Reactions of Carbanions with 1,3-Benzodioxin-4-ones: Facile Routes to Flavones, Aurones, and Acyl Phloroglucinols

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Received 22 February 2008; revised 28 April 2008

Abstract: Two 1,3-benzodioxin-4-ones react with enolates, acetylides and aryllithium reagents to afford adducts that were converted into flavones, aurones, and an acyl phloroglucinol.

Key words: carbanions, ketones, natural products, nucleophilic addition

The carbanion addition chemistry of 1,3-benzodioxin-4-ones has been little studied. To the best of our knowledge, only two reactions of 1,3-benzodioxin-4-ones with a carbanion have been reported. In one case an organozinc reagent reacted with a 1,3-benzodioxin-4-one to afford a tertiary alcohol and in the other case a Grignard reagent reacted to provide a ketone. The infrequent use of 1,3-benzodioxin-4-ones was in part due to the absence of a convenient general method of preparation. Recently, Takahashi reported an improved synthesis of 1,3-benzodioxin-4-ones such as 1. Methylation of 1 using potassium carbonate and methyl iodide afforded 2 in 100% yield. Protection of 1 using benzenesulfonfyl chloride and triethylamine gave 3 in 98% yield.

Because of the ready availability of 2 and 3, we evaluated their reactions against a panel of carbanions. These reactions are depicted below in Table 1. The reaction of the enolate of acetophenone [prepared by deprotonation of acetophenone with lithium diisopropylamide (LDA) in THF at –78 °C] with 2 did not take place and only the starting materials were recovered. However, the reaction of the enolate with the more electrophilic reagent 3 generated β-diketone 4 in 77% yield. Unexpectedly, no reaction of the enolate of 4-methoxycacetophenone with 3 took place and only the starting materials were recovered. Fortunately, the LDA-derived enolate of 4-benzenesulfonyl oxyacetophenone reacted efficiently with 3 to produce the β-diketone 5 in 66% yield.

Treatment of 2 with the lithium anion of phenylacetylene at 0 °C (generated from phenylacetylene and n-butyllithium at –78 °C) afforded the acetylenic ketone 6 in 45% yield. Similarly, the anion of 3,4-dimethoxyphenylacetylene furnished the ketone 7 in 31% isolated yield. When 3,4-dimethoxybromobenzene was metlated with n-butyllithium in THF at –78 °C and reacted with 3, adduct 8 was produced in 74% yield. When 4-benzoxo-3-methoxybromobenzene was lithiated and reacted with 2, benzophenone 9 was generated in 70% yield. The reaction of phenyllithium with 2 produced adduct 10 in 75% yield whose spectra matched the literature data.

We next studied the conversion of adducts from Table 1 into natural products. Diketone 4 was readily cyclized using PTSA and then deprotected using potassium carbonate in methanol to afford the natural product chrysin (11) in 69% overall yield from acetophenone (Scheme 2). The 1H and 13C NMR spectra of our synthetic material were identical to the spectra obtained from an authentic sample of chrysin. The β-diketone 5 could be cyclized using PTSA and deprotected to provide apigenin (12) in 42% overall yield from 5. Again, 1H and 13C NMR spectra of our synthetic material matched the spectra of an authentic sample of apigenin. Apigenin is a natural antioxidant that occurs in a number of species of Hypericum. It has been shown to promote cell cycle arrest and apoptosis in various malignant cell lines and is also a potent inhibitor of glucosyltransferase activity.

Ketone 6 was rapidly cyclized to aurone 13 upon reaction with potassium carbonate in boiling acetone. The exclusive 5-exo reaction pathway has precedent in the work of Garcia. The NMR spectrum of our material is identical to that of the natural product. The melting point of 13 compares closely with the literature value. Similarly, adduct 7 was converted into aurone 14 in 80% yield (Scheme 3). The 1H NMR spectrum of 14 matched the literature data.

Scheme 1

SYNTHESIS 2008, No. 15, pp 2427–2431
Advanced online publication: 17.07.2008
DOI: 10.1055/s-2008-1078597; Art ID: M01008SS
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Acyl phloroglucinols are a diverse class of natural products that exhibit antibacterial activity, anticancer activity and antitubercular activity. Removal of the benzyl protecting group from ketone 9 using hydrogen and 10% palladium on carbon afforded the acyl phloroglucinol 15 in 73% yield (Scheme 4). The identity of synthetic benzophenone 15 was confirmed by comparison of our 1H NMR, 13C NMR, LRMS, and HRMS data with the published spectra for the natural product. This is the first synthesis of benzophenone 15.

In summary, 1,3-benzodioxin-4-ones 2 and 3 react with a number of commonly used carbanions to provide adducts in good yields. The adducts could be converted into the flavones chrysin and apigenin, aurones, and an acyl phloroglucinol.
Tetrahydrofuran was distilled from sodium benzophenone ketyl. Dichloromethane, toluene and HMPT were distilled over calcium hydride. All experiments were performed under argon atmosphere. Organic extracts were dried over anhydrous sodium sulfate. Infrared spectra were obtained on a Perkin-Elmer model 1320 spectrophotometer. Nuclear magnetic resonance experiments were performed with either a Varian 300 MHz or a Bruker 400 MHz instrument. High-resolution mass spectra were recorded on a Kratos model MS-50 spectrometer and low-resolution mass spectra were performed with a Finnigan 4023 mass spectrometer. Standard grade silica gel (60 Å) was used for flash column chromatography.

5.7-Dimethoxy-2,2-dimethylbenzo[1,3]dioxin-4-one (2)
To 1 (0.40 g, 1.14 mmol) and Et2N (0.25 g, 2.5 mmol), followed by slow addition of benzzenesulfonyl chloride (0.44 g, 2.5 mmol). The mixture was warmed slowly to r.t. and stirred overnight. The solution was neutralized with 0.5 M aq AcOH, diluted with H2O (20 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (10 mL) and dried (MgSO4). Evaporation of the solvent and purification of the residue by flash chromatography (hexanes-EtOAc, 2:1) afforded compound 2 (0.34 g, ~100%) as a light yellow solid; mp 128–129 °C; 1H NMR (300 MHz, CDCl3): δ = 1.68 (s, 3 H), 3.83 (s, 3 H), 3.91 (s, 3 H), 6.06 (d, J = 3 Hz, 1 H), 6.13 (d, J = 3 Hz, 1 H).

5.7-Dibenzenesulfonyl-oxy-2,2-dimethylbenzo[1,3]dioxin-4-one (3)
To 1 (0.24 g, 0.011 mmol) in THF (20 mL) at 0 °C was added Et2N (0.25 g, 2.5 mmol), followed by slow addition of benzzenesulfonyl chloride (0.44 g, 2.5 mmol). The mixture was warmed slowly to r.t. and stirred overnight. The solution was neutralized with 0.5 M aq AcOH, diluted with H2O (20 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (10 mL) and dried (MgSO4). Evaporation of the solvent and purification of the residue by flash chromatography (hexanes-EtOAc, 2:1) afforded compound 3 (0.55 g, 98%) as a white solid; mp 132–133 °C; 1H NMR (300 MHz, CDCl3): δ = 1.61 (s, 6 H), 6.68 (d, J = 2.4 Hz, 1 H), 6.75 (d, J = 2.4 Hz, 1 H), 7.52–7.63 (m, 4 H), 7.66–7.77 (m, 2 H), 7.87–7.90 (m, 2 H), 9.95–9.79 (m, 2 H).

5.7-Dibenzenesulfonyl-oxy-2,2-dimethylbenzo[1,3]dioxin-4-one (4)
To a solution of 3,4-dimethoxyphenylacetylene (200 mg, 1.24 mmol) in THF (5 mL) was added -BuLi (2.5 M solution in hexanes, 0.5 mL, 1.24 mmol). After 1 h at 0 °C, the solution was cooled to –78 °C, and then quenched with aq 4.3 N AcOH. The resulting solution was diluted with EtOAc and the EtOAc layer was washed with brine (20 mL) and dried (MgSO4). Evaporation of the solvent and purification of the residue by flash chromatography (hexanes-EtOAc, 2:1) afforded compound 4 (10 mL) and dried (MgSO4). Evaporation of the solvent and purification of the residue by flash chromatography (hexanes-EtOAc, 2:1) afforded the purified product (Table 1).

1-(2,4-Dibenzenesulfonyloxy-6-hydroxyphenyl)-3-phenylpropane-1,3-dione (5)
Compound 5 was taken on directly to 12 without purification.

1-(2,4-Dihydroxyphenyl)-3-phenylprop-2-ynone (6)
To phenylacetylene (20 mg, 0.2 mmol) in THF (5 mL) at 0 °C was added -BuLi (2.5 M solution in hexanes, 1 equiv) in THF (2 mL/mmol) was added slowly. After 5 min, the temperature was raised to 0 °C for 1 h and the mixture was warmed slowly to r.t. and stirred for 2 h. The mixture was neutralized with 0.5 M aq AcOH, diluted with H2O (20 mL) and extracted with EtOAc (2 × 20 mL). The organic layers were washed with brine (10 mL) and dried (MgSO4). Evaporation of the solvent and purification of the residue by flash chromatography twice (hexanes-EtOAc, 2:1 and hexanes-Ch2Cl2, 1:2) afforded the starting material 2 (19 mg) and product (23 mg, 45% yield, 82% conversion); Rf = 0.24 (CH2Cl2–hexanes, 2:1).

1-(2,4-Dihydroxyphenyl)-3-(3,4-dimethoxyphenyl)prop-2-ynone (7)
To a solution of 3,4-dimethoxyphenylacetylene (200 mg, 1.24 mmol) in THF (10 mL) at 0 °C was added -BuLi (2.5 M solution in hexanes, 0.5 mL, 1.24 mmol). After 1 h at 0 °C, the solution was cooled to –78 °C, and then quenched with aq 4.3 N AcOH. The resulting solution was diluted with EtOAc and the EtOAc layer was washed with H2O (20 mL) and brine (10 mL) successively. The organic layer was dried (MgSO4), filtered, and evaporated in vacuo. The residue was purified twice by flash column chromatography on silica gel (hexanes-EtOAc, 6:1 and CH2Cl2-EtOAc, 19:1) to afford the acetylenic ketone 7 (66 mg, 31%).

1-(2,4-Dibenzenesulfonyloxy-6-hydroxyphenyl)-3-(3,4-dimethoxyphenyl)prop-2-ynone (8)
To a solution of 3,4-dimethoxyphenylacetylene (200 mg, 1.24 mmol) in THF (10 mL) at 0 °C was added -BuLi (2.5 M solution in hexanes, 0.5 mL, 1.24 mmol). After 1 h at 0 °C, the solution was cooled further to –78 °C, and then quenched with aq 4.3 N AcOH. The resulting solution was diluted with EtOAc and the EtOAc layer was washed with H2O (20 mL) and brine (10 mL) successively. The organic layer was dried (MgSO4), filtered, and evaporated in vacuo. The residue was purified twice by flash column chromatography on silica gel (hexanes-EtOAc, 6:1 and CH2Cl2-EtOAc, 19:1) to afford the acetylenic ketone 7 (66 mg, 31%).

1-(2,4-Dibenzenesulfonyloxy-6-hydroxyphenyl)-3-phenylprop-2-ynone (9)
To a solution of 3,4-dimethoxyphenylacetylene (200 mg, 1.24 mmol) in THF (10 mL) at 0 °C was added -BuLi (2.5 M solution in hexanes, 0.5 mL, 1.24 mmol). After 1 h at 0 °C, the solution was cooled further to –78 °C, and then quenched with aq 4.3 N AcOH. The resulting solution was diluted with EtOAc and the EtOAc layer was washed with H2O (20 mL) and brine (10 mL) successively. The organic layer was dried (MgSO4), filtered, and evaporated in vacuo. The residue was purified twice by flash column chromatography on silica gel (hexanes-EtOAc, 6:1 and CH2Cl2-EtOAc, 19:1) to afford the acetylenic ketone 7 (66 mg, 31%).

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To compound (2,4-Dibenzenesulfonyloxy-6-hydroxyphenyl)(3,4-dimethoxy-phenyl)methanone (8) 

\[
R_j = 0.14 \text{ (EtOAc–hexanes, 1:1).}
\]

1H NMR (300 MHz, CDCl3): \( \delta = 3.98 \text{ (s, 3 H), 3.91 (s, 3 H), 6.50 (d, J = 2.4 Hz, 1 H), 6.67 (d, J = 2.4 Hz, 1 H), 6.74 (d, J = 8.4 Hz, 1 H), 7.11–7.17 (m, 2 H), 7.40–7.42 (m, 4 H), 7.56–7.64 (m, 3 H), 7.69–7.73 (m, 1 H), 7.88–7.91 (m, 2 H).} \]

13C NMR (75 MHz, CDCl3): \( \delta = 56.27, 56.32, 109.4, 109.9, 110.7, 111.7, 115.8, 125.7, 128.1, 129.3, 129.7, 130.7, 134.6, 134.8, 135.0, 135.2, 147.8, 148.9, 152.7, 154.1, 161.4, 194.5. \]

MS: m/z = 570, 429, 287, 259, 164, 137.

HRMS: m/z calcd for C27H22O10S2: 570.0654; found: 570.0663.

To compound 11 (0.20 g, 90%) as a yellow solid; mp 148–151 °C (Lit. \text{10b mp 152–153 °C}).

4,6-Dimethoxyaurone (13) 

To compound 6 (10 mg) and K2CO3 (10 mg) in a sealed tube was added acetone (2 mL) and the mixture heated to 56 °C for 6 h. After the solution had cooled to r.t., the toluene was removed by evaporation in vacuo. The residue was treated with H2O and extracted with EtOAc (20 mL) and dried (MgSO4). Evaporation of the solvent and purification by flash chromatography on silica gel (hexanes–EtOAc, 2:1) afforded aurone 13 (9.5 mg, 95%) as a yellow solid; mp 148–151 °C (Lit. \text{10b mp 152–153 °C}).

HRMS (EI): m/z = 342 (M+ 100%), 311, 180.


2,4,6-Tetramethoxyaurone (14) 

To a solution of benzophenone (50 mg, 0.22 mmol) in acetone (5 mL), taken at r.t., was added K2CO3 (31 mg, 0.22 mmol) at r.t. The mixture was stirred for 18 h at r.t. under H2 atmosphere (H2 balloon), the mixture was filtered and the filtrate was evaporated in vacuo to afford 14 (20 mg, 80%).

HRMS (EI): m/z = 342 (M+ 100%), 311, 180.

HRMS (EI): m/z calcd for C27H24O8: 342.1103; found: 342.1108.
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(δ, J = 2.4 Hz, 1 H), 6.04 (s, 1 H), 5.97 (d, J = 2.0 Hz, 1 H), 3.93 (s, 3 H), 3.86 (s, 3 H), 3.54 (s, 3 H).

13C NMR (100 MHz, CDCl3): δ = 197.4, 166.0, 165.1, 161.6, 149.2, 146.1, 133.5, 124.3, 113.4, 111.0, 106.0, 93.9, 91.6, 56.3, 55.8, 55.4.

LRMS (EI): m/z = 304 (M+), 303 (100%), 287, 181.

HRMS (EI): m/z calc'd for C16H16O6: 304.0947; found: 304.0952.

Acknowledgment

We thank the National Institutes of Health (grant P01 ES12020) and the Office of Dietary Supplements for partial financial support through the Center for Research on Botanical Dietary Supplements at Iowa State University.

References

(6) The authentic sample was obtained from Aldrich Chemical Company.