3,3',5,5'-Tetramethoxybenzoin: a forgotten photolabile protecting group

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Abstract

Although reported several decades ago, 3,3',5,5'-tetramethoxybenzoin esters have not been used as a common photolabile protecting group, contrary to their unsymmetrical 3',5'-dimethoxybenzoin analogues. While the properties of the latter are superior, their tedious synthesis and chemical instability represent a drawback. In this article, we describe a reliable synthetic access to the symmetrical tetramethoxybenzoin derivatives, and show that their photochemical behaviour remain interesting, in particular chromatically orthogonality with respect to nitroveratryl esters.

Keywords Photochemistry · Protecting groups · Benzoin condensation · Quantum yield · Caged compounds

1 Introduction

Photolabile protecting groups have proven to be valuable tools in many fields, ranging from material science to biology, and of course including organic synthesis [1, 2]. Over the years, many different groups were developed and optimized for a specific property, such as most sensitive wavelength [3], speed [4], orthogonality [5–9], reliability, etc. In the currently available arsenal, a particular family of groups have emerged as one of the most popular, mainly by its robustness with respect to experimental conditions: the nitroveratryl (NV) derivatives **3** (commonly used as an oxycarbonyl derivative, NVOC) [10]. It is quite interesting to note that experimental convenience supersedes the fact that it is neither very fast, nor having a high quantum yield. On the other hand, 3',5'-dimethoxybenzoin derivatives (DMB **2**, Scheme 1) show a quite high photolysis quantum yield ($\phi=0.644$ in MeCN) [11], and are chromatically orthogonal with NVOC derivatives [12, 13], yet they are only rarely used [1, 14–16]. One of the reasons for its underutilization is the quite delicate synthesis, requiring the addition of a Grignard reagent to a silylated cyanohydrin [17]. A more recent synthesis was developed, involving an umpolung reaction with a dithiane [18, 19], but the latter deprotection

(under oxidative conditions) proved extremely sensitive to the quality of the reagents. In our own hands, despite the fact that we could reproduce the originally published yields, the reaction failed in an unpredictable way sometimes on large-scale batches [6]. A symmetrical analogue of this benzoin, the 3,3',5,5'-tetramethoxybenzoin **1** (TMB) would represent a much more easily available alternative, as a regular benzoin condensation would in principle afford it in a single step [12]. This triggered some interest in the late 80's and 90's, but the reaction was either found unreliable too [13], or required additional additives [20, 21]. In this technical note, we report both a reliable synthetic access and a brief study on its photochemical properties. These suggest that TMB represents an attractive replacement of DMB as a photolabile protecting group.

2 Results and discussion

a) Preparation

Benzoin **1** was prepared by a classical benzoin condensation in refluxing ethanol–water (6:1, v/v), using 10 mol-% of sodium cyanide as a catalyst (scheme 2). Purification by column chromatography gave the pure benzoin. The use of more catalyst (40 mol-%) was detrimental to the yield. Various ester derivatives were prepared from their acid chloride precursors in standard conditions (triethylamine, DMAP) at room temperature (scheme 3).

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Scheme 1. Benzoin-type photolabile protecting groups

Scheme 2. Preparation of benzoin **1**

Scheme 3. Preparation of esters **1a-c**

b) Photochemical properties

Contrary to 3',5'-dimethoxybenzoin acetate (**2b**), with an absorption maximum below 250 nm, tetramethoxybenzoin **1a-c** esters typically have a λ_{max} around 270 nm (268 nm for acetate **1b**) (Fig. 1). This may simplify experimental conditions, as LED UV sources, now commonly used, are considerably less expensive at this wavelength. In this study, 265 nm LED's were used.

The quantum yield of photolysis of ester **1a** was measured in acetonitrile, $\phi = 0.17$ (average of three runs, standard deviation 0.033). This is perfectly in line with the observation of Corrie and Trentham [13], quoting “four-fold less conversion” with respect

to Sheehan's reported quantum yield in acetonitrile ($\phi = 0.644 \pm 0.029$) for acetate **2b**. [11] The expected released product of the photolysis of **1b** being the volatile acetic acid, we repeated the reaction with lauric ester **1a**, and isolated 96% of lauric acid by acid/base extraction, together with variable amounts of tetramethoxybenzofuran **4** (Scheme 4). The latter is not photochemically stable, and further decomposition products were also detected (but not isolated). Its formation presumably arises from a similar mechanism as seen for the related derivatives of **2**. [1]

To probe its chromatic orthogonality with respect to nitroveratryl derivatives, a 3 mM mixture of **1a** and **3b** in acetonitrile was photolyzed at 265 nm with UV-LED's (estimated bandwidth 10 nm). After 85 min, 83% of **1a** was photolyzed, whereas 83% of acetate **3b** remained intact (Scheme 5). The same experiment was repeated at 405 nm. After 88 h, **1a** remained fully intact, whereas 64% of **3b** reacted. Despite the very long reaction time, reflecting the inertness of the tetramethoxybenzoin

Fig. 1 UV–Vis spectrum of **1b** and **2b**

Scheme 4. Photolysis of ester **1a** Scheme 5. Chromatic orthogonality of esters **1** and **3**

esters and the low quantum efficiency of the nitroveratryl esters, both groups are unambiguously chromatically orthogonal, in a similar way as our original pair DMB/NV pair [5, 6]. By shortening the wavelength from 405 to 365 nm, some orthogonality was retained, but to a more modest extent (after 11 min: 70% of **1a** was intact and 71% of **3b** had reacted).

3 Conclusion

In conclusion, we can observe that TMB is significantly easier to prepare, and its photochemical performances, although slightly degraded with respect to its DMB parent, remain in a reasonable range and thus make it a good substitute. A particularly interesting feature is its chromatic orthogonality with nitroveratryl esters.

4 Experimental part

4.1 Synthetic procedures

4.1.1 3,3',5,5'-tetramethoxybenzoin **1**

A solution of sodium cyanide (33.2 mg, 0.110 equiv., 677 μmol) in water (0.5 mL) was added to a hot solution of 3,5-dimethoxybenzaldehyde (1020.4 mg, 1 equiv., 6.1403 mmol) in EtOH (3.0 mL), which was then heated to reflux for 25 h. After the solution was allowed to cool down to room temperature a sat. NaHCO_3 solution was added. The mixture was extracted four times with Et_2O . The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure, yielding an orange crude product. Purification by column chromatography (silica gel; EtOAc:*n*-pentane 1:9 to 1:4) yielded 1,2-bis(3,5-dimethoxyphenyl)-2-hydroxyethan-1-one **1** (599.6 mg, 1.804 mmol, 59%) as an orange oil that solidified over time turning into a yellow solid. λ (MeCN)/nm 268 and 319 ($\epsilon/10^3 \cdot \text{L} \cdot \text{mol}^{-1} \cdot \text{cm}^{-1}$ 8.1 and 2.4). $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) 3.75 (6 H, s), 3.78 (6 H,

s), 4.45 (1 H, br. S.), 5.80 (1 H, s), 6.37 (1 H, t, $J=2.3$ Hz), 6.48 (2 H, d, $J=2.3$ Hz), 6.62 (1 H, t, $J=2.3$ Hz), 7.07 (2 H, d, $J=2.3$ Hz). $^{13}\text{C-NMR}$ (101 MHz, CDCl_3): δ (ppm) 55.4, 55.5, 76.3, 77.2, 100.5, 105.8, 106.4, 106.9, 135.2, 141.1, 160.8, 161.3, 198.5. **FT-IR** (golden gate, 600–4000 cm^{-1}) 3481, 3016, 2974, 2938, 2837, 1669, 1592, 1454, 1427, 1355, 1301, 1293, 1268, 1229, 1208, 1200, 1156, 1085, 1060, 1048, 1014, 947, 924, 887, 849, 842, 816, 789, 731, 703, 676, 655, 634. **HR-MS** (ESI) for (M-Na^+): calcd 355.1152, found 355.1133.

4.1.2 Lauryl ester 1a

Benzoin **1** (0.99 g, 1 equiv., 3.0 mmol) and *N,N*-dimethylpyridin-4-amine (0.124 g, 0.34 equiv., 1.01 mmol) were dissolved in anhydrous CH_2Cl_2 (2 mL) and cooled with an icebath. Triethylamine (0.30 g, 0.42 mL, 1.0 equiv., 3.0 mmol) and later dodecanoyl chloride (0.72 g, 0.76 mL, 1.1 equiv., 3.3 mmol) were added dropwise to the solution. The reaction was left to slowly warm up to room temperature overnight. After 22 h, EtOAc was added. The organic phase was washed three times with 1 M HCl and then water and a sat. NaHCO_3 solution. The organic phase was concentrated under reduced pressure, and purified by reverse-phase chromatography (C18, 20–100% MeCN in water), yielding **1a** (1.2205 g, 2.3715 mmol, 80%) as a yellow oil that solidified over time turning into a white/yellowish solid. λ (MeCN)/nm 268 and 322 ($\epsilon/10^3 \cdot \text{L} \cdot \text{mol}^{-1} \cdot \text{cm}^{-1}$ 8.8 and 2.5). $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) 0.88 (3 H, t, $J=6.6$ Hz), 1.12–1.42 (17 H, m), 1.68 (2 H, quin, $J=7.3$ Hz), 2.27–2.72 (2 H, m), 3.77 (6 H, s), 3.79 (6 H, s), 6.42 (1 H, t, $J=2.3$ Hz), 6.53–6.67 (3 H, m), 6.69 (1 H, s), 7.09 (2 H, d, $J=2.2$ Hz). $^{13}\text{C-NMR}$ (101 MHz, CDCl_3): δ (ppm) 14.1, 22.7, 24.8, 29.1, 29.26, 29.32, 29.4, 29.6, 31.9, 34.0, 55.4, 55.5, 77.2, 77.5, 101.2, 106.0, 106.56, 106.58, 135.7, 136.4, 160.8, 161.2, 173.3, 193.4. **FT-IR** (golden gate, 600–4000 cm^{-1}) 2998, 2953, 2923, 2852, 1728, 1698, 1605, 1594, 1462, 1427, 1380, 1357, 1333, 1316, 1296, 1260, 1206, 1192, 1154, 1066, 1043, 1010, 972, 946, 931, 877, 849, 827, 787, 757, 723, 698, 671, 644, 630. **HR-MS** (ESI) for (M-Na^+): calcd 515.3003, found 515.2992.

4.1.3 Acetate 1b

Benzoin **1** (540.3 mg, 1 equiv., 1.626 mmol) and *N,N*-dimethylpyridin-4-amine (24.7 mg, 0.124 equiv., 202 μmol) were dissolved in anhydrous CH_2Cl_2 (5.0 mL) and cooled with an icebath. Triethylamine (0.17 mg, 0.23 mL, 1.0 equiv., 1.7 mmol) and later acetyl chloride (0.14 g, 0.13 mL, 1.1 equiv., 1.8 mmol) were added dropwise to the solution. The reaction was allowed to warm up slowly to room temperature overnight. After 23 h, EtOAc was added and the organic

phase was washed three times with 1 M HCl, followed by water and brine. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The product was purified by reverse-phase chromatography (C18, 20–100% MeCN in water) yielding **1b** (0.2756 g, 736.1 μmol , 45%) as an off-white solid. λ (MeCN)/nm 268 and 320 ($\epsilon/10^3 \cdot \text{L} \cdot \text{mol}^{-1} \cdot \text{cm}^{-1}$ 8.3 and 2.3). $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) 2.22 (3 H, s), 3.77 (6 H, s), 3.79 (6 H, s), 6.43 (1 H, t, $J=2.3$ Hz), 6.52–6.65 (3 H, m), 6.69 (1 H, s), 7.08 (2 H, d, $J=2.2$ Hz). $^{13}\text{C-NMR}$ (101 MHz, CDCl_3): δ (ppm) 20.8, 55.4, 55.5, 77.2, 77.8, 101.3, 106.0, 106.59, 106.64, 135.6, 136.3, 160.8, 161.2, 170.4, 193.2. **FT-IR** (golden gate, 600–4000 cm^{-1}) 3012, 2960, 2934, 2841, 1727, 1691, 1592, 1457, 1425, 1373, 1361, 1347, 1301, 1284, 1257, 1241, 1206, 1153, 1063, 1045, 1016, 1005, 991, 964, 937, 925, 894, 848, 836, 786, 758, 700, 681, 645, 637, 604. **HR-MS** (ESI) for (M-Na^+): calcd 397.1258, found 397.1242.

4.1.4 Phenacyl ester 1c

Benzoin **1** (511.7 mg, 1 equiv., 1.540 mmol) and *N,N*-dimethylpyridin-4-amine (81.5 mg, 0.433 equiv., 667 μmol) were dissolved in anhydrous CH_2Cl_2 (5.0 mL) and cooled with an icebath. Triethylamine (18 mg, 25 μL , 0.12 equiv., 0.18 mmol) and later phenylacetyl chloride (267 mg, 230 μL , 1.12 equiv., 1.73 mmol) were added dropwise to the solution. The reaction was allowed to warm up slowly to room temperature overnight. After 29 h, EtOAc was added and the organic phase was washed three times with 1 M HCl followed by water and brine. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The product was purified by reverse-phase chromatography (C18, 20–100% MeCN in water) yielding **1c** (0.2629 g, 583.6 μmol , 38%) as a yellow oil. λ (MeCN)/nm 269 and 317 ($\epsilon/10^3 \cdot \text{L} \cdot \text{mol}^{-1} \cdot \text{cm}^{-1}$ 8.6 and 2.4). $^1\text{H-NMR}$ (400 MHz, CD_3CN): δ (ppm) 3.65–3.89 (15 H, m), 6.46 (1 H, t, $J=2.3$ Hz), 6.58 (2 H, d, $J=2.3$ Hz), 6.68 (1 H, t, $J=2.3$ Hz), 6.80 (1 H, s), 7.06 (2 H, d, $J=2.2$ Hz), 7.20–7.50 (5 H, m). $^{13}\text{C-NMR}$ (101 MHz, CD_3CN): δ (ppm) 41.3, 56.3, 56.5, 78.9, 101.7, 106.7, 107.3, 107.6, 128.1, 129.6, 130.5, 135.3, 136.9, 137.5, 162.2, 162.4, 172.0, 194.2. **FT-IR** (golden gate, 600–4000 cm^{-1}) 3091, 3064, 3004, 2961, 2939, 2839, 1737, 1696, 1592, 1455, 1427, 1348, 1298, 1250, 1204, 1151, 1061, 1041, 1005, 991, 977, 926, 843, 785, 745, 713, 694, 676, 645, 614. **HR-MS** (ESI) for (M-Na^+): calcd 473.1571, found 473.1551.

4.1.5 Benzofuran 4

A solution of **1b** (101.9 mg, 1 equiv., 272.2 μmol) in MeCN (7 mL) was irradiated in a Rayonet photoreactor

equipped with 16 254 nm tubes for 10 h. The solvent and volatiles were removed in vacuo and the crude mixture was purified by reverse-phase chromatography (C18, 20–100% MeCN in water) yielding **4** (26.3 mg, 83.7 μ mol, 31%) as a brown solid. λ (MeCN)/nm 217 and 300 ($\epsilon/10^3 \cdot \text{L} \cdot \text{mol}^{-1} \cdot \text{cm}^{-1}$ 31.7 and 25.4). $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) 3.86 (3 H, s), 3.88 (6 H, s), 4.02 (3 H, s), 6.39–6.60 (2 H, m), 6.63 (1 H, d, $J=2.2$ Hz), 6.94 (1 H, s), 7.02 (2 H, d, $J=2.3$ Hz). $^{13}\text{C-NMR}$ (101 MHz, CDCl_3): δ (ppm) 55.5, 55.9, 56.1, 77.2, 94.5, 97.4, 101.0, 102.4, 103.1, 130.4, 132.2, 139.5, 145.5, 156.4, 156.9, 161.1

4.2 Uncaging and isolation of lauric acid

A solution of **1a** (106.4 mg, 1 equiv., 206.7 μ mol) in MeCN (7 mL) was irradiated in a Rayonet photoreactor equipped with 16 254 nm tubes for 4 h. The solution was concentrated under reduced pressure. The crude mixture was dissolved in CHCl_3 , extracted three times with a NaOH solution. The combined aqueous layers were acidified with 1 M HCl. The acidic solution was extracted three times with CHCl_3 . Evaporation of the solvent yielded a brown/white solid residue, which was dissolved in CHCl_3 and filtered. Concentration under reduced pressure yielded dodecanoic acid (39.9 mg, 199 μ mol, 96%).

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Author contributions CB and DB designed the experiments. DB carried out the experimental work. CB wrote the manuscript.

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Availability of data and materials Supplementary information containing spectra and other data are available.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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