# THE SELECTIVE BENZYLIC BROMINATION OF o-XYLENES. A USEFUL SYNTHESIS OF PHTHALIDES

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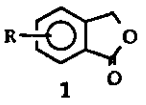
Abstract - The free radical bromination of aryl methyl groups can be controlled by the strategic positioning of a remote stereo-electronic blocking group on the aryl ring. This tactic leads to the efficient synthesis of selectively benzylically brominated molecules which are useful synthetic intermediates. This methodology has been applied to the synthesis of some phthalides.

## INTRODUCTION

Phthalides (1) occur naturally,[1] are the targets of innovative syntheses[2] and have been used as synthetic intermediates.[3] We needed an efficient synthetic route to phthalides which would tolerate a wider range of functionality than is possible using the current methods and which could be scaled up considerably. o-Xylenes (2) are cheap and the reported[4] transformation of 2,3-dimethylphenyl acetate (3) into the compound (4) seemed auspicious. We therefore investigated these benzylic bromination reactions.



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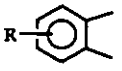

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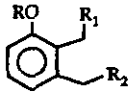
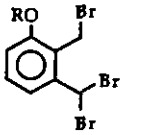


3 R = $COCH_3$, $R_1 = R_2 = H$
6 R = H, $R_1 = R_2 = H$
7 R = $CH_3$, $R_1 = R_2 = H$
8 R = $CH_3$, $R_1 = Br$, $R_2 = H$
9 R = $CH_3$, $R_1 = H$, $R_2 = Br$
10 R = $CH_3$, $R_1 = R_2 = Br$



4 R = $COCH_3$
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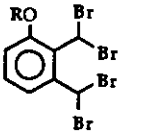
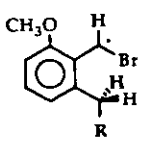


5 R = $COCH_3$
12 R = $CH_3$

DISCUSSION

The methylation of 2,3-dimethylphenol (6) (using dichloromethane, iodomethane, aqueous potassium hydroxide and tetra-N-butylammonium hydrogen-sulphate) gave 2,3-dimethylanisole (7), quantitatively. The free radical bromination reactions of the compound (7) and its derivatives, using N-bromo-succinimide (NBS), were done on 0.02 molar solutions[5] of the anisoles in carbon tetrachloride, under nitrogen. The rapidly stirred reactions were heated and irradiated with visible light from a 250 watt sunlamp.

Bromination of compound (7) using one equivalent of NBS produced only the compound (8) in 98% yield, after 1 hour. None of the compound(9) was formed. Using two equivalents of NBS gave the compound (10) quantitatively, after 2.5 hours; and 3 equivalents of NBS gave the compound (11) in 98% yield, after 3 hours. Prolonged exposure of the compound (11) to 1 equivalent of NBS gave the compound (12) in 98% yield, after 12 hours.



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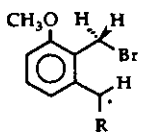
13A R = Br



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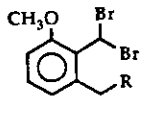
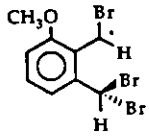
14A R = Br



15 R = H
15A R = Br



16

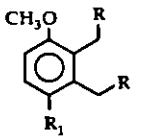
The radical (13) was not formed because its coplanar conformations would have been destabilized by electrostatic repulsion between the oxygen functionality and the bromine atom attached to the benzylic radical center; and by the steric interactions between the bromine atom and the ortho methyl group. Thus, the easier formation of the more stable radical (14) determined the course of the reaction. Undoubtedly, similar electronic and steric factors were involved in the reaction of the compound (10) in which the radical (13A) must have been much higher in energy than the radical (14A), so leading to the exclusive formation of the compound (11). Bromomethyl groups undergo further free radical bromination reluctantly in comparison to methyl groups.[6] However, the bromomethyl group of compound (10) had reacted reasonably rapidly. Thus, the inability to produce the compounds (15) and (15A) was significant and indicated that a bromomethyl group which was flanked by an alkyl group and a methoxyl (or acetoxyl) group particpated much more reluctantly in the radical formation process than a bromomethyl group which was flanked only by an alkyl group. Thus, the steric and dipolar repulsions between the bromine atom of the bromomethyl group and the flanking methoxyl (or acetoxyl) group played a major

role in the inhibition of this radical formation process. The factors affecting the formation of radical (16) and hence the slow formation of the compound (12) can now be rationalized.

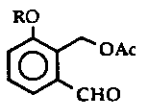
In order to demonstrate the generality and effectiveness of this remote (not attached to the reacting atom) stereo-electronic inhibition of the selective bromination of the o-xylenes, we brominated 4-bromo-2,3-dimethylanisole, (17), which possessed a methoxyl group (whose influence on the reaction had now been demonstrated) and a suitably sited bromine atom which might also act as a remote stereo-electronic blocking group.

The compound (17) was prepared, quantitatively, by the very slow addition of NBS to a 30% solution of 2,3-dimethylanisole in carbon tetrachloride, at 0 °C. The bromination of compound (17), using an excess (three equivalents) of NBS, produced the compound (18) quantitatively. The only intermediate detected during the reaction was 4-bromo-2-bromomethyl-3-methyl-anisole. Significantly, neither bromomethyl group of compound (18) participated in further bromination, even under the conditions which provided the compound (12) from the compound (11), proving the effectiveness of the aryl bromine atom and the methoxyl group of compound (17) as a remote stereo-electronic blocking groups.

Bromine atoms attached to aromatic rings can be replaced by hydrogen,[7] or other functional groups, via simple organometallic intermediates, and so the tactic of using a suitably sited aryl bromine atom to achieve regiocontrol of a free radical benzylic bromination process will be valuable, as will be seen below.



17 R = H, $R_1$ = Br
18 R = Br, $R_1$ = Br
21 R = OH, $R_1$ = H



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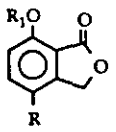
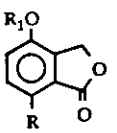


22 R = H, $R_1$ = $CH_3$
23 R = Br, $R_1$ = $CH_3$
24 R = Br, $R_1$ = H



20 R = H, $R_1$ = $CH_3$
25 R = Br, $R_1$ = $CH_3$
26 R = Br, $R_1$ = H

The polybrominated anisoles prepared above were easily transformed into phthalides. Thus, the (sodium acetate/acetic acid) acetolysis of the compound (11) provided the acetate (19), whose basic hydrolysis (potassium hydroxide in aqueous methanol), followed by oxidation of the hemiacetal intermediate using the Jones reagent, gave the phthalide (20).

Acetolysis of the compound (10) followed by the basic hydrolysis of the diacetate

gave the diol (21) which was oxidized by the Jones reagent to the mixture of phthalides (20) and (22), in 96% yield. If the oxidation was performed at 0 °C, then the ratio of (20) to (22) was 1:4. When the oxidation was done in refluxing acetone, the product ratio was reversed.

Similarly, the compound (18) gave a 9:1 mixture of phthalides (23) and (25). Here, the regioselectivity of the Jones oxidation of the intermediate diol was independent of the temperature at which the oxidation reaction was performed. The phthalides (23) and (25) were identified by their ease of demethylation by aluminium chloride and propanethiol.[8] This demethylation of the phthalide (23) gave the phthalide (24) after 15 minutes (98% yield), whilst the phthalide (25) reacted very slowly to produce the phthalide (26), after 8 hours (also in 98% yield). Most of the modern methods of phthalide synthesis[2] would not be suitable for the preparation of the phthalides (23) to (26) from brominated precursors, because the bromine atom would be removed by the reagents used.

The recognition of the roles of heteroatoms attached to the aromatic nucleus in the selectivity of the bromination reactions is important. This synthesis of phthalides from o-xylenes possesses the advantages of using well established experimental methods; being easily performed; and requiring cheap, available starting materials and reagents.

## EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 247 grating spectrophotometer. Proton magnetic resonance spectra were recorded on a Varian EM-360A (60 MHz), or an IBM NR/300 FT NMR (270 MHz), or an IBM WP/200-SY (200 MHz), or a JEOL/JNM/GX-400 FT NMR (400 MHz) spectrometer, and were done in deuterochloroform (unless otherwise stated) with tetramethylsilane as the internal reference. Mass spectra were measured on an AEI MS-902S double focusing high resolution mass spectrometer, or on a Finigan CH5 single focusing mass spectrometer. Column chromatography was performed with silica gel 60 mesh. Evaporations were done under reduced pressure using a rotary evaporator. Combustion analyses were performed by Schwarzkoff Microanalytical Laboratory (New York, NY, U.S.A.). Tetrahydrofuran and diethyl ether were purified by distillation from sodium under an atmosphere of dry nitrogen.

2,3-Dimethylanisole (7)

2,3-Dimethylphenol (12.20 g, 100 mmol) and tetrabutylammonium hydrogensulfate (3.40 g, 10 mmol) were dissolved in dichloromethane (200 mL) and aqueous potassium hydroxide (28.0 g, 0.5 mol, in 140 mL of water) was added, followed by iodomethane (21.3 g, 150 mmol). The mixture was stirred for 2 hours at room temperature, the layers were separated and the aqueous layer extracted with three 25 mL portions of dichloromethane. The combined organic solutions was evaporated, the residue was dissolved in diethyl ether (200 mL) and the precipitated salts were removed by filtration. The filtrate was concentrated and the residue was distilled (15 mm Hg, 110 °C) to give 2,3-dimethylanisole (13.6 g, 100% yield): ir (neat, $cm^{-1}$) 3000 (m), 2945 (s), 2850 (w), 2835 (m), 1585 (s), 1470 (s), 1305 (m), 1260 (s), 1105 (s), 1015 (m), 770 (s); $^1H$ nmr (60 MHz, ppm) 6.90 (t, 1H, J=8 Hz), 6.65-6.45 (m, 2H), 3.70 (s, 3H), 2.20 (s, 3H), 2.10 (s, 3H).

4-Bromo-2,3-dimethylanisole (17)

N-Bromosuccinimide (1.78 g, 10.0 mmol) was added slowly, in small portions, to a rapidly stirred solution of 2,3-dimethylanisole (1.36 g, 10.0 mmol) in carbon tetrachloride (5 mL) at 0 °C. The reaction mixture was then allowed to warm to room temperature and, after an hour, carbon tetrachloride (100 mL) was added. The succinimide was removed by filtration and the solvent was evaporated to give 4-bromo-2,3-dimethylanisole (2.15 g, 100% yield): $^1H$ nmr (60 MHz, ppm) 7.25 (d, 1H, J=8 Hz), 6.40 (d, 1H, J=8 Hz), 3.70 (s, 3H), 2.30 (s, 3H), 2.10 (s, 3H).

2,3-Bis(bromomethyl)anisole (10): General Procedure for Brominations

2,3-Dimethylanisole (13.62 g, 100 mmol) and N-bromosuccinimide (37.38 g, 210 mmol) were dissolved in dry carbon tetrachloride (1.5 L) and the mixture was stirred under nitrogen for 2.5 hours, while being exposed to a 250 watt high intensity sunlamp (which simultaneously irradiated and heated the solution to boiling). The solution was cooled to room temperature, the suspended succinimide was removed by filtration and the solvent was evaporated. The residue was recrystallized from hexane-diethyl ether (5:1) to give compound (10) as white crystals (27.06 g, 92% yield, m.p. 69-70 °C): ir (nujol, $cm^{-1}$) 1590 (m), 1285 (m); $^1H$ nmr (60 MHz, ppm) 7.50 (t, 1H, J=8 Hz), 7.15 (d, 1H, J=8 Hz), 7.05 (d, 1H, J=8 Hz), 4.90 (s, 2H), 4.75 (s, 2H), 3.95 (s, 3H).

2-Bromomethyl-3-methylanisole (8)

Irradiation of 2,3-dimethylanisole (1.36 g, 10.0 mmol) and N-bromosuccinimide(1.96 g, 11.0 mmol) in dry carbon tetrachloride (100 mL), as above, gave monobromo-

compound (8) (2.15 g, 100% yield): $^1$H nmr (60 MHz, ppm) 7.15 (t, 1H, J=8 Hz), 6.85-6.55 (m, 2H), 4.55 (s, 2H), 3.80 (s, 3H), 2.35 (s,3H).

4-Bromo-2,3-bis(bromomethyl)anisole (18)

Irradiation of 2,3-dimethylanisole (1.36 g, 10.0 mmol) and N-bromosuccinimide (5.52 g, 31.0 mmol) in dry carbon tetrachloride (50 mL), as above, gave tribromo-compound (18) (3.73 g, 100% yield), which separated as white crystals (m.p. 102-103 °C) from hexane-chloroform (2:1): $^1$H nmr (60 MHz, ppm) 7.50 (d, 1H, J=9 Hz), 6.70 (d, 1H, J=9 Hz), 4.75 (s, 2H), 4.70 (s, 2H), 3.85 (s, 3H). Anal. Calcd for $C_9H_9O_1Br_3$: C, 28.99; H, 2.43; Br, 64.29. Found: C, 29.27; H, 2.22; Br, 64.35.

Compound (18) was also produced by the irradiation of compound (17) and N-bromosuccinimide as above.

2-Bromomethyl-3-(dibromomethyl)anisole (11)

Irradiation of 2,3-dimethylanisole (1.36 g, 10.0 mmol) and N-bromosuccinimide (5.52 g, 31.0 mmol) in dry carbon tetrachloride (400 mL), as above, gave tribromo-compound (11) (3.66 g, 98% yield), which separated as white crystals (m.p. 84-85 °C) from hexane-chloroform (5:1): ir (nujol, $cm^{-1}$) 1585 (w), 1280 (m); $^1$H nmr (60 MHz, ppm) 7.55 (dd, 1H, J=8 Hz, J=2.5 Hz), 7.35 (t, 1H, J=8 Hz), 7.05 (s, 1H), 6.85 (dd, 1H, J=8 Hz, J=2.5 Hz), 4.65 (s, 2H), 3.90 (s, 3H). Anal. Calcd for $C_9H_9O_1Br_3$: C, 28.99; H, 2.43; Br, 64.29. Found: C, 29.27; H, 2.22; Br, 64.35.

2,3-bis(dibromomethyl)anisole (12)

The irradiation of compound (11) (1.86 g, 5.0 mmol) and N-bromosuccinimide (1.84 g, 10.0 mmol) in carbon tetrachloride, as above, for 12 hours, produced the compound (12) (2.21 g, 98% yield) which crystallized from chloroform as white needles (m.p. 149-150 °C): ir (nujol, $cm^{-1}$) 1585 (w), 1290 (m), 1265 (m), 1140 (m), 1060 (m); $^1$H nmr (60 MHz, ppm) 7.65 (s, 1H), 7.45 (s, 1H), 7.55-6.75 (m, 3H), 3.90 (s, 3H). Anal. Calcd for $C_9H_8O_1Br_4$: C, 23.93; H, 1.78. Found: C, 24.42; H, 1.84.

2-acetoxymethyl-3-methoxybenzaldehyde (19): General Procedure for Acetolyses

Compound (11) (18.65 g, 50.0 mmol) and anhydrous sodium acetate (14.94 g, 180.0 mmol) were dissolved in glacial acetic acid (250 mL) and the stirred solution was refluxed for 3 hours. The acetic acid was evaporated, the residue was dissolved in ethyl acetate, the salts were removed by filtration, and the filtrate was stirred with 4% HCl. After the layers were separated, the aqueous layer was extracted with three 100 mL portions of ethyl acetate. The combined organic solutions was dried over magnesium sulfate, filtered, evaporated and the residue resolved by column chromatography (hexane-ethyl acetate, 1.5:1) to give compound (19) (10.10 g, 97%

yield) as a viscous liquid which solidified when it was cooled: ir (nujol, $cm^{-1}$) 1765 (s), 1690 (s); $^1H$ nmr (60 MHz, ppm) 10.15 (s, 1H), 7.60 (m, 2H), 7.30 (m, 1H), 5.60 (s, 2H), 3.90 (s, 3H), 2.05 (s, 3H); ms m/z, calcd for C11H12O4 208.0736, obsd 208.0735.

2,3-bis(acetoxymethyl)anisole (12)

Acetolysis of compound (10) gave compound (12) (m.p. 90-91 °C): $^1H$ nmr (60 MHz, ppm) 7.65-6.70 (m, 3H), 5.30 (s, 2H), 5.20 (s, 2H), 3.85 (s, 3H), 2.08 (s, 3H), 2.05 (s, 3H). Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 61.37; H, 6.32.

2,3-bis(hydroxymethyl)anisole (21): General Procedure for Hydrolyses

The compound (12) (12.60 g, 50.0 mmol) was dissolved in methanol (250 mL) and potassium carbonate (15.18 g, 110.0 mmol) was added to the stirred solution. Water was then added slowly until the solution just became cloudy. The mixture was stirred for 4 hours at room temperature, concentrated, diluted with water (100 mL) and then it was extracted with three 100 mL portions of chloroform. The combined organic solutions was washed twice with water and once with brine, dried over magnesium sulfate, filtered and evaporated. The residue was recrystallized from chloroform-hexane (1:1) to afford the diol (21) (7.64 g, 91% yield, m.p. 96-97 °C): $^1H$ nmr (60 MHz, with 1 drop $D_2O$, ppm) 7.25-6.60 (m, 3H), 4.80 (s, 2H), 4.75 (s, 2H), 3.85 (s, 3H). Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 63.40; H, 7.29.

Oxidation of Compound (21): General Procedure for Oxidations

The compound (21) (8.30 g, 50.0 mmol) was dissolved in acetone (250 mL) and Jones reagent was added dropwise to the stirred, refluxing solution until the reaction mixture retained a red-orange colour (about 25 mL of 3.0 M Jones reagent). The excess reagent was destroyed with 2-propanol, the acetone was removed by evaporation and the residue was suspended in 50 mL of water. The mixture was extracted with three 50 mL portions of chloroform, dried over magnesium sulfate, filtered and evaporated. The crude product was resolved by chromatography (silica gel, hexane-ethyl acetate, 1:1) into two components, (20) and (22) (combined weight 7.87 g, yield 96%).

4-Methoxyphthalide (20) (85% yield, m.p. 128-129 °C): ir (KBr, $cm^{-1}$) 2975 (s), 2940 (s), 2855 (s), 1785 (s); $^1H$ nmr (270 MHz, ppm) 7.52-7.45 (m, 2H), 7.12 (dd, 1H, J=5.8 Hz, J=1.7 Hz), 5.24 (s, 2H), 3.93 (s, 3H); $^{13}C$ nmr (200 MHz, ppm) 171.16, 154.26, 134.90, 130.85, 127.23, 117.04, 114.84, 68.11, 55.65. Anal. Calcd for

$C_9H_8O_3$: C, 65.84; H, 4.91. Found: C, 65.42; H, 4.85.

7-Methoxyphthalide (22) (15%, yield, m.p. 108-109 °C): ir (KBr, $cm^{-1}$) 1780; $^1H$ nmr (60 MHz, ppm) 7.50 (t, 1H, 8 Hz), 6.90 (d, 1H, J=8 Hz), 6.80 (d, 1H, J=8 Hz), 5.22 (s, 2H), 3.96 (s, 3H); $^{13}C$ nmr (200 MHz, ppm) 169.22, 158.71, 149.45, 136.34, 113.78, 113.19, 110.61, 68.82, 55.99.

4-Methoxyphthalide (20)

The hydrolysis of compound (19), as above, gave the desired hemiacetal (85% yield, m.p. 111-112 °C): ir (chloroform, $cm^{-1}$) 3600-3150 (br), 2950 (m), 2900 (w), 2870 (w), 1585 (s), 1460 (s); $^1H$ nmr (270 MHz, with 1 drop $D_2O$, ppm) 7.23 (t, 1H, J=8.3 Hz), 6.98 (d, 1H, J=7.5 Hz), 6.75 (d, 1H, J=8.0 Hz), 6.59 (d, 1H, J=2.1 Hz), 5.23 (dd, 1H, J=12.9, J=2.0 Hz), 5.05 (d, 1H, J=12.9 Hz), 3.81 (s, 3H). Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.06. Found: C, 64.87; H, 6.18.

Oxidation of the hemiacetal, as above, produced 4-methoxyphthalide (20) in 100% yield.

4-Bromo-7-methoxyphthalide (23) and 7-bromo-4-methoxyphthalide (25)

Acetolysis of the compound (18), as above, gave the expected diacetate (95% yield, m.p. 133-134 °C): $^1H$ nmr (60 MHz, ppm) 7.60 (d, 1H, J=9 Hz), 6.85 (d, 1H, J=9 Hz), 5.30 (s, 2H), 5.25 (s, 2H), 3.85 (s, 3H), 2.08 (s, 3H), 2.05 (s, 3H); $^{13}C$ nmr (200 MHz, ppm) 170.60, 170.41, 157.87, 135.67, 134.19, 126.06, 116.92, 113.14, 63.14, 57.78, 56.11, 20.88, 20.72. Anal. Calcd for $C_{11}H_{15}O_5Br_1$: C, 47.15; H, 4.57. Found: C, 46.71, H, 4.53.

The hydrolysis of the diacetate, as above, gave the corresponding diol (96% yield, m.p. 130-131 °C): $^1H$ nmr (60 MHz, ppm) 7.40 (d, 1H, J=8.5 Hz), 6.65 (d, 1H, J=8.5 Hz), 4.85 (s, 2H), 4.80 (s, 2H), 3.80 (s, 3H), 2.80 (br, 2H). Anal. Calcd for $C_9H_{11}O_3Br_1$: C, 43.75; H, 4.49. Found: C, 43.80; H, 4.28.

Oxidation of the diol, as above, or at room temperature, gave a mixture of 4-bromo-7-methoxyphthalide (23) and 7-bromo-4-methoxyphthalide (25).

4-Bromo-7-methoxyphthalide (23) (90% yield, m.p. 197-198 °C): ir (chloroform, $cm^{-1}$) 1775 (s); $^1H$ nmr (270 MHz, DMSO, ppm) 7.73 (dd, 1H, J = 7.84 Hz, J = 1.11 Hz), 6.97 (d, 1H, J = 7.77 Hz), 5.14 (s, 2H), 3.99 (s, 3H). Anal. Calcd for $C_9H_7O_3Br_1$: C, 44.48; H, 2.90; Br, 32.87. Found: C, 44.58; H, 2.53; Br, 33.00.

7-Bromo-4-methoxyphthalide (25) (10% yield, m.p. 207-208 °C): ir (nujol, $cm^{-1}$) 1780 (s); $^1H$ nmr (270 MHz, DMSO, ppm) 7.68 (d, 1H, J = 7.66 Hz), 7.26 (d, 1H, J = 7.62 Hz), 5.26 (s, 2H), 3.92 (s, 3H); Anal. Calcd for $C_9H_7O_3Br_1$: C, 44.48; H, 2.90; Br, 32.87. Found: C, 44.13; H, 2.82.

Demethylation of 4-bromo-7-methoxyphthalide (23)

*Compound* (23) (2.43 g, 10.0 mmol), dissolved in dichloromethane (20 mL), was added, over 15 minutes, to a stirred solution of aluminium chloride (1.47 g, 11.0 mmol) in *n-propanethiol* (0.84 g, 1.02 mL, 11.0 mmol), at 0 °C. The reaction mixture was then allowed to warm to room temperature and was stirred for a further period of 15 minutes. *The reaction mixture was poured into water, acidified with 10% HCl, and* extracted twice with 30 mL portions of dichloromethane. The combined organic solutions was shaken *with brine, dried over magnesium sulfate,* filtered and then evaporated. The crude material was resolved by chromatography (silica gel) to give compound (24) (2.24 g, 98% yield, m.p. 166-167 °C): ir (*nujol*, $cm^{-1}$) 3600-3050 (br), 1765 (s); $^1$H nmr (270 MHz, DMSO, ppm) 7.58 (d, 1H, J = 8.67 Hz), 6.91 (d, 1H, J = 8.56 Hz), 5.11 (s, 2H), 3.55 (br, 1H). Anal. Calcd for $C_8H_5O_3Br$: C, 41.91; H, 2.20; Br, 34.89. Found: C, 40.76; H, 2.34; Br, 34.50.

Demethylation of 7-bromo-4-methoxyphthalide (25)

The same reaction described above was performed with compound (25) to give, after 8 hours, compound (26): $^1$H nmr (60 MHz, DMSO, ppm) 7.55 (d, 1H, J = 8.4 Hz), 7.10 (d, 1H, J = 8.4 Hz), 5.30 (s, 2H).

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