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Reinvestigation relative to the regioselectivity of the aryne cycloaddition. Synthesis of the tricyclo[6.2.0.0^{2,5}]-1,5,7-triene-3,10-dione

Philippe Maurin, Malika Ibrahim-Ouali* and Maurice Santelli*

Laboratoire de Synthèse Organique, UMR no 6009, Centre de St-Jérôme, Av. Esc. Normandie-Niemen, 13397 Marseille Cedex 20, France

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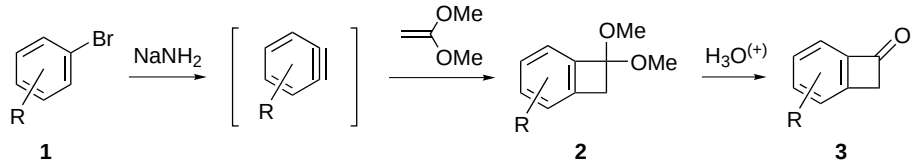
Abstract—A rapid and total synthesis of a tricyclo[6.2.0.0]deca-1,5,7-triene-3,10-dione **7b** is described. Its synthesis involves the [2+2] cycloaddition of a benzyne to 2-methylene-1,3-dioxepane followed by hydrolysis to the corresponding ketone. This reaction is totally regioselective and the real structure of the molecule is given thanks notably to the X-ray crystal structure of the intermediate benzo-bis-cyclobutene. © 2001 Elsevier Science Ltd. All rights reserved.

Benzocyclobutenes have become valuable intermediates in organic synthesis.[1] Until now, a wide variety of steroid analogs has been efficiently synthesized by our group using them as starting materials.[2]

Stevens and Bisacchi have found a simple and straightforward method for the synthesis of substituted benzocyclobutenones.[3] They have shown that 1,1-dimethoxyethylene participated in a [2+2] reaction with benzynes generated by the $NaNH_2$-induced dehydrobromination of bromobenzenes **1**, and after hydrolysis of the intermediate benzocyclobutenone ketals **2**, substituted benzocyclobutenones **3** are obtained (Scheme 1). Such cycloadditions involving an unsymmetric olefin and benzyne partners have received very little attention.[4] The regioselectivity of the [2+2] cycloadditions can be attributed to a combination of steric and electronic effects.[3] It is known that the orientation of attacking nucleophiles is influenced by the steric environment near the benzyne bond and substituent-induced polarization of the benzyne bond.[5] In most cases, only one regioisomer is produced.

Another interesting point, which has motivated our study, is the fact that the use of 1,1-dimethoxyethylene is not very attractive as its preparation is not convenient. This alkoxyethylene is made from bromoacetaldehyde dimethylacetal by the method of Corey et al.[6] Thus, we attempted a reaction using 2-methylene-1,3-dioxepane,[†] which is commercially available, in place of the less accessible 1,1-dimethoxyethylene.

We simply repeated the Stevens and Bisacchi chemistry. Under these conditions, with 1 equiv. of $NaNH_2$, the benzyne generation and 2-methylene-1,3-dioxepane [2+2] reaction proceeded smoothly. Reaction was complete within 6–12 h and led to a mixture of two ketal regioisomers **4a** and **4b** in an 8/2 ratio. Hydrolysis of



Scheme 1.

Keywords: benzyne; benzocyclobutene; [2+2] cycloaddition; 2-methylene-1,3-dioxepane.

* Corresponding authors. Fax: (33) 4 91 98 38 65; e-mail: m.santelli@lso.u-3mrs.fr

† Produced by Wacker Chemie GmbH, available from FLUKA, product number: 10885.

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each ketal to the corresponding benzocyclobutenone **5a** and **5b** proceeded in essentially quantitative yield at room temperature. It is found advantageous to effect separation after hydrolysis to the corresponding ketones. Much to our surprise, these cycloadducts appear to be new compounds (Scheme 2).

Treatment of 1,4-dibromobenzene with 3 equiv. of $NaNH_2$ in the presence of 2-methylene-1,3-dioxepane could lead to the formation of several regioisomers. Nevertheless, we observed the formation of only one compound in 20% yield for the two steps. Moreover, due to symmetry factors, NMR experiments made it impossible to determine which of **6a**–**c**, and after hydrolysis which of the corresponding ketones **7a**–**c**, was the good structure (Scheme 3).

We undertook a recrystallization and fortunately, we obtained exploitable crystals for the diketal **6**. The structure **6a** was confirmed unambiguously by a single crystal X-ray analysis (Fig. 1).[7]

Surprisingly, this corresponded to the most hindered regioisomer **6a**.[8] Indeed, we were really surprised because Liebeskind and co-workers previously reported that the reaction, conducted in the same conditions by using a less hindered alkoxyethylene, 1,1-dimethoxyethylene, produced the 'benzo-bis-cyclobutenone' **7b** in similar yield after acid-catalyzed hydrolysis (Scheme 4).[9] In fact, by making a comparison of the melting points and the NMR values reported

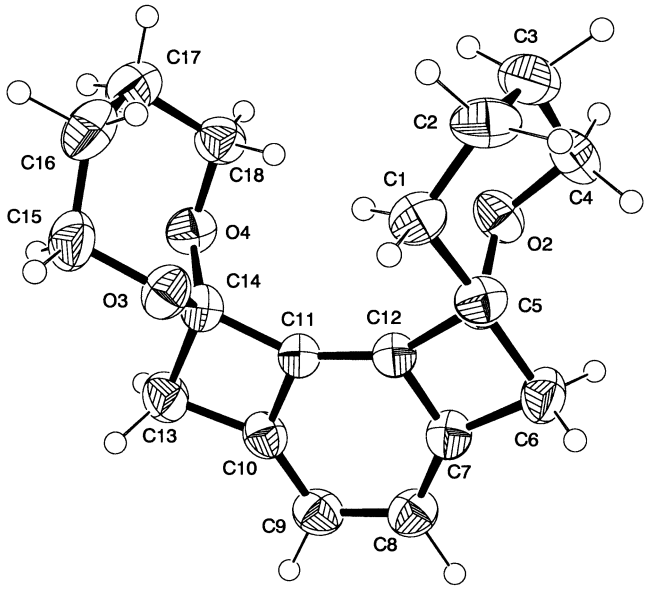
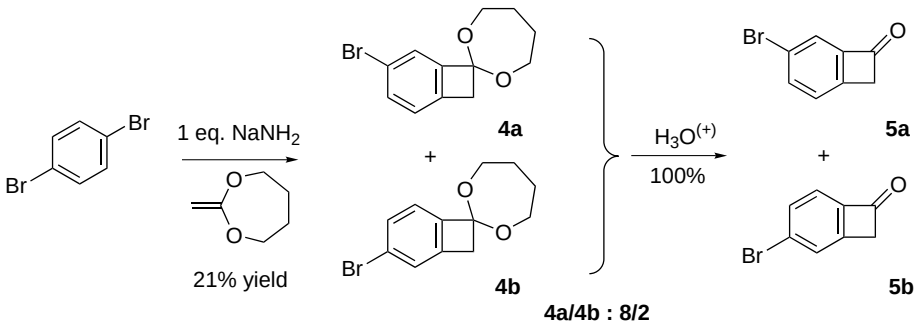
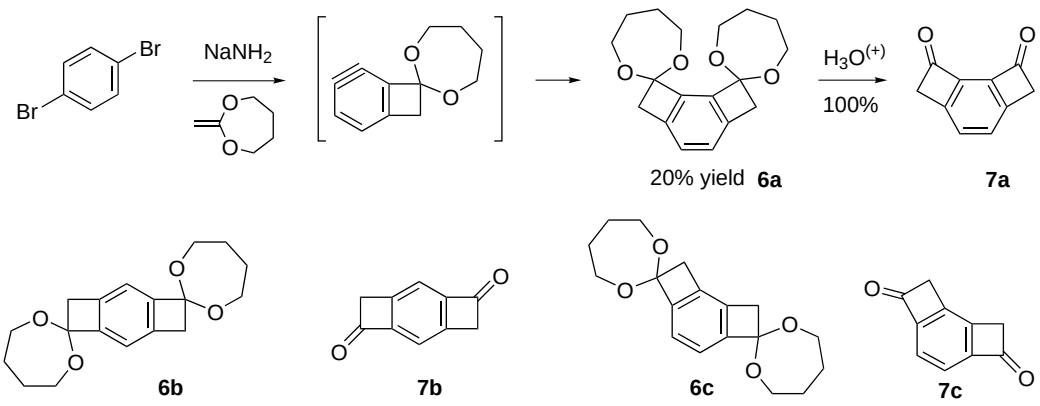


Figure 1. ORTEP drawing of the crystal structure of didioxepane **6a**.

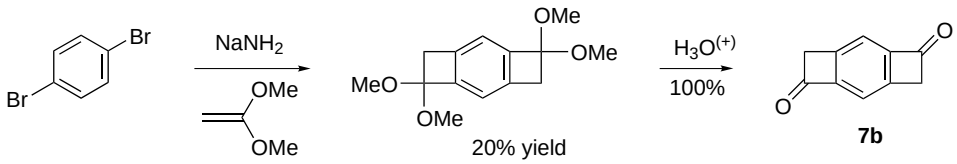
in literature for compound **7b** with our product, we found that they were identical. So, we could say without any doubt, as we had the crystal X-ray analysis of the intermediate **6a**, that they had isolated the regioisomer **7a** and certainly not **7b**. Interesting was to note the remarkable regioselectivity of the reaction. Otherwise, it appears now simpler to prepare the molecule **7a** by



Scheme 2.



Scheme 3.



Scheme 4.

using our approach insofar as 2-methylene-1,3-dioxepane is commercially available.

Conclusion: In this paper, we made a correction of a result previously reported relative to the synthesis of a 'benzo-bis-cyclobutenone' prepared from hydrolysis of the 'benzo-bis-cyclobutenone' ketal, which is generated from 1,4-dibromobenzene and $NaNH_2$ reacted in the presence of 2-methylene-1,3-dioxepane. The structure of the intermediate ketal is confirmed unambiguously by X-ray crystal analysis. The use of this 'novel' molecule for the synthesis of bissteroidal compounds based on the strategy developed by our group is under progress.

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8. Spectral data of **6a**: mp 137°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.75 (m, 4H); 3.37 (s, 2H); 3.84–4.03 (m, 8H); 7.11 (s, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 29.4; 47.2; 64.6; 105.2; 139.0; 140.6. Spectral data of **7a**: mp 183°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.02 (m, 4H); 7.68 (s, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 52.7; 129.0; 140.5; 152.9; 184.5. ^{1}H NMR (acetone-d_6, 300 MHz): δ 4.05 (m, 4H); 7.86 (s, 2H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 53; 130; 141; 154; 185.
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