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Bocdene and Mocdene Derivatives of Catechols and Catecholamines

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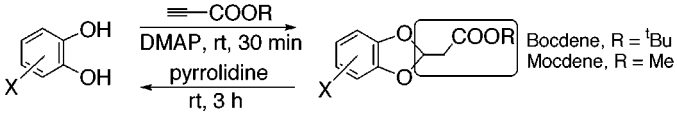
ABSTRACT



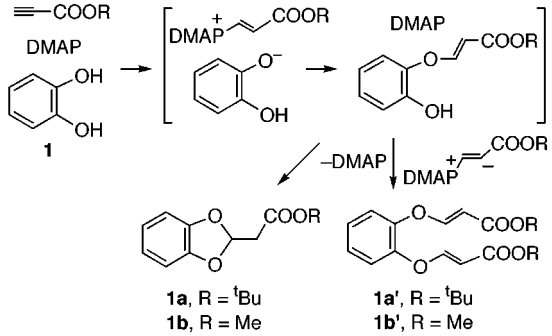
X = H, 2-CHO, 3-CHO, 3-CH(OH)Et, 3-OH, 3-CH_2CH_2NHZ ...

Catechols react chemoselectively, in the presence of either alcohols, 1,2-diols, or simple phenols, with *tert*-butyl propynoate and with methyl propynoate to give 2-Boc-ethylidene (Bocdene) and 2-Moc-ethylidene (Mocdene) acetals, respectively, in 96–100% yields within 30 min at room temperature, provided that 150 mol % of DMAP is added. Cleavage of these acetals with pyrrolidine readily takes place (at room temperature!) in 95–100% yields. By taking advantage of the features of Bocdene acetals, novel catecholamine-related phosphate mimetics have been prepared.

Conversion of vicinal dihydroxyarenes to cyclic acetals, before carrying out reactions in the aromatic nuclei and lateral chains, is the most standard protection protocol;[1] it has moreover a long tradition in polyphenol chemistry as it allows one to block adjacent hydroxyls without touching isolated phenol groups.[1] In this connection, we thought about the formation of cyclic acetals of polyhydroxyarenes by conjugate additions to alkyl propynoates (alkyl propiolates) that avoid drastic conditions.[2] Procedures that proceed in nearly quantitative yields and their application to the preparation of novel phosphate mimetics (that could be useful as "warheads" to proteins with SH2 domains)[3] are reported here.

By mixing catechol (**1**), an equimolar amount of *tert*-butyl propynoate, and 50 mol % of 4-(dimethylamino)pyridine (DMAP) as the catalyst, in CH_3CN at room temperature, a mixture of Boc-ethylidene (Bocdene) acetal **1a** and bis-Bocvinyl derivative **1a′**, in ca. 1:1 ratio, was obtained within 1 h; unreacted **1** remained.[4] By monitoring the reaction by ^1H NMR, some expected intermediates were detected (Scheme 1), but after 1 h the reaction progress was very slow.[4] When methyl propynoate was used, analogous products were formed, i.e., Mocdene acetal **1b** and bis-Mocvinyl

Scheme 1



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(2) Ariza, X.; Costa, A. M.; Faja, M.; Pineda, O.; Vilarrasa, J. *Org. Lett.* **2000**, *2*, 2809.

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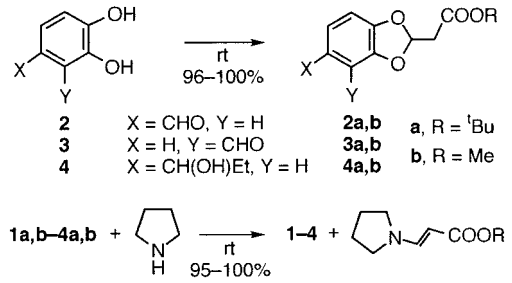
derivative **1b′**, as shown by NMR and by chromatographic comparison with the former series.[5] Apparently, a competition between the intramolecular cyclization and the second conjugate addition takes place.

Compounds **1a** and **1a′** were not convertible directly to each other under the reaction conditions; a sample of **1a**,[6] isolated by column chromatography, did not give **1a′** when treated with *tert*-butyl propiolate and DMAP for 3 days, while pure **1a′** [6] did not afford **1a** when treated with DMAP. Thus, the Bocdene group of **1a** and the Bocvinyl groups of **1a′** are stable against DMAP at room temperature. However, **1** plus **1a′** reacted slowly in the presence of DMAP, as they were mostly converted into **1a** after 18 h. This indicates a slow equilibrium reaction (**1** + **1a′** = 2 × **1a**) that is shifted toward **1a**. In other words, DMAP catalyzes a Bocvinyl transfer from **1a′** to **1** (to give two molecules of monosubstituted derivative, which cyclizes to **1a**). Therefore, the key for a quantitative conversion of catechols to acetals had to be the ratio between alkyl propiolate and DMAP: more propiolate than DMAP favors disubstitution, while more DMAP than propiolate favors cyclization, independently of the use of an excess or deficit of reagents.[7]

In practice, when **1**, 3,4-dihydroxybenzaldehyde (**2**), and 2,3-dihydroxybenzaldehyde (**3**) were independently treated with *tert*-butyl propiolate (1.1 mmol/mmol) and DMAP (1.5 mmol/mmol), 96−100% yields of Bocdene derivatives **1a**−**3a** were obtained within 15−30 min (Scheme 2).[8] With

Scheme 2



methyl propiolate, the corresponding Mocdene derivatives (**1b**−**3b**) were similarly obtained.[5] The DMAP excess appeared to be essential. With 1 mmol of DMAP or with mixtures of Et_3N (1.0−1.3 mmol) and DMAP (0.2−0.5 mmol), 18 h were required to complete the reaction.

Under these conditions, **1** *can be chemoselectively protected in the presence of alcohols and diols*. Only **1a** was formed by mixing equimolar amounts of **1** and benzyl alcohol or *meso*-1,2-diphenyl-1,2-ethanediol and treating the mixture with *tert*-butyl propynoate and excess of DMAP as above. The higher acidity of phenols explains this relevant fact. As pointed out in Scheme 1, the proton transfer from a phenolic hydroxy group to the alkyl propiolate-DMAP adduct may play a significant role in the reaction mechanism.

Catechols can also be selectively protected in the presence of phenols. For example, a mixture of **1**, 4-methylphenol, and 2-naphthol (1 mmol of each), when treated with 1.5 mmol of DMAP and 1.0 mmol of *tert*-butyl propiolate, afforded **1a** in practically quantitative yields; Bocvinyl derivatives of 4-methylphenol or 2-naphthol were not obtained. Apparently, the cyclization to **1a** is the driving force that shifts the DMAP-catalyzed equilibrium among the different Bocvinyl derivatives.

Deprotection of **1a**−**3a** with bases, via elimination and addition−elimination reactions, was very easy (Scheme 2, bottom). With 10 equiv of pyrrolidine, in CH_3CN at room temperature, deprotection was practically quantitative in 3 h (at 0.1 M concentration). In neat pyrrolidine, it was quantitative in 1 h. Separation of catechols from *tert*-butyl 3-(1-pyrrolidinyl)propenoate ("*N*-Bocvinyl-pyrrolidine") by extraction or by chomatography was simple. It is worth noting that Bocdene acetals are not hydrolyzed by 70:30 AcOH−H_2O after 24 h at room temperature. Cleavage of the corresponding Mocdene acetals (**1b**−**3b**) was also very efficient.[9]

Application to the Bocdene protecting group to a real example, in which an organometallic reagent was added to **2a**, follows. Treatment of **2a** with EtMgBr (1.1 equiv, from a 1.0 M solution in THF) at −78 °C for 5 min afforded **4a** in 90% yield;[10] deprotection with pyrrolidine in CH_3CN gave 1-(3,4-dihydroxyphenyl)-1-propanol (**4**). As summarized in Scheme 2, compound **4** was converted to **4a** and **4b** under our standard conditions without touching the alcohol function.

The case of pyrogallol (**5**) confirmed the previous results regarding (i) the competition between cyclization and disubstitution, (ii) the equilibrium between the starting material and Bocvinyl derivatives, (iii) the practical significance of the ratio between HC≡C−COOR and DMAP, and (iv) the

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(4) The yield of **1a** increased slowly, with disappearance of **1**, when stirring was continued; after 18 h the yield reached a maximum value of 70%.

(5) Ethyl propynoate also gave identical results.

(6) Data for **1a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.80 (br s, 4H), 6.46 (t, J = 5.2 Hz, 1H), 2.89 (d, J = 5.2 Hz, 2H), 1.46 (s, 9H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 167.5, 147.1, 121.5, 108.6, 107.9, 81.7, 41.4, 28.0. Data for **1a′**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.65 (d, J = 12.2 Hz, 2H), 7.1−7.3 (m, 4H), 5.26 (d, J = 12.2 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 165.7, 158.2, 145.6, 125.9, 120.4, 103.7, 80.8, 28.0.

(7) Even by using 2.0 mmol of *tert*-butyl propiolate (per mmol of substrate), provided that 3.0 mmol of DMAP was present in the reaction flask, the disubstituted product (**1a′**) was formed in minute amounts; the **1a**/**1a′** ratio was 95:5. With 2.0 mmol of *tert*-butyl propiolate and 1.0 mmol of DMAP, the **1a**/**1a′** ratio was 3:97.

(8) **Typical Experimental Procedure.** To **2** (138 mg, 1.0 mmol) and DMAP (183 mg, 1.5 mmol) in CH_3CN (10 mL), under nitrogen, was added *tert*-butyl propynoate (150 μL, 1.1 mmol). Stirring for 30 min, evaporation of the solvent under vacuum, and separation of the residue by flash chromatography on silica gel (75:25 hexanes−EtOAc) afforded **2a** (259 mg, 98% yield).

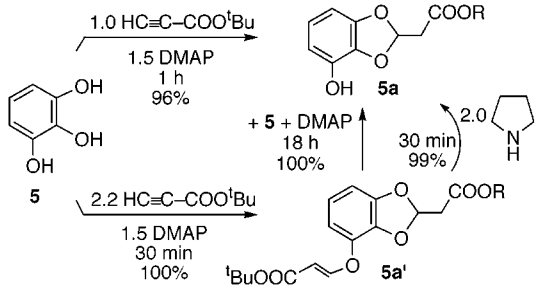
(9) **Typical Experimental Procedure.** To a solution of **2b** (91 mg, 0.41 mmol) in CH_3CN (4 mL) was added pyrrolidine (0.35 mL, 4.1 mmol). Stirring at room temperature for 2.5 h, removal of the solvent, and separation by chromatography on silica gel (from CH_2Cl_2 to 95:5 CH_2Cl_2−MeOH) afforded **2** (55 mg, 97%).

(10) Only one product is seen by TLC and ^{1}H and ^{13}C NMR spectroscopy (although very small splittings appear when the ^{13}C spectrum is expanded), as the stereocenters are far away to each other.

ready deprotection of Bocdene acetals of catechols with bases such as pyrrolidine. In practice, reaction of **5** with equimolar amounts of *tert*-butyl propynoate and DMAP gave 70% of Bocdene derivative **5a** and 15% of disubstituted compound **5a′**, but 18 h later the percentage of **5a** had increased at expenses of those of **5** and **5a′**.

By using appropriate ratios of reagents (Scheme 3, all

Scheme 3

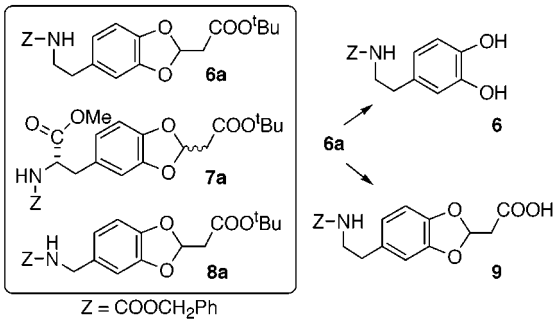


reactions in 0.1 M CH_3CN solutions at room temperature), the conversions among **5**, **5a**, and **5a′** became practically quantitative. Complete reversion of **5a** to **5** and of **5a′** to **5** by using 10 equiv of pyrrolidine occurred in 3 h (not indicated in Scheme 3 for the sake of simplification). Identical results were obtained with methyl propynoate.

Finally, reaction of dopamine-related derivatives with *tert*-butyl propiolate was investigated. Dopamine, L-DOPA methyl ester, and 3,4-dihydroxybenzylamine, after conversion to the respective benzyl carbamates (**6**−**8**), were subjected to our best reaction conditions (110 mol % of *tert*-butyl propiolate, 150 mol % of DMAP, CH_3CN, rt, 3 h). After purification by chromatography on silica gel, compounds **6a**−**8a**,[11] with the expected molecular formulas (ES−HRMS), were isolated in >90% yields.

Deprotection reactions were tested on **6a** (Scheme 4). Cleavage of the Bocdene group of **6a**, with 10 equiv of pyrrolidine, did work chemoselectively (90%, after ca. 5 h). Cleavage of *tert*-butyl group of **6a** was carried out in 90:10 trifluoroacetic acid−water at room temperature, in almost quantitative yield (>95%), to afford carboxylic acid **9**. Although expected, it is worth noting that the cyclic acetal

Scheme 4



of this carboxylic acid is not cleaved by treatment with pyrrolidine, even with neat pyrrolidine for a long time. Compound **9** and its analogues (arising from **7a** and **8a**) are promising as precursors of novel phosphate mimetics.[3,12] Studies in this regard are in course and will be reported elsewhere.

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(11) Data for **6a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (m, 5H), 6.70 (d, J = 7.8 Hz, 1H), 6.61 (m, 2H), 6.45 (t, J = 5.2 Hz, 1H), 5.10 (s, 2H), 4.73 (br s, 1H), 3.40 (q, J = 6.7 Hz, 2H), 2.88 (d, J = 5.2 Hz, 2H), 2.72 (t, J = 6.8 Hz, 2H), 1.47 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.5, 156.3, 147.5, 145.9, 136.5, 132.3, 128.5, 128.1, 121.6, 109.0, 108.4, 108.3, 81.8, 77.2, 66.6, 42.3, 41.4, 35.7, 28.0. Data for **7a**:[10] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5H), 6.67 (d, J = 7.9 Hz, 2H), 6.52 (m, 2H), 6.44 (t, J = 4.8 Hz, 1H), 5.24 (m, 1H), 5.10 (s, 2H), 4.59 (m, 1H), 3.73 (s, 3H), 3.02 (t, J = 4.9 Hz, 2H), 2.87 (d, J = 5.1 Hz, 2H), 1.46 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.6, 166.8, 154.9, 146.8, 145.7, 135.4, 128.4, 127.7, 127.1, 121.6, 108.8, 107.7, 107.6, 81.1, 76.5, 66.2, 54.1, 51.6, 40.6, 37.0, 27.3. Data for **8a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5H), 6.75−6.72 (m, 3H), 6.46 (t, J = 5.4 Hz, 1H), 5.13 (s, 2H), 5.01 (br s, 1H), 4.27 (d, J = 5.9 Hz, 2H), 2.87 (d, J = 5.1 Hz, 2H), 1.47 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.9, 156.7, 148.0, 147.1, 136.8, 132.6, 128.9, 128.6, 121.2, 108.9, 108.7, 108.6, 77.6, 67.3, 45.4, 41.8, 28.4.

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