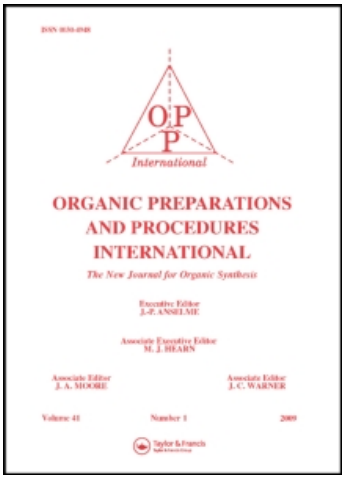

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A SIMPLE PREPARATION OF 4-SUBSTITUTED-6,7-DIMETHOXYISOQUINOLINES

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A SIMPLE PREPARATION OF 4-SUBSTITUTED-6,7-DIMETHOXYISOQUINOLINES

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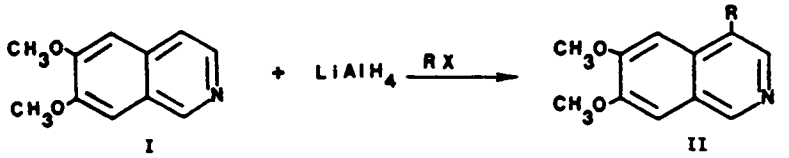
Earlier syntheses of biologically active[1,2] 4-substituted-6,7-dimethoxyisoquinolines (isopapaverine analogs)[3,4] often require multi-step procedures. We now report a simpler, direct one-flask method to II from I, which overcomes the problem of introducing eletrophilic substituents to



I II

the β-position of π-deficient azaarenes;[5] the technique has never been applied to substituted isoquinolines, especially with methoxy substituents. With $LiAlH_4$ and 3,4-dimethoxybenzyl chloride, I gives a 43% yield of 4-(3,4-dimethoxybenzyl)-6,7-dimethoxyisoquinoline (IIa). The 6,7-dimethoxyisoquinoline is readily prepared[6] from 3,4-dimethoxybenzaldehyde and aminoacetaldehyde in a 56% overall yield. 3,4-Dimethoxybenzyl

chloride was obtained in 44% yield by a known procedure[7] using veratryl alcohol and thionyl chloride.

TABLE 1. 4-Substituted-6,7-dimethoxyisoquinolines (II)

	R	Yield(%)[a]	mp. (°C)
IIa	3,4-Dimethoxylbenzyl	43	137-138
IIb	Methyl	34	122-124
IIc	Ethyl	37	99-101

a) Isolated yield based on the limiting reagent (LAH).

The results of the series of reactions was carried out in tetrahydrofuran (THF) in which the molar ratios of 6,7-dimethoxyisoquinoline (I) and 3,4-dimethoxybenzyl chloride to $LiAlH_4$ were varied are summarized in Table 2.[8] The most efficient conversion to IIa occurred with a ration of I to 3,4-dimethoxybenzyl chloride of 3.5:3.0.

TABLE 2. Effect of Ratio of Reagents on the Yield of IIa[a]

	Ratio of LAH:I:3,4-Dimethoxybenzyl Chloride		
	1:2.5:2.5	1:3.5:3.0	1:4:4
Yield (% based on $LiAlH_4$):	42	92	57

a) Percentage yield determined by HPLC analysis.

The present simple one-flask alkylation of I to 4-substituted-6,7-dimethoxyisoquinolines, in yields comparable to or better than those reported earlier, avoids the multi-step procedures. The above procedure would also be applicable for radiolabeled isopapaverines.

EXPERIMENTAL SECTION

Mps were determined with a Buchi melting point apparatus. All mps are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 227B spectrophotometer. NMR spectra were recorded at 90 MHz on a Varian EM390 spectrometer; chemical shifts are reported in parts per million (δ) relative to Me_4Si as internal standard. Analytical high pressure liquid

chromatography (HPLC) was performed with a 150 x 4.5 mm Spherisorb 5 μm ODS column in a Varian 5000 liquid chromatograph. The mobile phase was 60:40 5% (v/v) MeCN in MeOH/0.01 M NaH_2PO_4. Preparative HPLC was performed with a 150 x 10 mm Spherisorb 5 μm ODS column using a 50:45:5 water/MeOH/MeCN mobile phase. THF was freshly distilled from $LiAlH_4$ before each reaction. Solutions of reaction mixtures were dried over sodium sulfate.

4-(3,4-Dimethoxybenzyl)-6,7-dimethoxyisoquinoline (IIa).- A solution of 4.26 g (22 mmol) of 6,7-dimethoxyisoquinoline in 10 ml of dry THF was added over 0.5 h to a stirred solution of 6.5 ml (6.5 mmol) of 1 M $LiAlH_4$ in THF under argon at room temperature. The mixture was then refluxed for 22 hrs. After cooling to room temperature, a solution of 3.61 g (19 mmol) of 3,4-dimethoxybenzyl chloride in 10 ml of THF was added over 15 min. The mixture was stirred and refluxed for 16 hrs, and then quenched with 25 ml of 10% H_2SO_4. The acidic solution was extracted with dichloromethane (2 x 25 ml), and the organic phase was washed with 10% H_2SO_4 (2 x 15 ml). All the acidic extracts were combined and made basic with 50 ml of 6 N NaOH. After extraction of the basic layer with dichloromethane (2 x 50 ml) and ether (3 x 40 ml), the combined organic extracts were dried. Evaporation of the solvent provided 5.00 g of brown solid. The crude product was recrystallized from benzene to obtain 0.9 g (43%) of pale yellow crystals. An analytical sample, mp. 137-138°, lit.[7] 133-134°, was obtained by repeated recrystallization from benzene. ^1H NMR: δ 3.75 (s, 3H), 3.83 (s, 3H), 3.87 (s, 3H), 4.00 (s, 3H), 4.23 (s, 2H), 6.70 (m, 1H), 7.06 (s, 1H), 7.16 (s, 1H), 8.25 (s, 1H), 8.95 (s, 1H).

Anal. Calcd. for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13

Found: C, 70.97; H, 6.32; N, 4.12

4-Methyl-6,7-dimethoxyisoquinoline (IIb).- The synthesis followed the procedure outlined for preparation of IIa except for the use of methyl iodide in place of 3,4-dimethoxybenzyl chloride. From 1.15 g (6.1 mmol) of 6,7-dimethoxyisoquinoline, 0.40 g of crude product was obtained. The crude product was purified by preparative HPLC. The yield of pure IIb,

mp. 122-124°, lit.[3] 128° was (34%). IR (CCl_4): 1620, 1570, 1500, 1480, 1245, 1162 cm^{-1}; ^1H NMR: δ 2.42, (s, 3H), 3.95-4.0 (d, 6H), 7.0 (s, 1H), 7.1 (s, 1H), 8.2 (br s, 1H), 8.9 (br s, 1H). High Resolution MS Calcd. for $C_{12}H_{13}NO_2$: m/e 203.09462; found m/e 203.094.62.

4-Ethyl-6,7-dimethoxyisoquinoline (IIc).- The synthesis followed the procedure outlined for preparation of IIa except for the use of ethyl iodide in place of 3,4-dimethoxybenzyl chloride. From 1.15 g (6.1 mmol) of 6,7-dimethoxyisoquinoline, 1.00 g of crude product was obtained. The crude product was purified by preparative HPLC. The yield of pure IIc was 0.14 g (37%), mp. 99-101°, lit.[3] 88°. IR (CCl_4): 1625, 1580, 1505, 1485, 1225, 1165, cm^{-1}; ^1H NMR: δ 1.3-1.48 (t, 3H), 2.85-3.1 (q, 2H), 4.0-4.05 (d, 6H), 7.1 (s, 1H), 7.14 (s, 1H), 8.2 (br s, 1H), 8.88 (br s, 1H): High Resolution MS Calcd. for $C_{13}H_{15}NO_2$: m/e 217.11027; found m/e 217.11085.

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8. The yield was based on LAH because LAH is the limiting reagent.

A SHORT AND CONVENIENT SYNTHESIS OF 12-OXO-E-10-DODECENOIC ACID (TRAUMATIN)

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Traumatin (1) is a cleavage product of oxidized unsaturated C_{18} fatty acids from plants,[1-3] which has been implicated as a "wound hormone".[3] Most of the synthetic effort directed at 1 has centered on cleavage of fatty acid or ester diols (Eq. 1);[4] only recently has the first practical synthesis of 1 appeared (Eq. 2).[5] This latter route, which provides 1 in five steps from 10-undecenoic acid in 11% overall yield, suffers from the necessity of preparing the C_{10} aldehyde 3 by batch ozonolysis of the methyl ester of 10-undecenoic acid. This procedure exposes the worker to