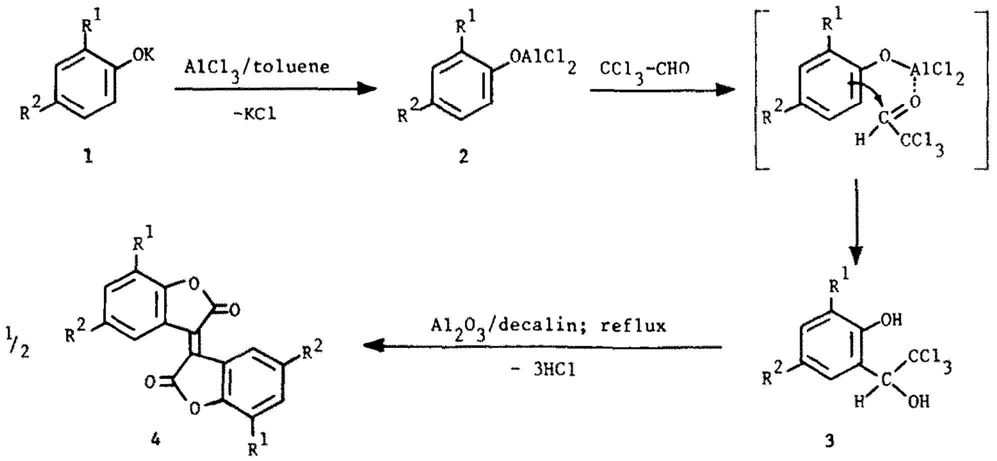

Table 2. Isoxindigos 4a-f prepared

Compound	R^1	R^2	Yield[a] (%)	m.p. (°C)	Found (%) (Required) C	H	Molecular formula	weight
4a	H	H	25	282-283[b]	72.61 (72.73)	3.09 (3.05)	$C_{16}H_8O_4$	264.2
4b	$C(CH_3)_3$	H	58	188-189	76.49 (76.57)	6.56 (6.43)	$C_{24}H_{24}O_4$	376.4
4c	$C(CH_3)_3$	CH_3	60	247-248[c]	77.31 (77.20)	6.89 (6.98)	$C_{26}H_{28}O_4$	404.5
4d	CH_3	$C(CH_3)_3$	42	213-214	77.27 (77.20)	7.04 (6.98)	$C_{26}H_{28}O_4$	404.5
4e	CH_3	H	36	244-245	73.81 (73.96)	4.26 (4.14)	$C_{18}H_{12}O_4$	292.3
4f	$CH(CH_3)_2$	H	38	218-219	75.99 (75.84)	5.81 (5.79)	$C_{22}H_{20}O_4$	348.4

[a] Isolated yield, based on starting phenol. [b] Lit.[4c], m.p. 283°. [c] Lit.[3], m.p. 250-251°.

Table 3. Spectral data for isoxindigos 4a-f

Compound	IR (KBr) ν_{max} [cm^{-1}]	UV (CH$_2$Cl$_2$) λ_{max} [nm] (logε)	^{1}H NMR (CDCl$_3$) δ [ppm]	Mass *m/e* (% rel. abundance)
4a	1780, 1620, 1120, 745	227(4.15), 252(4.10), 254(4.10), 395(4.12), 433(4.13)	7.1-7.6(m,6Harom), 9.10(dd,2H,H-4 and H-4',J=8.0 and 1.0 Hz)	264(50), 223(22),200 (45), 187(33), 135(41), 117(100)
4b	2950, 1765, 1410, 1273, 1090, 740	228(4.06)^a, 255(4.08)^a, 260(4.10), 401(4.19)^a, 415(4.22)	1.43(s,18H,C(CH$_3$)$_3$), 6.8-7.6(m,4Harom), 8.90(dd,2H,H-4 and H-4',J=80 and 1.2Hz)	376(71), 361(100), 333 (23), 247(40), 173(37) 159(30), 145(60), 131 (32), 117(22)
4c	2960, 1774, 1264, 1093	227(4.06), 259(4.08)^a, 263(4.12), 421(4.23)	1.45(s,18H,C(CH$_3$)$_3$), 2.38(s,6H,CH$_3$), 7.20(d,2H,H-6 and H-6',J=1.2Hz), 8.67 (d,2H,H-4 and H-4',J=1.2 Hz)	404(22), 389(22), 275 (19), 262(24), 215(33), 203(60), 187(100), 173 (40), 159(52)
4d	2955, 1768, 1265, 1130, 1100, 1043	227(4.19), 258(4.09)^a, 262(4.09), 422(4.26)	1.36(s,18H,C(CH$_3$)$_3$), 2.30(s,6H,CH$_3$), 7.26(d,2H,H-6 and H-6',J=1.5Hz), 8.95 (d,2H,H-4 and H-4', J=1.5 Hz)	404(24), 389(100), 187 (10), 173(10), 159(17), 145(8)
4e	1773, 1125, 1025, 740	227(4.06)^a, 254(4.06)^a, 258(4.09), 400(4.19)^a, 411(4.21)	2.35(s,6H,CH$_3$), 7.23(t,2H,H-5 and H-5', J=8.0 Hz), 7.46(dd,2H,H-6 and H-6',J=8.0 and 1.2 Hz), 9.60(dd,2H,H-4 and H-4', J=8.0 and 1.2 Hz)	292(65), 264(100), 219 (13), 189(10), 178(12), 165(16)
4f	2960, 1768, 1430, 1126, 1075, 745	227(3.95), 255(4.06)^a, 258(4.08), 421(4.28)	1.32(d,12H,CH(CH$_3$)$_2$,J=7.0 Hz), 3.26 (hept,2H,CH(CH$_3$)$_2$,J=7.0 Hz), 6.9-7.6 (m,4Harom), 8.92(dd,2H,H-4 and H-4', J=8.0 and 1.2 Hz)	348(100), 333(48), 320 (12), 305(57), 263(12), 233(44), 215(12), 202 (16), 189(16), 178(14)

[a] Shoulder.

the IR spectra and an absorption band at about 420 nm ($\pi \rightarrow \pi^*$ transition) in the UV spectra, common to all isoxindigos.[3] Furthermore, the ^{1}H NMR spectra reveal a characteristic signal around 9 ppm due to hydrogen-bonded H-4 and H-4' (doublet, J=1.2 Hz or doublet of doublets, J=8.0 and 1.2 Hz). As previously reported,[2] the structure of **4b** as been also ascertained by X-ray analysis.

In comparison with the few existing routes to isoxindigos, the present procedure has the advantage that compounds **4** are obtained in one-pot reaction, without isolating reaction intermediates. However, as far as the reaction yield is concerned, a marked dependence of yield upon the structure of the phenolic substrate was observed, the bulky substituted phenols being more efficient than less hindered ones.

In conclusion, the compounds described in this paper are now readily available and other symmetrical isoxindigos should be accessible from the appropriate phenols using the described methodology.

EXPERIMENTAL

All chemicals were reagent grade and were used without further purification. Melting points were obtained on a Büchi melting-point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 298 spectrophotometer in KBr pellets. UV spectra for solutions in dichloromethane were measured on a Jasco UVIDEC 505 spectrophotometer. ^{1}H NMR spectra were determined on a Varian EM-360 spectrometer, and the values are given on the δ scale in ppm. Mass spectra were obtained on a Varian MAT CH-5 spectrometer using direct insertion probe (70 eV). Microanalyses were carried out by Istituto di Chimica Farmaceutica dell'Universita' di Parma, Italy.

(E)-[3,3']Bibenzofuranylidene-7,7'-di-tert-butyl-2,2'-dione (**3b**). Typical Procedure.

To an equimolar mixture of 2-tert-butylphenol and potassium 2-tert-butylphenoxide [prepared in situ from 2-tert-butylphenol (15.0 g, 100 mmol) and potassium pellets (1.95 g, 50 mmol)] in anhydrous toluene (400 ml) aluminum trichloride (6.6 g, 50 mmol) was added. The slurry was heated under reflux with stirring for 10 min, while a stream of dry nitrogen was passing. The resulting mixture was cooled to room temperature and a solution of anhydrous trichloroacetaldehyde (14.8 g, 100 mmol) in toluene (100 ml), was added dropwise over a period of ca. 15 min, then the mixture was allowed to stand overnight. After complete removal of toluene, decalin (400 ml) was added and basic alumina (25 g) was put into the flask. The mixture was heated under reflux with stirring for 2 hr then quenched with 10% hydrochloric acid. After separation of alumina and extraction with three 50 ml portions of dichloromethane, the solvent was removed by heating in vacuo and the residual oil chromatographed on silica gel (Merck) using hexane/ethyl acetate (9:1 v/v) to give 10.92 g (58%) of **4b** as orange needles, m.p. 184-187°. Recrystallization from toluene/ethanol raised the melting point to 188-189°.

All other isoxindigos listed in Table 2 were prepared in a similar way. Significant spectroscopic data are reported in Table 3.

Alumina-promoted Conversion of **3b** into **4b** (Expt 1 in Table 1).

A solution of **3b** (2.98 g, 10 mmol) in decalin (40 ml) was refluxed in the presence of basic alumina (5 g) for 2 hr. A workup as above gave 1.62 g (86%) of **4b**; orange needles from toluene/ethanol, m.p. 188-189°.

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