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

Gerhard Bringmann,* Torsten Geuder, Sven Harmsen
Institut für Organische Chemie der Universität Würzburg, Am Hubland, D-97074 Würzburg, Germany
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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 lithium salts, or by Frielied-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 Frielied-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 AlCl₃) 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 other 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 reactions7 to give the novel C₃-symmetric double aminylamines 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 Frielied-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 meth-

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, monoacetylated products were not obtained in any of the reactions. The best yields of 1a were achieved with the lithium cuprate Me₃CuLi.

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.
All reagents were of commercial quality: BuLi (1.6 M, in hexane) and MeLi (1.6 M, in Et₂O) were purchased from Aldrich Chemical Co., CuI(Pr) from Riedel-de Haen AG, and 3-methoxypropionic acid from Fluka GmbH. The reactions were performed under N₂. 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 spectrometer using TMS as internal reference. Mass spectra were recorded on a Finnigan MAT 8200 spectrometer.

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Yield (%) of 1a</th>
<th>6a</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeLi</td>
<td>Et₂O</td>
<td>−15</td>
<td>12</td>
<td>b 20</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>MeLi/Cu</td>
<td>Et₂O</td>
<td>−78</td>
<td>15</td>
<td>46</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>Me₂CuLi²⁻</td>
<td>Et₂O</td>
<td>−15</td>
<td>62</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>Me₂CuMgLi¹⁻</td>
<td>THF- Me₂S</td>
<td>−15</td>
<td>17</td>
<td>b 7</td>
<td></td>
</tr>
</tbody>
</table>

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 C₃ units in a one-pot procedure. Because of the difficulties with the direct diacylation of 3 reported in the literature,⁶,⁸ 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 bispinated arenes has been reported in the literature, namely 1,4-dicyclopenta-2,3,5,6-tetrafluorobenzene.¹³ However, this bispinated 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.¹⁵ 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.

### Reaction of 7 with MeLi in Et₂O (see Table, Entry 1):

To a solution of 7 (180 mg, 0.56 mmol) in dry Et₂O (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 extract from the aqueous layer and dried (MgSO₄). 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 CHCl₃-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 (CHCl₃-ligroin).

IR (KBr): v = 2860, 2840, 1700, 1460, 1395, 1290, 1060 cm⁻¹.

¹H NMR (CDCl₃): δ = 2.46 (s, 6 H, 2CH₃), 3.80 (s, 12 H, 4OCH₃).

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 (CHCl₃-ligroin).

IR (KBr): v = 3480, 2950, 2920, 2815, 1435, 1380, 1340, 1260, 1045 cm⁻¹.

¹H NMR (CDCl₃): δ = 1.63 (s, 12 H, 4CH₃), 3.81 (s, 12 H, 4OCH₃), 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 (53), 28 (4).

### Reaction of 7 with Me₂CuLi in Et₂O (see Table, Entry 3):

To a solution of 7 (973 g, 3.01 mmol) in dry Et₂O (10 mL), Me₂CuLi (7.25 mmol), which had been prepared according to literature standard procedures¹² in Et₂O, 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 curupus slurry was filtered off, the organic layer was separated, combined with the CH₂Cl₂ extracts (5 × 5 mL) from the aqueous layer and passed through a silica gel column using CH₂Cl₂ 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 CH₂Cl₂-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 CuI in Et₂O (see Table, Entry 4):

To a solution of 7 (973 g, 3.01 mmol) in dry Et₂O (10 mL), Me₂CuLi (7.25 mmol), which had been prepared according to literature standard procedures¹² in Et₂O, 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 curupus slurry was filtered off, the organic layer was separated, combined with the CH₂Cl₂ extracts (5 × 5 mL) from the aqueous layer and passed through a silica gel column using CH₂Cl₂ 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 CH₂Cl₂-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 Et₂O and Me₂CuMgl in THF–Me₂S were performed under standard conditions on a 0.32–1.37 mmol scale as given in the literature. 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 3'4 (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 NH₄Cl solution (10 mL), the organic layer was separated, washed with sat. brine (2×5 mL), dried (Na₂SO₄) and evaporated to dryness in vacuo. The orange residue was dissolved in Et₂O (2 mL) and passed through a silica gel column (15 cm×4 cm, 0.032–0.063 mesh) with Et₂O as eluent. The filtrate was concentrated in vacuo and subsequent addition of ligroin (4 mL) and CH₂Cl₂ (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'-methoxypropionyl)benzene (1b):
According to the one-pot procedure described above, 3'4 (2.43 g, 12.3 mmol) in dry THF (50 mL) was dehydrogenated 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)/Et₂O, 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 (CDCl₃): δ = 3.00 (t, 4H, J = 6.4 Hz, 2CH₂), 3.33 (s, 6H, 2OCH₃ at C-3'), 3.73 (t, 4H, J = 6.4 Hz, 2CH₂), 3.78 (s, 12H, 4OCH₃).

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

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