The Synthesis of Highly Functionalized Naphthalene Derivatives

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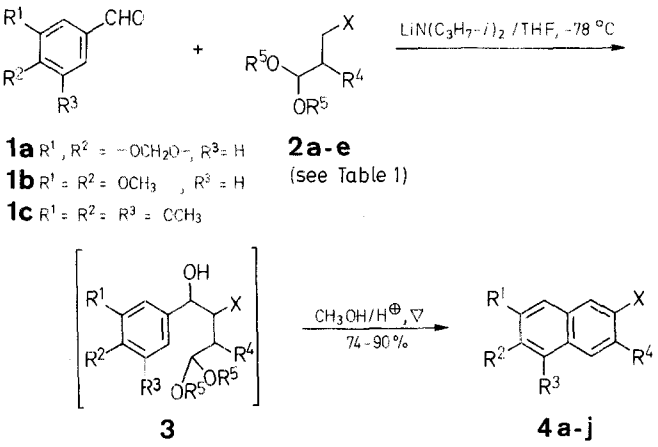
Condensation of the α-lithio derivative of 3-substituted 4,4-dialkoxybutanoates, butanenitriles, and butanamides with methoxy-activated aromatic aldehydes, followed by treatment with refluxing dilute sulfuric acid gives rise to substituted naphthalene products. In this manner, 2,6,7-tri- and 2,3,6,7-tetrasubstituted naphthalenes are synthesized in high yields on a multigram scale.

During our investigations into the synthesis of a variety of natural lignans, involving the nucleophilic addition of organolithium reagents to chiral 2-naphthyloxazolines[2], it became necessary to prepare a number of highly functionalized naphthalene substrates. The required 2,6,7-tri- and

2,3,6,7-tetrasubstituted naphthalenes are particularly difficult to synthesize by aromatic substitution reactions, but are often found as degradation products of lignan-derived materials[3,4]. In recent years Diels-Alder reactions of *o*-quinodimethane[5], isobenzofuran[6], and benzynes[7], as well as Michael-induced ring closure[8] have been used to fuse additional rings onto aromatic compounds. Several of these procedures require the synthesis of moderately functionalized substrates to facilitate the annelation step.

We have elaborated upon the earlier work of Loozen[9] to synthesize these compounds in an efficient manner on a multigram scale. The reaction of a strongly activated aldehyde (**1a–c**) with the lithio derivative of an appropriate annelating reagent (**2a–e**; Table 1) at −78 °C affords the intermediate condensation product **3**. The crude alcohol is then treated with refluxing 20% aqueous sulfuric acid for 2 h to give the substituted naphthalenes **4a–j** (Table 2).



The crude, crystalline naphthalenes **4** are isolated from the aqueous solution in high yields and can be purified by

Table 1. Annelating Reagents **2a–e**

Reagent No.	X	R^4	R^5	R^5	b.p. [°C]/torr	Reference
2a	—CN	H	C_2H_5	C_2H_5	47–49°/0.2	10
2b	—$COOCH_3$	H		—$(CH_2)_3$—	100–102°/4	11
2c	—CN	CH_3	CH_3	CH_3	68–70°/2.5	12
2d	—$COOCH_3$	CH_3	CH_3	CH_3	82–85°/1.5	–
2e	—CO—$N(CH_3)_2$	CH_3	CH_3	CH_3	109–111°/0.5	–

Table 2. Substituted Naphthalenes **4** prepared

Substrates	Product	Yield [%][a]	m.p. [°C]	Molecular Formula[b] or Lit. m.p. [°C]	I.R. (KBr) ν[cm⁻¹]	¹H-N.M.R. ($CDCl_3$/TMS_{int}, 270 MHz) δ[ppm]
1a + **2a**	**4a**	82	144–145°	$C_{12}H_7NO_2$ (197.2)	2225	6.11 (s, 2H); 7.14 (s, 2H); 7.47 (d, J = 8.4 Hz, 1H); 7.70 (d, J = 8.4 Hz, 1H); 8.00 (s, 1H)
1a + **2b**	**4b**	74	133–134°	133–134°[3]	1725	3.92 (s, 3H); 6.11 (s, 2H); 7.10 (s, 2H); 7.53 (d, J = 8.4 Hz, 1H); 7.79 (d, J = 8.4 Hz, 1H); 8.32 (s, 1H)
1b + **2a**	**4c**	80	120–121°	$C_{13}H_{11}NO_2$[c] (213.2)	2230	3.96 (s, 3H); 3.97 (s, 3H); 7.16 (s, 1H); 7.45 (d, J = 8.4 Hz, 1H); 7.68 (d, J = 8.4 Hz, 1H); 8.01 (s, 1H)
1b + **2b**	**4d**	78	126–127°	$C_{14}H_{14}O_4$[c] (246.3)	1720	3.91 (s, 3H); 3.96 (s, 3H); 3.97 (s, 3H); 7.06 (s, 1H); 7.12 (s, 1H); 7.47 (d, J = 8.4 Hz, 1H); 7.10 (d, J = 8.4 Hz, 1H); 8.00 (s, 1H)
1a + **2c**	**4e**	82	191–192°	$C_{13}H_9NO_2$ (211.2)	2225	2.60 (s, 3H); 6.08 (s, 2H); 7.04 (s, 1H); 7.08 (s, 1H); 7.52 (s, 1H); 7.95 (s, 1H)
1a + **2d**	**4f**	83	124–125°	$C_{14}H_{12}O_4$ (244.2)	1725	2.67 (s, 3H); 3.92 (s, 3H); 6.05 (s, 2H); 7.04 (s, 1H); 7.13 (s, 1H); 7.47 (s, 1H); 8.30 (s, 1H)
1b + **2d**	**4g**	84	108–109°	105–106°[4]	1725	2.69 (s, 3H); 3.93 (s, 3H); 4.00 (s, 3H); 4.01 (s, 3H); 7.04 (s, 1H); 7.14 (s, 1H); 7.50 (s, 1H); 8.36 (s, 1H)
1c + **2d**	**4h**	82	94–95°	$C_{16}H_{18}O_5$ (290.3)	1720	2.72 (s, 3H); 3.93 (s, 3H); 3.95 (s, 3H); 3.99 (s, 3H); 4.04 (s, 3H); 6.97 (s, 1H); 7.85 (s, 1H); 8.34 (s, 1H)
1a + **2e**	**4i**	90	151–152°	$C_{15}H_{15}NO_3$ (257.3)	1650	2.37 (s, 3H); 2.84 (s, 3H); 3.16 (s, 3H); 6.01 (s, 2H); 7.27 (s, 1H); 7.35 (s, 1H); 7.46 (s, 2H)
1b + **2e**	**4j**	90	141–142°	141–142°[4]	1650	2.37 (s, 3H); 2.84 (s, 3H); 4.00 (s, 3H); 4.02 (s, 3H); 7.27 (s, 1H); 7.35 (s, 1H); 7.44 (s, 1H); 7.46 (s, 1H)

[a] Yield of isolated and purified material.
[b] Satisfactory microanalyses obtained (C ±0.05, H ±0.1, N ±0.2) for products **4a**, **4f**, **4h**, **4i**.
[c] No experimental data available in Ref.[6].

recrystallization from methanol. A small amount of the corresponding naphthoic acid is obtained as the sole by-product when using annelating reagents containing an ester group. This series of reactions can be run on a large scale (1 mol or larger) and in a short period of time. In conclusion, this methodology appears to be an excellent alternative to the existing processes for the preparation of polysubstituted naphthalenes

Methyl 1,3-Dioxolane-3-propanoate (2b):
2-Bromoethyl-1,3-dioxolane (15 g, 83 mmol) in tetrahydrofuran (50 ml) is added dropwise to a stirred suspension of magnesium turnings (3.75 g, 150 mmol) in tetrahydrofuran (200 ml) and the resulting grey solution is heated at reflux for 1 h. The mixture is then cooled to −78 °C and treated dropwise with methyl carbonochloridate (10.5 g, 111 mmol) in tetrahydrofuran (30 ml) at a rate sufficient to maintain a reaction temperature below −70 °C. The mixture is stirred for an additional 1 h at −78 °C then allowed to warm to ambient temperature. The resulting solution is decanted from the excess magnesium and quenched with saturated aqueous ammonium chloride (100 ml). The tetrahydrofuran is evaporated, the residue diluted with water (200 ml), and the product is extracted with ether. The combined organic fractions are dried with potassium carbonate and evaporated to give a yellow oil which is distilled; yield: 8.5 g (65%); b.p. 100–102 °C/4.0 torr.

I.R. (film): ν = 1740 cm^{-1} (s, C=O).

^{1}H-N.M.R. ($CDCl_3$): δ = 1.9–2.2 (m, 2H); 2.43 (t, J = 6.2 Hz, 2H); 3.67 (s, 3H); 3.75–4.00 (m, 4H); 4.94 ppm (t, J = 6.2 Hz, 1H).

4,4-Dimethoxy-3-methylbutanenitrile (2c):
Diethyl phosphonoacetonitrile[13] (17.7 g, 100 mmol) in tetrahydrofuran (30 ml) is added to a stirred suspension of sodium hydride (2.4 g, 100 mmol) in tetrahydrofuran (200 ml). After stirring at ambient temperature for 1 h, the mixture is treated dropwise with pyruvaldehyde dimethylacetal (12 g, 100 mmol) in tetrahydrofuran (30 ml). The mixture is stirred at ambient temperature for 3 h then quenched with water (60 ml). The tetrahydrofuran is evaporated and the product extracted with ether. The combined extracts are dried with sodium sulfate and the solvent evaporated to give a yellow oil. The crude oil is diluted with dry methanol (100 ml) and hydrogenated using 10% palladium on carbon (300 mg) as catalyst with a hydrogen pressure of 2000 torr for 12 h. The mixture is filtered through a pad of celite and the methanol evaporated to give a yellow oil which is distilled; yield: 10.3 g (72%); b.p. 68–70 °C/2.5 torr.

I.R. (film): ν = 2250 cm^{-1} (w, C≡N).

^{1}H-N.M.R. ($CDCl_3$): δ = 1.07 (d, J = 7 Hz, 3H); 2.0–2.7 (m, 3H); 3.41 (s, 6H); 4.15 ppm (d, J = 6 Hz, 1H).

Methyl 4,4-Dimethoxy-3-methylbutanoate (2d):
By the same procedure, the anion of diethyl phosphonomethylacetate[13] (21 g, 100 mmol) is condensed with pyruvaldehyde dimethylacetal (12 g, 100 mmol) and the product hydrogenated to give a yellow oil which is distilled; yield: 14.4 g (82%); b.p. 82–85 °C/1.5 torr.

$C_8H_{16}O_4$	calc.	C 54.53	H 9.14
(176.2)	found	54.49	9.09

I.R. (film): ν = 1740 cm^{-1} (s, C=O).

^{1}H-N.M.R. ($CDCl_3$): δ = 0.95 (d, J = 6.8 Hz, 3H); 2.09–2.53 (m, 3H); 3.36 (s, 6H); 3.67 (s, 3H); 4.05 ppm (d, J = 6.2 Hz, 1H).

4,4-Dimethoxy-3-methyl-(*N*,*N*-dimethyl)-butanamide (2e):
Dimethylamine (20 ml, 400 mmol) in tetrahydrofuran (20 ml) at −78 °C is treated with *n*-butyllithium (10.4 ml, 2.7 molar in hexane, 28 mmol). The resulting white suspension is stirred at −78 °C for 0.5 h then methyl 4,4-dimethoxy-3-methylbutanoate (**2d**; 3 g, 17 mmol) in tetrahydrofuran (5 ml) is added dropwise. After stirring for 1 h at −78 °C the reaction is quenched with water (10 ml) and allowed to warm to ambient temperature. The product is extracted with chloroform, the combined extracts are dried with potassium carbonate, and concentrated to give a yellow oil which is distilled; yield: 2.73 g (82%); b.p. 109–111 °C/0.5 torr.

$C_9H_{19}NO_3$	calc.	C 57.60	H 10.11
(189.2)	found	57.88	10.15

I.R. (film): ν = 1640 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 0.97 (d, J = 7 Hz, 3H); 2.07–2.56 (m, 3H); 2.95 (s, 3H); 3.02 (s, 3H); 3.37 (s, 6H); 4.15 ppm (d, J = 5 Hz, 1H).

2-Methoxycarbonyl-3-methyl-6,7-methylenedioxynaphthalene (4f); Typical Procedure:
Methyl 4,4-dimethoxy-3-methylbutanoate (**2d**; 13.1 g, 0.08 mol) in tetrahydrofuran (25 ml) is added dropwise to a −78 °C solution of lithium diisopropylamide (0.085 mol) in tetrahydrofuran (75 ml). After the addition is complete, the mixture is stirred for 1 h at −78 °C. 3,4-Methylenedioxybenzaldehyde (**1a**; 12 g, 0.08 mol.) in tetrahydrofuran (25 ml) is added dropwise and the mixture is allowed to warm to ambient temperature. The mixture is quenched with water (80 ml), the tetrahydrofuran evaporated, and the product extracted with chloroform. The combined extracts are evaporated to give a crude yellow oil which is dissolved in methanol (70 ml). The resulting solution is added dropwise to a refluxing solution of 20% aqueous sulfuric acid (1800 ml). When the addition is complete, the solution is allowed to reflux for 1.5 h before cooling and extracting the product with chloroform. The combined extracts are dried with magnesium sulfate and evaporated to give a light brown solid. This crude product is dissolved in boiling carbon tetrachloride (100 ml) and filtered. The filtrate is concentrated and recrystallized from methanol; yield: 16.2 g (83%, **4f**); the filter cake affords 1.0 g of the free acid analog.

$C_{10}H_{12}O_2$	calc.	C 68.85	H 4.95
(244.2)	found	68.83	4.75

This investigation was supported by grant number GM 33200 awarded by the National Institute of Health to Professor A.I. Meyers. We wish to thank Professor Meyers for use of equipment and materials and for financial support to G.P.R.. S.J.T. gratefully acknowledges S.E.R.C. for a fellowship.

Received: October 11, 1985

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