An Efficient One-Pot Synthesis of 1,4-Diacyl-2,3,5,6-tetramethoxybenzenes via Biscuprated Precursors

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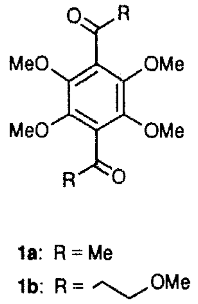
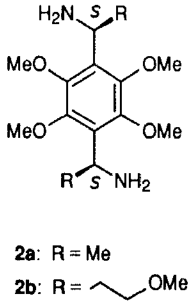
Received 1 February 1994; revised 3 June 1994

The efficient double acylation of 1,2,4,5-tetramethoxybenzene via the corresponding dicopper species is described; this reaction could not be attained either via the corresponding dilithium salts, or by Friedel-Crafts reaction. According to our method, the hitherto unknown diketones **1a** and **1b** are obtained in only one step in good yields. Further synthetic access to the compound **1a** is realized by bismethylation of the corresponding terephthaloyl dichloride **7**.

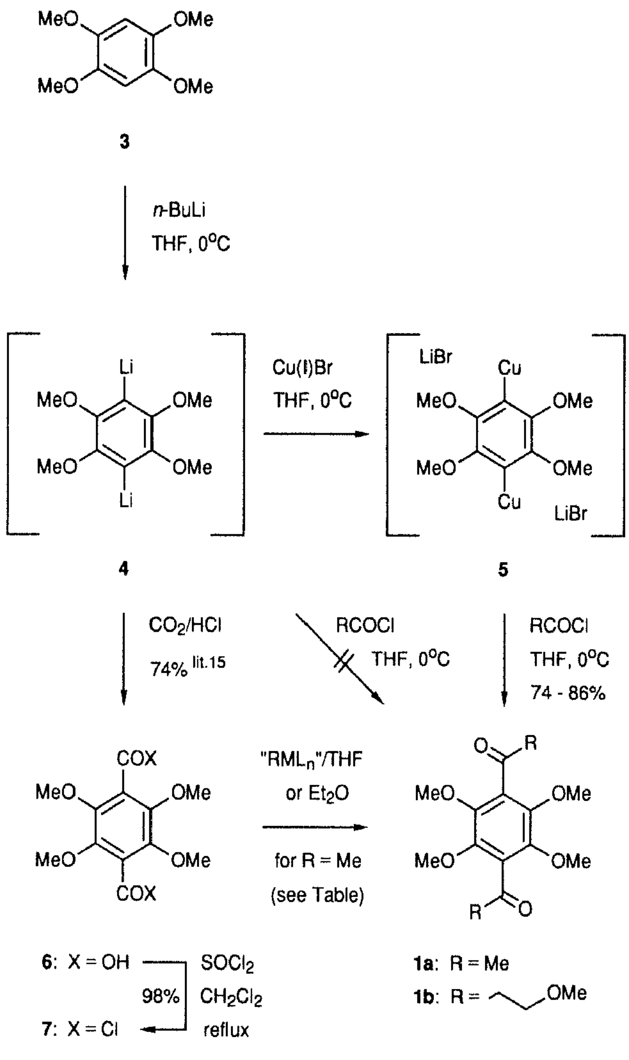
Despite its considerable synthetic value, the Friedel–Crafts acylation suffers from several limitations.[1,2] The formation of a bulky initial complex between the acyl halide (RCOX) and the Lewis acid (usually $AlCl_3$) greatly hampers attack at more sterically hindered positions. Furthermore, the simultaneous introduction of more than one acyl group into the aromatic ring is limited to a few special cases.[3] As a result of the drastic reaction conditions often required, side reactions may play an appreciable role. In addition, Lewis acid catalyzed ether cleavage reactions of alkoxylated substrates, although sometimes avoidable,[4] occur frequently.[5] A convenient modern procedure for the smooth conversion of anisole derivatives is based upon the use of cuprated precursors.[6] In this paper, we report the first synthetic access to the diketone **1a**, either by bismethylation of the corresponding dicarboxylic dichloride **7** or, more efficiently, by a mild one-pot method for the aromatic diacylation, starting from the biscuprated precursor **5**. The diketone **1b** was also prepared in good yield by this method.





Diketones **1a** and **1b** constitute interesting potential substrates for twofold stereoselective reductive amination reactions[7] to give the novel C_2-symmetric double arylalkylamines **2a** and **2b**. A straightforward synthetic access to **1a** should be the direct bisacylation of 1,2,4,5-tetramethoxybenzene (**3**). In the literature, this substrate did not react at all with acetyl chloride under standard Friedel–Crafts conditions,[8,9] and under more drastic reaction conditions, monoacetylation with concomitant demethoxylation to 2,4,5-trimethoxyacetophenone was reported to take place.[9]

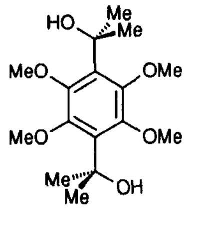
An alternative approach to **1a** might involve a stepwise introduction of the acetyl units (see Scheme 1) by methylation of the new dichloride **7** of diacid **6**. The known diacid **6** can be prepared by bislithiation of **3** with butyllithium (to give **4**) followed by treatment with solid CO_2.[10]



Scheme 1

The dicarboxylic acid **6** was transformed into **7** and treated with various nucleophilic methyl-transfer reagents which had been prepared according to literature procedures.[11,12] As seen in the Table, severe problems of an overreaction to give the tertiary alcohol **8** had to be overcome. Interestingly, monoacylated products were not obtained in any of the reactions. The best yields of **1a** were achieved with the lithium cuprate Me_2CuLi.

This reaction sequence does not only open up synthetic access to the as yet unknown diketone **1a** in particular, but also constitutes the first straightforward transformation of an aromatic diacid into the corresponding diacetyl compound.



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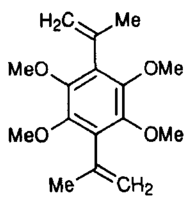

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Table. Products obtained from the reaction of 7 with various methylating agents

Entry	Reagent	Solvent	Temp. (°C)	Yield (%) of 1a	6[a]	8
1	MeLi	Et_2O	−15	12	–[b]	20
2	MeLi/CuI[11]	Et_2O	−78	15	46	12
3	Me_2CuLi[12]	Et_2O	−15	62	–	13
4	Me_2CuMgI[12]	THF–Me_2S	−15	17	–[b]	–[b]

[a] Formed during hydrolytic workup (1 N HCl).

[b] Detected by TLC, but not isolated.

However, this approach proved to be specific to the production of **1a**. It failed to lead to the direct synthesis of the more specialized diketone **1b** because the corresponding lithium dialkylcuprate could not be prepared. In addition, due to the relatively lengthy synthesis even of **1a** from **3** through the stepwise incorporation of the two sets of carbon atoms, we envisaged the direct introduction of the two entire C_2 units in a one-pot procedure. Because of the difficulties with the direct diacylation of **3** reported in the literature,[8,9] we tried to acylate its dilithio derivative **4**. However, all efforts using acetyl chloride, acetic anhydride and, for the attempted preparation of **1b**, 3-methoxypropionyl chloride, were unsuccessful.

A well established strategy to overcome such typical problems arising from the high basicity of organolithium compounds is to use the corresponding cuprates.[6] Although this approach has been successfully realized for several monometallated aromatics,[6] only one example of the preparation and use of biscuprated arenes has been reported in the literature, namely 1,4-dicuprio-2,3,5,6-tetrafluorobenzene.[13] However, this biscuprated species has also been generated from the corresponding dicadmium reagent with copper(I) bromide.[13] In our system, addition of copper(I) bromide (2.5 equivalents) to the dilithiated intermediate **4** at 0 °C, followed by treatment with the corresponding acid chloride, gave the target molecules **1a** and **1b** in very high yields for the first time. This efficient one-pot procedure avoids the toxic cadmium-containing intermediate used in literature.[13] Although the exact structure of the copper species is as yet unknown, our suggestion for the existence of a highly nucleophilic dicopper intermediate **5** with a very low basicity is based on the analogy of the formation of a corresponding monocopper species from the respective monolithium precursors.[6] Work to investigate the structure and reactivity of such synthetically useful intermediates in more detail is in progress.

All reagents were of commercial quality: BuLi (1.6 M, in hexane) and MeLi (1.6 M, in Et_2O) were purchased from Aldrich Chemical Co., Cu(I)Br from Riedel-de Haen AG, and 3-methoxypropionic acid from Fluka GmbH. The reactions were performed under N_2. Melting points were measured with a Kofler hot-stage apparatus and are corrected. Satisfactory microanalyses were obtained for all compounds: C ± 0.36, H ± 0.28 and were performed by the microanalytical laboratory of the Inorganic Institute of the University of Würzburg. IR spectra were recorded on a Perkin-Elmer 298 Infrared spectrophotometer. ^1H NMR spectra were obtained on a Bruker AC 200 spetrometer using TMS as internal reference. Mass spectra were recorded on a Finnigan MAT 8200 spectrometer.

2,3,5,6-Tetramethoxyterephthaloyl Dichloride (7):

To a solution of **6**[10] (200 mg, 0.69 mmol) in dry CH_2Cl_2 (5 mL) was added freshly distilled $SOCl_2$ (5 mL). The mixture was refluxed under N_2 and the reaction monitored by TLC (**7** was detected as its ethyl ester, as formed by alcoholysis of a sample of **7** with EtOH). When the reaction was complete (1 hr) the solvent and excess reagent were distilled off under reduced pressure. Recrystallization of the resulting white solid from petroleum ether (40–60 °C) gave the diacid chloride **7** as colorless needles, 218 mg (98 %); mp 112.5 °C [petroleum ether (40–60 °C)].

IR (KBr): ν = 3005, 2980, 2940, 2860, 2840, 1780, 1465, 1400, 1280, 1240, 1130, 1050, 940, 925, 810, 800, 750, 670 cm^{-1}.

^1HNMR ($CDCl_3$): δ = 3.92 (s, 12 H, $4OCH_3$).

MS: m/z (%) = 324 (M + 1, 11), 323 (2), 289 (33), 287 (100), 272 (6), 259 (11), 229 (12).

Reaction of 7 with MeLi in Et_2O (see Table, Entry 1):

To a solution of **7** (180 mg, 0.56 mmol) in dry Et_2O (50 mL), MeLi (0.67 mmol) was added at −15 °C. The color of the reaction mixture spontaneously turned yellow and a white solid precipitated. After stirring at r.t. for 1 h the solution was quenched with 1 N HCl (2 mL), the organic layer was separated, combined with the ether extracts from the aqueous layer and dried ($MgSO_4$). Subsequent evaporation of the solvent under reduced pressure gave a white solid from which the products **1a** and **8** were obtained by fractional recrystallization from CH_2Cl_2–ligroin 1 : 2 (3 mL). The yields are given in the Table (Entry 1).

1,4-Diacetyl-2,3,5,6-tetramethoxybenzene (**1a**): mp 119–120 °C (CH_2Cl_2–ligroin).

IR (KBr): ν = 2860, 2840, 1700, 1460, 1395, 1290, 1060 cm^{-1}.

^1HNMR ($CDCl_3$): δ = 2.48 (s, 6 H, $2CH_3$), 3.80 (s, 12 H, $4OCH_3$).

MS: m/z (%) = 283 (M + 1, 16), 282 (100), 267 (59), 252 (7), 239 (32), 209 (14), 207 (33), 43 (95), 28 (29).

1,4-Bis(1-hydroxy-1-methylethyl)-2,3,5,6-tetramethoxybenzene (**8**): mp 85–86 °C (CH_2Cl_2–ligroin).

IR (KBr): ν = 3480, 2950, 2920, 2815, 1435, 1380, 1340, 1260, 1045 cm^{-1}.

^1HNMR ($CDCl_3$): δ = 1.63 (s, 12 H, $4CH_3$), 3.81 (s, 12 H, $4OCH_3$), 5.82 (s, 2 H, 2OH).

MS: m/z (%) = 315 (M + 1, 10), 314 (1), 298 (33), 282 (100), 268 (29), 267 (8), 253 (13), 239 (2), 209 (3), 43 (33), 28 (4).

Reaction of 7 with Me_2CuLi in Et_2O (see Table, Entry 3):

To a solution of **7** (973 g, 3.01 mmol) in dry Et_2O (10 mL), Me_2CuLi (7.25 mmol), which had been prepared according to literature standard procedures[12] in Et_2O, was added dropwise at −15 °C. After stirring at r. t. for 30 min, the yellow suspension was quenched with 1 N HCl (1 mL). The grey cuprous slurry was filtered off, the organic layer was separated, combined with the CH_2Cl_2 extracts (5 × 5 mL) from the aqueous layer and passed through a silica gel column using CH_2Cl_2 as eluent. Evaporation of the solvent in vacuo gave a yellow oil, from which the products **1a** (527 mg, 62 %) and **8** (123 mg, 13 %) were obtained as white needles by fractional recrystallization from CH_2Cl_2–petroleum ether (40–60 °C) (4 mL, 1 : 3). The melting points and the spectral data of **1a** and **8** were identical with those mentioned above.

Reaction of 7 with Other Methyl-Transfer Reagents (see Table, Entries 2 and 4):
The reaction of 7 with MeLi-CuI in Et_2O and Me_2CuMgI in THF–Me_2S were performed under standard conditions on a 0.32–1.37 mmol scale as given in the literature.[11,12] The respective reaction temperatures and the resulting products are summarized in the Table.

One-Pot Synthesis of 1,4-Diacetyl-2,3,5,6-tetramethoxybenzene (1a):
To a solution of 3[14] (1.36 g, 6.88 mmol) in dry THF (50 mL) was added BuLi (17.2 mmol) at 0 °C under Ar. The yellow suspension was stirred for 4 h at r.t. On addition of copper(I) bromide (2.46 g, 17.2 mmol) at 0 °C, the color of the suspension changed to brown. The copper(I) bromide dissolved readily within 5 min. A solution of acetyl chloride (4.32 g, 55.0 mmol) in dry THF (20 mL) was added dropwise to the ice-cooled reaction mixture, which was stirred for another 1 h while the temperature was allowed to rise to r.t. The resulting clear orange solution was then treated with sat. aq NH_4Cl solution (10 mL), the organic layer was separated, washed with sat. brine (2 × 5 mL), dried (Na_2SO_4) and evaporated to dryness in vacuo. The orange residue was dissolved in Et_2O (2 mL) and passed through a silica gel column (15 cm × 4 cm, 0.032–0.063 mesh) with Et_2O as eluent. The filtrate was concentrated in vacuo and subsequent addition of ligroin (4 mL) and CH_2Cl_2 (1 mL) afforded the product **1a** as colorless needles; yield: 1.43 g (74 %); mp 119–120 °C (ligroin).

2,3,5,6-Tetramethoxy-1,4-bis(3′-methoxypropanoyl)benzene (1b):
According to the one-pot procedure described above, 3[14] (2.43 g, 12.3 mmol) in dry THF (50 mL) was dilithiated with BuLi (30.8 mmol). After addition of copper(I) bromide (4.40 g, 30.8 mmol) at 0 °C, the color of the suspension turned brown and the copper(I) bromide dissolved readily within 10 min. Stirring was continued at r.t. for 4 h. A solution of freshly prepared 3-methoxypropionyl chloride (9.40 g, 98.3 mmol) (obtained from the corresponding acid with oxalyl chloride) in dry THF (20 mL) was added dropwise to the ice-cooled reaction mixture. Stirring was continued for 1 h and the temperature was allowed to rise to r.t. After workup as described for **1a** and subsequent recrystallization from petroleum ether (40–60°C)–Et_2O, **1b** was obtained as white crystals; yield: 3.91 g (86 %); mp 57–58 °C.

IR (KBr): ν = 2940, 1705, 1465, 1405, 1330, 1270, 1170, 1070, 1035, 1000 cm^{-1}.

^1H NMR ($CDCl_3$): $\delta = 3.00$ (t, 4H, $J = 6.4$ Hz, $2CH_2$), 3.33 (s, 6H, $2OCH_3$ at C-3′), 3.73 (t, 4H, $J = 6.4$ Hz, $2CH_2$), 3.78 (s, 12H, $4OCH_3$).

MS: $m/z = 371$ (M + 1, 3), 370 (12), 355 (12), 282 (3), 266 (15), 233 (3), 59 (7).

We wish to thank the Fonds der Chemischen Industrie for generous financial support of our work.

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