

An Efficient Preparation of 6-Alkoxy-substituted Benzocyclobutenones

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Abstract: A short, efficient route to 3-alkoxybenzynes has been developed, starting from readily available compounds. This has enabled rapid access to 6-alkoxybenzocyclobutenones, which are valuable synthetic intermediates.

Key words: benzynes, benzocyclobutenone derivatives, [2+2] cycloadditions, metalations, protecting groups

A key structural component of the naphthylisoquinoline and michellamine alkaloids is the 1,8-dioxygenated naphthalene moiety and much synthetic effort has been expended on the development of efficient syntheses of such compounds.^{1,2} Despite this, there is still a need for a flexible and efficient route to the naphthalene core which would enable functionality to be introduced at a variety of positions around the ring. Benzocyclobutenones **1** are versatile precursors to substituted tetralones and naphthalenes. Addition of vinylic and acetylenic nucleophiles to the carbonyl group, followed by thermolysis of these adducts provides a simple and efficient route to these ring systems (Figure 1).³ It was envisaged that this strategy could be adapted to allow for the development of a synthesis of 1,8-dioxygenated naphthalenes, which would meet our goal of a flexible, efficient route. To achieve this, access to significant quantities of 6-alkoxybenzocyclobutenone derivatives **1** is necessary. However, while there are many methods available for the synthesis of functionalized benzocyclobutenones, the majority of these require precursors that are only available from 3 to 5 step syntheses, thus limiting the utility of these approaches.⁴

The most amenable approach to the 6-alkoxy-substituted benzocyclobutenones is a two step procedure where 3-methoxybenzyne (**2**) is reacted with either a dialkyl ketene acetal^{5,6} or a silyl ketene acetal,⁷ then the resulting acetal is hydrolyzed to give the ketone **3** (Scheme 1). However, initial work on this route was plagued by the poor reproducibility of the benzyne formation.^{6,7} This led Suzuki and co-workers⁷ to develop a new benzyne precursor, the iodotriflate **4**, which generates benzyne **2** in an efficient manner upon treatment with butyllithium at -78°C .

A drawback to this sequence is that a four step route is required to synthesize iodotriflate **4**, with the key step involving the generation of an aryllithium species that is

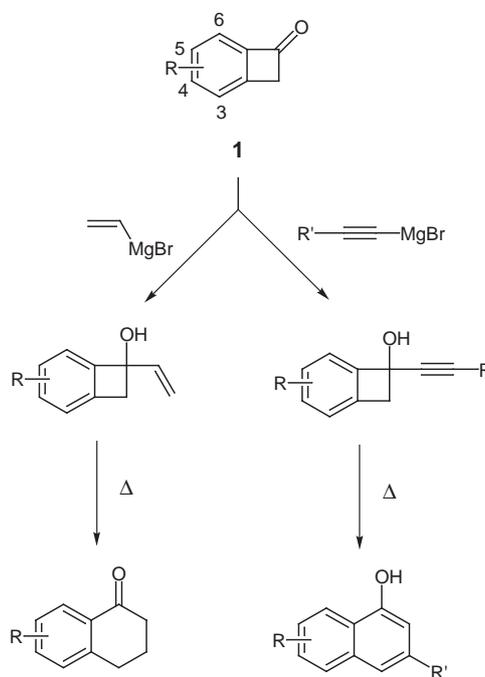
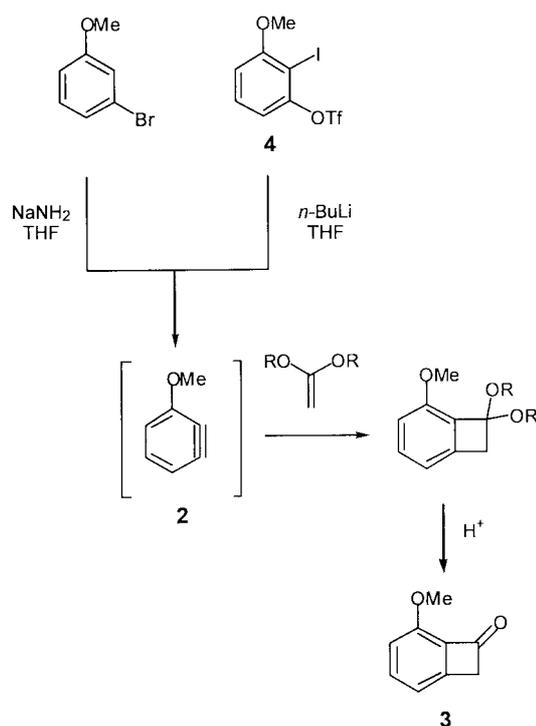


Figure 1

trapped with iodine in modest yield.⁸ In this paper, we wish to report alternative benzyne precursors **5a,b,c**, (Scheme 2) which are readily generated in large quantities from commercially available starting materials.

As detailed in Scheme 2, benzyne precursor **5a** is readily obtained from 2-methoxyphenol (**6**). Bromination of **6** in the presence of 2 equivalents of *tert*-butylamine selectively produces the *o*-bromophenol **7** in excellent yield.⁹ Initially, the phenol group in bromide **7** was activated by converting it to the tosylate **8** using TsCl and triethylamine in dichloromethane. Halogen-metal exchange with BuLi to generate an aryllithium species, followed by elimination of the tosylate group was expected to generate the 3-methoxybenzyne (**2**). However, reaction of tosylate **8** with BuLi in the presence of 1,1-diethoxyethylene (**9**) afforded only minor quantities of the desired adduct, with the main product isolated being the debrominated material **10**.¹⁰

The lack of reactivity of the tosylate – whether due to insufficient leaving group ability or competitive metallation – directed our attention to the use of a triflate group. Triflate **5a** was obtained in near quantitative yield when phenol **7** was reacted with triflic anhydride and pyridine. In contrast to the tosylate **8**, reaction of triflate **5a** with BuLi

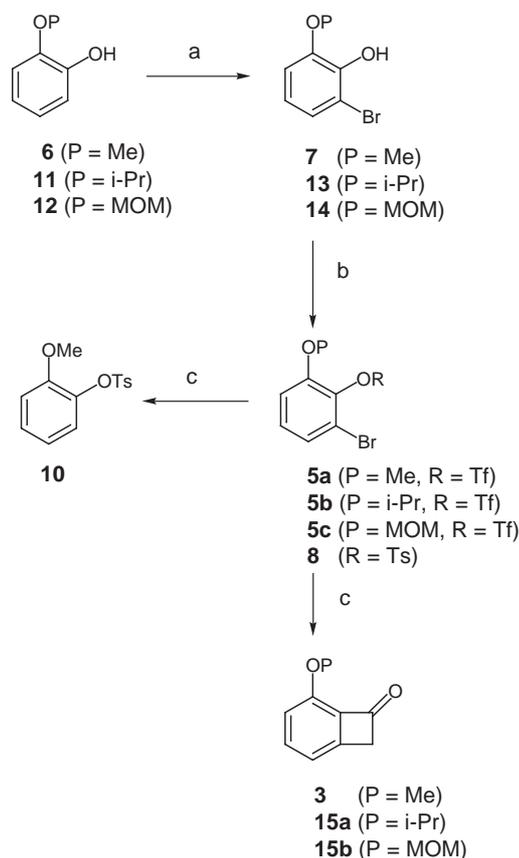


Scheme 1

in the presence of 1,1-diethoxyethylene (**9**) at -95°C proceeded smoothly and after an acidic workup, benzocyclobutenone **3**¹¹ was isolated in 72% yield. The benzyne reaction using bromotriflate **5a** has been carried out on a 20 g scale, allowing access to significant quantities of **3**.

In the total synthesis of the michellamine alkaloids, the choice of protecting group on the naphthalenes is critical, with the isopropyl and methoxymethyl (MOM) groups having proven to be optimal.¹ Thus, the preparation of benzocyclobutenones **15** (where P = *i*-Pr or MOM) would allow further flexibility in our proposed syntheses. While benzocyclobutenone **3** could be readily deprotected with hydrogen bromide in acetic acid at reflux, reaction of the resulting phenol¹² with either 2-bromopropane or chloromethyl methyl ether led to complex mixtures, which meant that the protecting group needed to be introduced earlier in the synthesis. Thus, the bromotriflates **5b** and **5c** were prepared as detailed in Scheme 2. Using the earlier described *ortho*-bromination and triflate formation conditions, the phenols **11** and **12**¹³ were converted into the benzyne precursors **5b** and **5c**, respectively, in excellent overall yield. Generation of the 3-alkoxybenzyne with BuLi at -95°C in the presence of **9** proceeded smoothly, and after an acidic workup the benzocyclobutenones **15a,b** were obtained in 62% and 55% yield, respectively. The slightly lower yields for the benzyne addition reaction are a reflection of how readily **15a,b** sublime.

In conclusion, a short route to precursors for 3-alkoxybenzyne has been developed, starting from readily available compounds. This has allowed an efficient, large scale syn-



Scheme 2 Reagents and conditions: (a) $\text{Br}_2/t\text{-BuNH}_2$ [**7** (91%), **13** (85%), **14** (80%)] (b) $\text{TsCl}/\text{Et}_3\text{N}/\text{CH}_2\text{Cl}_2$ (99%) or $\text{Tf}_2\text{O}/\text{pyridine}$ [**5a** (98%), **5b** (88%), **5c** (89%)] (c) $\text{BuLi}/\text{THF}/1,1\text{-diethoxyethylene}$ (**9**), -95°C , followed by 3% v/v H_2SO_4 [**3** (72%), **15a** (62%), **15b** (55%)]

thesis of 6-alkoxybenzocyclobutenones. These compounds are useful synthetic intermediates which can be readily functionalized to allow further synthetic elaboration. Our current focus is on the utilization of these benzocyclobutenones as intermediates in the preparation of 1,8-dioxygenated naphthalenes.

All reactions were performed in dry glassware under oxygen-free nitrogen. NMR spectra were recorded on either a Varian Unity 300 or Varian XL300 instrument. All chemical shifts are reported relative to residual CHCl_3 (7.26 ppm) for proton, and CDCl_3 (77.0 ppm) for carbon NMR spectra. IR spectra were recorded on a Shimadzu FTIR-8201PC spectrophotometer, either as KBr plates or films. Melting points were determined using an Electrothermal melting point apparatus and are uncorrected. HRMS were obtained on a Kratos MS80RFA instrument operating in EI mode at 70 eV and 4 kV accelerating potential. Flash chromatography was performed using Merck60 silica gel (230–400 mesh). THF was distilled over sodium/benzophenone immediately before use. Toluene, *tert*-butylamine, *N,N*-diisopropylethylamine, Et_3N , pyridine and CH_2Cl_2 were distilled from CaH_2 immediately before use. Phenols **6** and **11** were purchased from Aldrich Chemical Company. Petroleum ether used had bp $50\text{--}70^{\circ}\text{C}$. Note: All organic extracts were washed with brine and dried (Na_2SO_4).

ortho-Bromination of Phenols 6, 11 and 12; General Procedure

A solution of anhyd tert-butylamine (2.0 equiv) in anhyd toluene (1 M) was cooled to -30°C . Br_2 (1.0 equiv) was added dropwise and the resulting solution stirred at -30°C for 30 min. The turbid solution was cooled to -78°C and a solution of the appropriate phenol **6**, **11** or **12** (1.0 equiv) in anhyd CH_2Cl_2 (6 M) was added slowly. The reaction was allowed to warm to r.t. over a period of 5 h. After this time Et_2O and H_2O were added and the aqueous layer was acidified to pH 1 with 1 M aq HCl solution. The aqueous layer was extracted with a further portion of Et_2O and the combined organic extracts were washed in turn with 1 M aq HCl solution and satd $\text{Na}_2\text{S}_2\text{O}_3$ solution. After removing the solvent in vacuo, the residue was purified by bulb to bulb distillation.

2-Bromo-6-methoxyphenol (7)

Yield: 91%.⁹

2-Bromo-6-isopropoxyphenol (13)

Yield: 85%; bp $113^{\circ}\text{C}/11$ Torr.

$^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta = 7.07$ (dd, $J = 8.3, 1.5$ Hz, 1 H), 6.81 (dd, $J = 7.8, 1.5$ Hz, 1 H), 6.71 (dd, $J = 8.3, 8.3$ Hz, 1 H), 6.04 (br s, 1 H), 4.58 (m, 1 H), 1.37 (d, $J = 6.4$ Hz, 6 H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3): $\delta = 145.1, 143.9, 124.6, 120.3, 112.2, 108.0, 72.1, 21.8$.

IR (film): $\nu = 3508$ cm^{-1} .

HRMS: m/z Calcd for $\text{C}_9\text{H}_{11}^{79}\text{BrO}_2$ (M^+) 229.9943, found 229.9940.

2-Bromo-6-methoxymethoxyphenol (14)

Yield: 80%; bp $135^{\circ}\text{C}/11$ Torr.

$^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta = 7.16$ (m, 1 H), 7.05 (m, 1 H), 6.72 (t, $J = 8.3$ Hz, 1 H), 6.25 (br s, 1 H), 5.21 (s, 2 H), 3.52 (s, 1 H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3): $\delta = 144.9, 143.7, 126.2, 120.6, 114.6, 108.8, 95.7, 56.3$.

IR (film): $\nu = 3501$ cm^{-1} .

HRMS: m/z Calcd for $\text{C}_9\text{H}_9^{79}\text{BrO}_3$ (M^+) 231.9735, found 231.9733.

Triflates 5a-c; General Procedure

Triflic anhydride (1.5 equiv) was added dropwise via syringe to a solution of phenol **6**, **11** or **12** (1.0 equiv) in anhyd pyridine (1.8 mL) at 0°C . The reaction was stirred at this temperature for 5 min, then allowed to warm to r.t. overnight. The resulting solution was poured into H_2O and extracted with Et_2O (4×20 mL). The combined organic extracts were washed in turn with 10% HCl solution (v/v) and H_2O . The solvent was removed in vacuo to afford an oil, which was purified by bulb to bulb distillation.

2-Bromo-6-methoxyphenyl Trifluoromethanesulfonate (5a)

Yield: 98%; bp $95^{\circ}\text{C}/3$ Torr.

$^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta = 7.23$ (dd, $J = 8.3, 2.0$ Hz, 1 H), 7.18 (dd, $J = 8.3, 7.8$ Hz, 1 H), 6.98 (dd, $J = 7.8, 2.0$ Hz, 1 H), 3.92 (s, 3 H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3): $\delta = 152.6, 136.9, 129.3, 125.1, 118.6$ (q, $J_{\text{C-F}} = 321$ Hz), 116.5, 112.0, 56.3.

HRMS: m/z Calcd for $\text{C}_8\text{H}_6^{79}\text{BrF}_3\text{O}_4^{32}\text{S}$ (M^+) 333.9123, found 333.9122.

2-Bromo-6-isopropoxyphenyl Trifluoromethanesulfonate (5b)

Yield: 88%; bp $130^{\circ}\text{C}/11$ Torr.

$^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta = 7.11$ – 7.19 (m, 2 H), 6.95 (m, 1 H), 4.69 (m, 1 H), 1.39 (d, $J = 6.0$ Hz, 6 H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3): $\delta = 150.9, 137.5, 129.1, 124.5, 116.6, 118.5$ ($J_{\text{C-F}} = 321$ Hz), 113.5, 72.2, 21.3.

HRMS: m/z Calcd for $\text{C}_{10}\text{H}_{10}^{79}\text{BrF}_3^{32}\text{SO}_4$ (M^+) 361.9436, found 361.9433.

2-Bromo-6-methoxymethoxyphenyl Trifluoromethanesulfonate (5c)

Yield: 89%; bp $135^{\circ}\text{C}/11$ Torr.

$^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta = 7.24$ – 7.29 (m, 2 H), 7.15 (dd, $J = 8.3, 7.8$ Hz, 1 H), 5.25 (s, 2 H), 3.52 (s, 3 H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3): $\delta = 150.4, 137.3, 129.3, 126.2, 118.5$ ($J_{\text{C-F}} = 321$ Hz), 116.4, 115.2, 95.3, 56.6.

HRMS: m/z Calcd for $\text{C}_9\text{H}_8^{79}\text{BrF}_3^{32}\text{SO}_5$ (M^+) 363.9228, found 363.9226.

6-Alkoxybenzocyclobutenones 3, 15a,b; General Procedure

A stirred solution of triflate **5a–c** (1.0 equiv) and 1,1-diethoxyethylene¹⁴ (2.0 equiv) in anhyd THF (0.2 M) was cooled to -95°C . A solution of BuLi in hexanes (1.74 M, 2.0 equiv) was added dropwise via syringe and the resulting mixture stirred at -95°C for 30 min, and then allowed to warm to r.t. overnight. The resulting acetal was hydrolyzed in situ by the addition of aq H_2SO_4 solution (3% v/v, 0.83 M), followed by stirring at r.t. for 3 h. The resulting solution was poured into H_2O , and extracted with Et_2O (4×20 mL). The combined organic extracts were washed in turn with sat aq NaHCO_3 solution and H_2O . The solvent was removed in vacuo to give an oily residue, which was purified by flash chromatography on silica gel using the solvents indicated.

6-Methoxybenzocyclobutenone (3)

10% EtOAc/petroleum ether; white solid (72%); mp 34 – 35°C (Lit.¹¹ mp 32 – 33°C).

$^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta = 7.43$ (dd, $J = 8.3, 6.8$ Hz, 1 H), 7.03 (d, $J = 6.8$ Hz, 1 H), 6.80 (d, $J = 8.3$ Hz, 1 H), 4.12 (s, 3 H), 3.93 (s, 2 H).

6-Isopropoxybenzocyclobutenone (15a)

5% Et_2O /petroleum ether; white solid (62%); mp: 34 – 35°C .

$^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta = 7.41$ (dd, $J = 8.3, 7.3$ Hz, 1 H), 6.97 (d, $J = 7.3$ Hz, 1 H), 6.77 (d, $J = 8.3$ Hz, 1 H), 5.09 (m, 1 H), 3.89 (s, 2 H), 1.34 (d, $J = 5.9$ Hz, 6 H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3): $\delta = 184.7, 151.8, 150.3, 137.6, 131.7, 116.7, 114.2, 74.4, 50.7, 22.0$.

IR (KBr): $\nu = 1765$ cm^{-1} .

HRMS: m/z Calcd for $\text{C}_{11}\text{H}_{12}\text{O}_2$ (M^+) 176.0837, found 176.0837.

6-Methoxymethoxybenzocyclobutenone (15b)

5% Et_2O /petroleum ether; white solid (55%); mp 37 – 40°C .

$^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta = 7.46$ (dd, $J = 8.3, 7.3$ Hz, 1 H), 7.08 (d, $J = 7.3$ Hz, 1 H), 6.89 (d, $J = 8.3$ Hz, 1 H), 5.48 (s, 2 H), 3.92 (s, 2 H), 3.48 (s, 3 H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3): $\delta = 184.6, 150.5, 149.4, 137.7, 132.8, 116.4, 115.8, 96.2, 56.6, 51.1$.

IR (KBr): $\nu = 1761$ cm^{-1} .

HRMS: m/z Calcd for $\text{C}_{10}\text{H}_{10}\text{O}_3$ (M^+) 178.0630, found 178.0630.

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