doi:10.2533/chimia.2018.870 Chimia 72 (2018) 870–873

Synthesis of Oxygenated *ortho*-Methylbenzaldehydes *via* Aryne [2+2] Cycloaddition and Benzocyclobutenol Ring Opening

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Dedicated to the late Professor Teruaki Mukaiyama, a great teacher who guided me to Switzerland.

Abstract: Herein, a two-step procedure for the preparation of oxygenated *ortho*-methylbenzaldehyde derivatives, starting from commercially available bromoarenes, is described. The synthesis features the simultaneous and highly regioselective installation of both the methyl and the formyl group onto the benzene core *via* benzyne [2+2] cycloadditions with acetaldehyde lithium enolate to give the corresponding benzocyclobutenols in high yields. Bond-selective ring opening of the benzocyclobutenols under basic conditions in methanol delivers the title compounds.

Keywords: Aryne · Benzaldehydes · Benzocyclobutenols · Cycloaddition · Ring opening

Keisuke Suzuki was born in 1954 in Chigasaki, Japan. He obtained his Doctor of Science degree in 1983 at the University of Tokyo under the guidance of Prof. Teruaki Mukaiyama. He was appointed Research Associate to the late Prof. Gen-ichi Tsuchihashi at the Department of Chemistry, Keio University (1983), promoted to Lecturer (1987), Associate Professor (1989), and Professor (1994). In 1990 he enjoyed the ETH Zürich for one year as a Visiting Professor with Prof. Dieter Seebach. In 1996, he moved to Department of Chemistry at the Tokyo Institute of Technology where he has carried out extensive research in the field of synthetic organic chemistry with particular emphasis on the development of new strategies and tactics for total synthesis of complex natural products.

1. Introduction

In connection with our synthetic studies on the pyranonaphthoquinone-class antibiotics,[1] we were in need of an efficient method for the preparation of *ortho*-methylbenzaldehydes, particularly of highly oxygenated derivatives, as building blocks (Fig. 1).

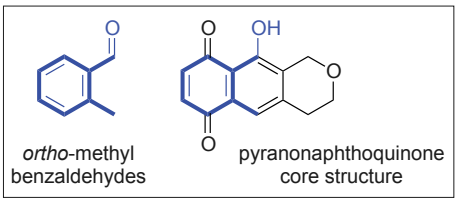
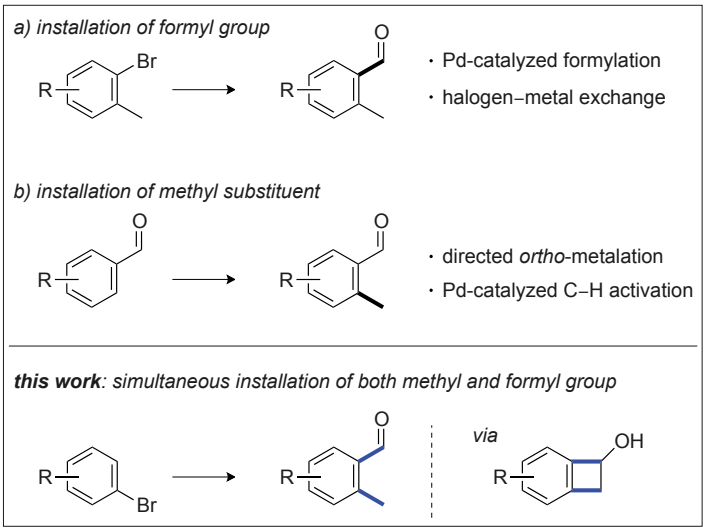


Fig. 1. Core structures of *ortho*-methylbenzaldehydes and pyranonaphthoquinones.

The pre-existing methodologies for preparing *ortho*-methylbenzaldehydes can be divided into two categories: a) installation of the formyl group and b) installation of the methyl substituent (Scheme 1).

The formylation of simple toluene derivatives is, naturally, not the method of choice due to regioselectivity issues. However, by employing pre-functionalized *ortho*-halotoluene derivatives, selective formylation can be achieved *via* halogen–metal exchange followed by trapping with a formylating agent,[2] or under palladium catalysis.[3]

On the contrary, the installation of the methyl substituent onto the *ortho*-position of benzaldehyde derivatives is the method of choice and commonly employed for simple arenes. Derivatization of the formyl group into an *ortho*-metalation director,[4] followed by lithiation and trapping with a methyl elec-



Scheme 1. Preparation of *ortho*-methylbenzaldehydes.

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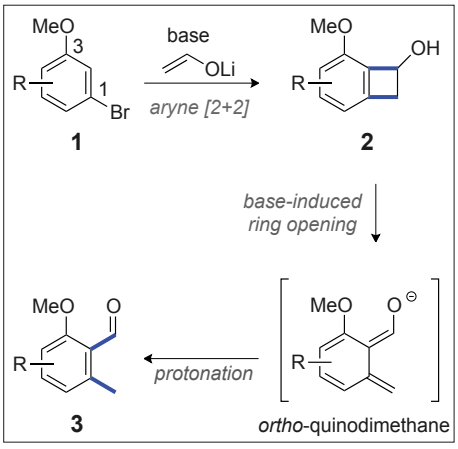
trophile allows access to the targeted structures. This can be achieved in a stepwise manner[5] or with a transient *ortho*-metalation directing group.[6] As the result of recent progress in transition metal catalyzed C–H activation,[7] the *ortho*-methylation of benzaldehydes can be accomplished under Pd-catalysis using a transient directing group.[8]

Herein, we wish to report our approach for the preparation of *ortho*-methylbenzaldehydes – with particular focus on highly oxygenated derivatives – starting from commercially available bromoarenes. The present methodology features the simultaneous installation of both the methyl and the formyl group onto the arene in a single step *via* aryne chemistry followed by selective ring opening of the benzocyclobutenols under basic conditions.

2. Working Hypothesis

For our purpose we planned to utilize 1-bromo-3-methoxyarenes **1** – cheap commercially available compounds – as starting materials (Scheme 2). Reaction of the benzynes,[9] generated from bromo-methoxyarenes **1** by deprotonation, yielded in the presence of acetaldehyde lithium enolate as the arynophile, the corresponding benzocyclobutenols **2** *via* thermal [2+2] cycloadditions. These compounds have found broad utility among the synthetic community as viable precursors for *ortho*-quinodimethanes[10] that can be generated *via* the thermally-allowed conrotatory ring opening. It has been known since 1988[11] that the ring opening of benzocyclobutenols is significantly facilitated – in fact, occurring even below room temperature – when quantitatively deprotonated to the alkoxide.[12] Despite Cavas and Muth' report on the clean formation of *ortho*-tolualdehyde from the parent benzocyclobutenol upon exposure to dilute NaOH solution,[13] the preparation of *ortho*-methyl-benzaldehydes **3** from the corresponding benzocyclobutenols has not been addressed.[14,15]



Scheme 2. Working hypothesis.

3. Results and Discussion

We started screening for optimal reaction conditions for the projected two-step synthesis of *ortho*-methylbenzaldehydes using bromoarene **1a** as the model substrate (Scheme 3). Concerning the first step, the cyclobutenol formation, we initially followed a literature-known procedure.[16] Upon deprotonation of **1a** with freshly prepared lithium 2,2,6,6-tetramethylpiperidide (LiTMP, 1.25 equiv.), the reaction of the generated benzyne with coexisting acetaldehyde lithium enolate (1.5 equiv.; conveniently prepared by fragmentation of THF with *n*BuLi at room temperature) gave benzocyclobutenol **2a** in 72% yield (entry 1).

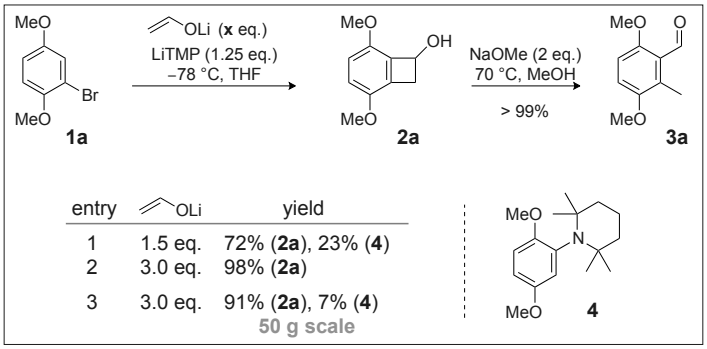
The major byproduct obtained was compound **4** as the result of competing addition of the protonated base to the aryne, despite the fact that 2,2,6,6-hexamethylpiperidine is known to be a rather poor aryne trap.[17] Hence, by increasing the amount of the enolate arynophile from 1.5 equiv. to 3 equiv. the desired benzocyclobutenol **2a** was obtained in 98% yield on a 100 mg test scale (entry 2). For the preparative aspect, we were pleased to find that slightly lower but still excellent yields were obtained under the same conditions on a 50 g scale (entry 3). Benzocyclobutenol **2a** was easily isolated in a total yield of 91% (80% by trituration and 11% by column chromatography of the concentrated filtrate). Only minor amounts of the base adduct **4** (7%) were obtained from the column chromatography.

For the base-induced ring opening, we chose sodium methoxide as a mild base and methanol as a protic solvent to immediately trap the *ortho*-quinodimethane by protonation.[18,19] Upon heating under gentle reflux of a methanol solution of **2a** (0.2 M) in the presence of sodium methoxide (2.0 equiv.), the desired *ortho*-methylbenzaldehyde **3a** was obtained almost quantitatively after evaporation of the solvent and simple workup.[20]

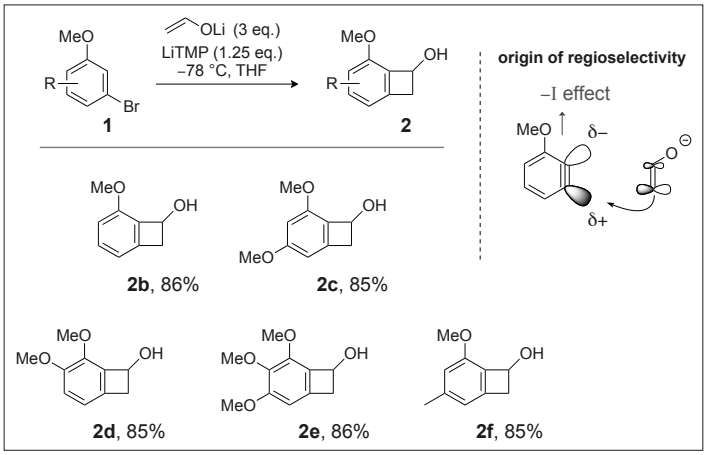
With the optimal conditions in hand we assayed the generality of this two-step protocol and prepared a small library of *ortho*-substituted benzaldehydes **3**.[21] Pleasingly, the commercially available bromoarenes **1b**–**1f** all reacted smoothly to give the respective benzocyclobutenols **2b**–**2f** in high yields (85–86%, Scheme 4).

All benzocyclobutenols were obtained as a single isomer as a result of the rigorous regioselectivity in the thermal [2+2] cycloaddition event[22] dictated by the inductive electron withdrawing effect (–I effect) of the proximal methoxy substituent.[23]

The base-induced ring opening proceeded smoothly for substrates **2b**, **2c** and **2f** and furnished the *ortho*-methylbenzaldehydes **3b**, **3c** and **3f** in nearly quantitative yields (Scheme 5) under the reaction conditions developed for substrate **2a** (*vide supra*). Thus, this protocol allows an easy and rapid access to oxygenated *ortho*-methyl-benzaldehydes **3**. Benzocyclobutenols **2d** and **2e**, bearing vicinal methoxy substituents at the benzene core, did not react as cleanly. Partial decomposition was



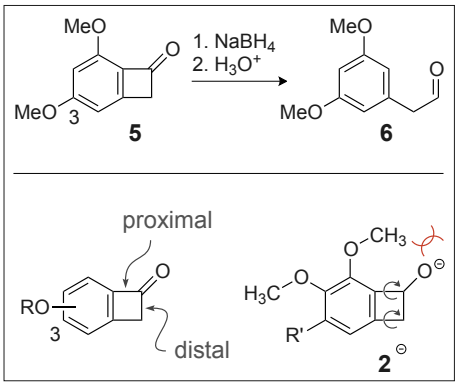
Scheme 3. Optimization of cyclobutenol formation and base-induced ring opening.



Scheme 4. Synthesis of benzocyclobutenols.

observed, and thus benzaldehydes **3d** and **3e** were obtained in moderate yield (80% and 75% respectively) after purification by preparative TLC, beside a plethora of polar byproducts.

The impact of the oxygen substitution pattern [especially at the C(3) position, *vide infra*] at the benzene core on the ring opening of benzocyclobutenones under basic conditions has been reported.[24] Distal vs. proximal bond scission strongly depends on the electronic properties of the benzene moiety, which influences the reaction pathway (Scheme 6). Furthermore, Olofson and co-workers reported the clean formation of arylacetaldehyde **6** from benzocyclobutenone **5** upon $NaBH_4$ reduction followed by aqueous acidic workup, whereas other derivatives of **5** gave the respective benzocyclobutenols.[25] The fact that substrate **2c**, cyclobutenol derivative of **5**, reacted cleanly (see Scheme 5) led us to the assumption, that, in the present case, the reason for the side reactions of benzocyclobutenols **2d** and **2e** might be of other nature and not dependent on the electronic properties of the benzene core. Rather the preferred conformation of the vicinal methoxy groups[26] in substrate **2d** (and **2e**) may cause deleterious steric repulsion with the alkoxide, and thus interfere with the outward motion of the conrotatory ring opening (as depicted for anions of **2d** [R' = H] and **2e** [R' = OMe]).[27]

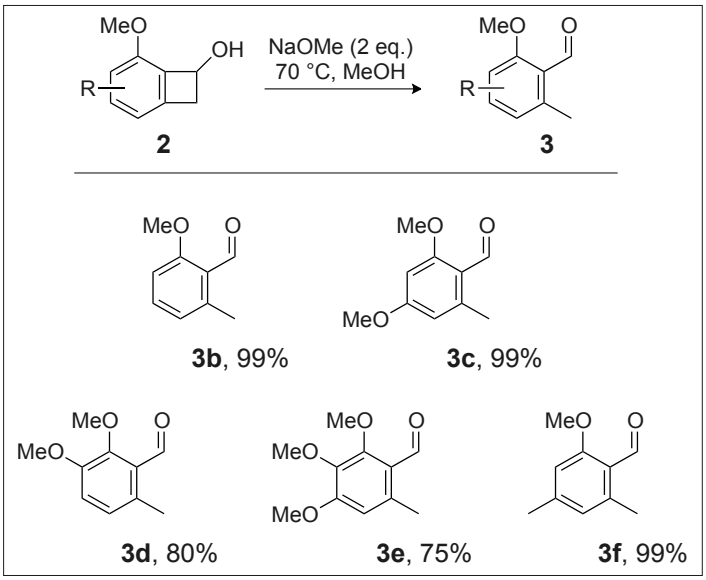


Scheme 6. Proximal bond scission of a benzocyclobutenone observed by Olofson and co-workers.[25] (top); rational for observed reactivity of substrates **2** with vicinal methoxy-substitution pattern (bottom).

4. Conclusion

In summary, we have developed an efficient synthetic route to access oxygenated *ortho*-methylbenzaldehydes *via* a two-step procedure, including: (1) a benzyne [2+2] cycloaddition, and (2) a base-induced benzocyclobutenol ring opening, starting from simple, commercially available bromoarenes. The present approach features the simultaneous installation of both the methyl and the formyl group – disguised as the cyclobutenol moiety – onto to the benzene ring with excellent regiocontrol.

Scheme 5. Ring opening of benzocyclobutenols to *ortho*-methylbenzaldehydes.



Acknowledgements

This work is supported by JSPS KAKENHI Grant JP16H06351. M. M. M. greatly acknowledges the German Research Foundation (DFG) for a postdoctoral fellowship (MA 7096/1).

Received: September 4, 2018

[1] For early contributions from our group, see: a) T. Matsumoto, H. Yamaguchi, M. Tanabe, Y. Yasui, K. Suzuki, *Tetrahedron Lett.* **2000**, *41*, 8393; b) K. Ohmori, K. Mori, Y. Ishikawa, H. Tsuruta, S. Kuwahara, N. Harada K. Suzuki, *Angew. Chem. Int. Ed.* **2004**, *43*, 3167; c) K. Ohmori, M. Tamiya, M. Kitamura, H. Kato, M. Oorui, K. Suzuki, *Angew. Chem. Int. Ed.* **2005**, *44*, 3871; d) K. Mori, Y. Tanaka, K. Ohmori, K. Suzuki, *Chem. Lett.* **2008**, *37*, 470; e) R. Masuo, K. Ohmori, L. Hintermann, S. Yoshida, K. Suzuki, *Angew. Chem. Int. Ed.* **2009**, *48*, 3462; f) A. Ben, D.-S. Hsu, T. Matsumoto, K. Suzuki, *Tetrahedron* **2011**, *67*, 6460; g) A. Takada, Y. Hashimoto, H. Takikawa, K. Hikita, K. Suzuki, *Angew. Chem. Int. Ed.* **2011**, *50*, 2297; h) Y. Yamashita, Y. Hirano, A. Takada, H. Takikawa, K. Suzuki, *Angew. Chem. Int. Ed.* **2013**, *52*, 6658. For our recent interests, see: i) Y. Ando, S. Hori, T. Fukazawa, K. Ohmori, K. Suzuki, *Angew. Chem. Int. Ed.* **2015**, *54*, 9650; j) T. Fukazawa, Y. Ando, K. Ohmori, T. Hayashi, K. Suzuki, *Org. Lett.* **2017**, *19*, 1470.

[2] F. Gallou, R. Haenggi, H. Hirt, W. Marterer, F. Schaefer, M. Seeger-Weibel, *Tetrahedron Lett.* **2008**, *49*, 5024.

[3] a) T. Ueda, H. Konishi, K. Manabe, *Angew. Chem. Int. Ed.* **2013**, *52*, 8611; b) K. Natte, A. Dumrath, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2014**, *53*, 10090; c) B. Yu, Z. Yang, Y. Zhao, L. Hao, H. Zhang, X. Gao, B. Han, Z. Liu, *Chem. Eur. J.* **2016**, *22*, 1097; d) G. Sun, X. Lv, Y. Zhang, M. Lei, L. Hu, *Org. Lett.* **2017**, *19*, 4235.

[4] V. Snieckus, *Chem. Rev.* **1990**, *90*, 879.

[5] a) L. A. Flippin, J. M. Muchowski, D. S. Carter, *J. Org. Chem.* **1993**, *58*, 2463; b) L. A. Flippin, J. Berger, J. S. Parnes, M. S. Gudiksen, *J. Org. Chem.* **1996**, *61*, 4812; c) K. Aksjonova, S. Belyakov, E. Liepinsh, A. Boman, T. Lundstedt, P. Lek, P. Trapencieris, *Synthesis* **2012**, *44*, 2200.

[6] D. L. Comins, J. D. Brown, *J. Org. Chem.* **1984**, *49*, 1078.

[7] X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094.

[8] X.-Y. Chen, E. J. Sorensen, *J. Am. Chem. Soc.* **2018**, *140*, 2789.

[9] For selected reviews on aryne chemistry, see: a) H. H. Wenk, M. Winkler, W. Sander, *Angew. Chem. Int. Ed.* **2003**, *42*, 502; b) H. Pellissier, M. Santelli, *Tetrahedron* **2003**, *59*, 701; c) P. M. Tadross, B. M. Stoltz, *Chem. Rev.* **2012**, *112*, 3550; d) S. Yoshida, T. Hosoya, *Chem. Lett.* **2015**, *44*, 1450.

[10] a) N. Martin, C. Seoane, M. Hanack, *Org. Prep. Proced. Int.* **1991**, *23*, 237; b) J. L. Segura, N. Martin, *Chem. Rev.* **1999**, *99*, 3199; c) A. K. Sadana, R. K. Saini, W. E. Billups, *Chem. Rev.* **2003**, *103*, 1539.

[11] W. Choy, H. Yang, *J. Org. Chem.* **1988**, *53*, 5796.

[12] N. Ishida, S. Sawano, Y. Masuda, M. Murakami, *J. Am. Chem. Soc.* **2012**, *134*, 17502.

[13] M. P. Cava, K. Muth, *J. Am. Chem. Soc.* **1960**, *82,* 652.

[14] Durst and co-workers used the base-induced ring opening and generation of the *ortho*-methylbenzaldehyde for structure confirmation of the respective benzocyclobutenol: K. L. Dhawan, B. D. Gowland, T. Durst, *J. Org. Chem.* **1980**, *45*, 922.

[15] Kametani and co-workers observed the quantitative formation of an *ortho*-methylbenzaldehyde in an unsuccessful intermolecular Diels-Alder cycloaddition attempt of a benzocyclobutenol: T. Kametani, T. Honda, H. Matsumoto, K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1* **1981**, 1383.

[16] P.-H. Chen, N. A. Savage, G. Dong, *Tetrahedron* **2014**, *70,* 4135.

[17] R. A. Olofson, C. M. Dougherty, *J. Am. Chem. Soc.* **1973**, *95,* 582.

[18] The dimerization of benzocyclobutenols under basic conditions in non-protic solvents has been observed: D. Craig, M. J. Robson, S. J. Shaw, *Synlett* **1998**, *12,* 1381.

[19] The findings in ref. [18] were extended to cross hetero Diels-Alder reactions with benzaldehydes as dienophiles for *ortho*-quinodimethanes: S. J. Shaw, *Synth. Commun.* **2007**, *37,* 4183.

[20] In a control experiment, no reaction was observed upon heating of a methanol solution of **2b** at 70 °C for 3 h in the absence of a base.

[21] This compound class is of special interest to the photochemical community due to the enoliza-

tion upon irradiation: a) N. C. Yang, C. Rivas, *J. Am. Chem. Soc.* **1961**, *83*, 2213; b) B. Gosch, C. N. Orlebar, E. Herdtweck, W. Massa, T. Bach, *Angew. Chem. Int. Ed.* **2003**, *42*, 3693; c) Y. Masuda, N. Ishida, M. Murakami, *J. Am. Chem. Soc.* **2015**, *137*, 14063; d) B. Yang, K. Lin, Y. Shi, S. Gao, *Nat. Commun.* **2017**, *8*, 622. For a review on photoenolization, see: P. G. Sammes, *Tetrahedron* **1976**, *32*, 405.

[22] a) D. M. Hayes, R. Hoffmann, *J. Phys. Chem.* **1972**, *76*, 656; b) S. Inagaki, K. Fukui, *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2240.

[23] a) R. V. Stevens, G. S. Bisacchi, *J. Org. Chem.* **1982**, *47*, 2393; b) T. Hosoya, T. Hasegawa, Y. Kuriyama, T. Matsumoto, K. Suzuki, *Synlett* **1995**, *2,* 177; c) J. M. Medina, J. L. Mackey, N. K. Garg, K. N. Houk, *J. Am. Chem Soc.* **2014**, *136*, 15789.

[24] a) G. M. Iskander, F. Stansfield, *J. Chem. Soc.* **1965**, 1390; b) J. O. Amupitan, F. Stansfield, *J. Chem. Soc., Perkin Trans. 1* **1974**, 1949.

[25] J. J. Fitzgerald, N. E. Drysdale, R. A. Olofson, *J. Org. Chem.* **1992**, *57*, 7122.

[26] M. Gerzain, G. W. Buchanan, A. B. Driega, G. A. Facey, G. Enright, R. A. Kirby, *J. Chem. Soc., Perkin Trans. 2,* **1996**, 2687.

[27] Miller and co-workers observed a strong influence of the substitution pattern on the reaction time in a thermal cyclobutenol ring opening under neutral conditions: J. E. Almlöf, M. W. Feyereisen, T. H. Jozefiak, L. L. Miller, *J. Am. Chem. Soc.* **1990**, *112*, 1206.