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Formation of benzocyclobutenes from substituted oxocycloocta-2,8-diene-1,2-dicarboxylates

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Dedicated to the memory of Professor Alan Roy Katritzky

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ABSTRACT

Substituted benzocyclobutenes were isolated from the reaction of substituted oxocycloocta-2,8-diene-1,2-dicarboxylates with DMAD which were themselves formed by the microwave assisted [2+2] cycloaddition of cyclic enaminones to dimethyl acetylenedicarboxylate. The high pressure hydrogenation of (1*E*,2*Z*)-dimethyl 3-(dimethylamino)-7-oxocycloocta-2,8-diene-1,2-dicarboxylate gave oxabicyclo[3.3.1]non-3-ene-2,3-dicarboxylates, while use of low pressure hydrogenation resulted in only the carbonyl group being reduced to give the corresponding hydroxyl derivative which was proposed as an intermediate of the oxabicyclo[3.3.1]nonanes formed using high pressure hydrogenation.

Introduction

Bicyclo[4.2.0]octa-1,3,5-trienes (benzocyclobutenes) are an important structural motif in active pharmaceutical ingredients and valuable building blocks in organic synthesis, especially for the synthesis of polycyclic natural products, steroids, alkaloids, anthracyclines, fullerenes, and cyclophanes.[1]

Several methods for the synthesis of benzocyclobutenes have been described in the literature. They have been prepared from cyclohexane derivatives,[2] by 1,4-eliminations,[3] Parham cyclization,[4] photochemical approaches,[5] and extrusion reactions,[6] Diels–Alder cycloadditions,[7] [2+2][8] and [2+2+2] cycloadditions,[9] ring expansion methods,[10] and from allene intermediates.[11] Several review articles have been published in the last few decades.[1,12] Despite their high synthetic value, very few general and chemoselective methods currently exist for the preparation of functionalized benzocyclobutenes, which seriously limits their availability as synthetic intermediates.[8b,c,13] Recently, the novel palladium-catalyzed C–H activation of *gem*-dialkyl groups on bromo- and iodobenzenes giving olefins or benzocyclobutenes[14] and a general method for the preparation of substituted benzocyclobutenes by palladium-catalyzed C–H activation of benzylic methyl groups have been published.[15]

The microwave-assisted [2+2] cycloaddition reaction of 2-amino-3-dimethylaminopropenoates with acetylenecarboxylates has been shown to furnish highly functionalized 1-amino-4-(dimethylamino)buta-1,3-dienes that are suitable for the preparation of various heterocyclic systems.[16] Recently, we reported the thermal reactions of cyclic enaminones, derived from the reaction of cyclic five- and six-membered 1,3-diones and dimethyl acetylenedicarboxylate (DMAD), which gave a mixture of ring-expanded products as a result of a [2+2] cycloaddition as well as Michael adducts.[17] In several cases, the reaction of the cyclic enaminones with DMAD gave other products, such as the known tetramer of dimethyl acetylenedicarboxylate.[18]

Results and discussion

Recently we reported the thermal [2+2] cycloaddition of cyclic enaminones with electron-poor acetylenes, affording ring-enlarged products. For example, the cycloaddition of enaminones **2**, derived from cyclohexa-1,3-diones **1**, with DMAD afforded cycloocta-1,3-dienes **3** and Michael adducts **4** as the main products. Trace amounts of side products, which were not isolated, were also formed. Upon prolonged reaction times, especially in the case of less reactive enaminones, the amounts of these side-products were

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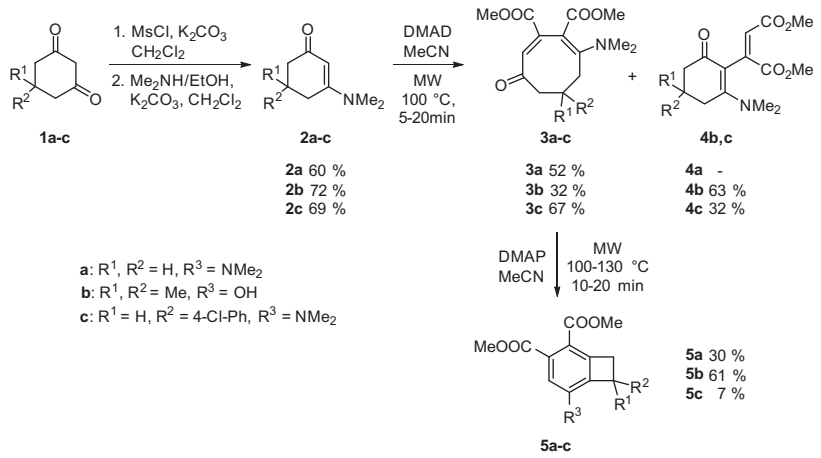
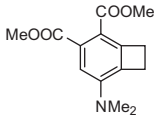
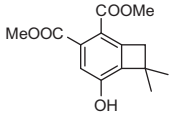
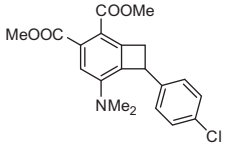
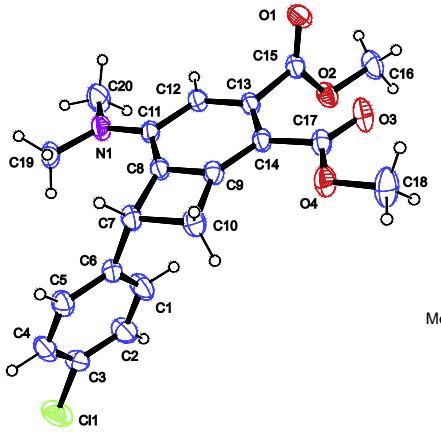


Scheme 1. Microwave assisted formation of benzocyclobutenes **5a–c**.

Table 1
DMAP, MeCN, MW, 100–130 °C, 10–20 min

		t (min)	*T* (°C)	Yield (%)
5a		20	100	30
5b		10	130	61
5c		20	120	7



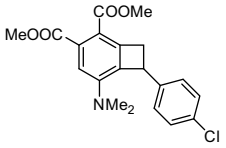
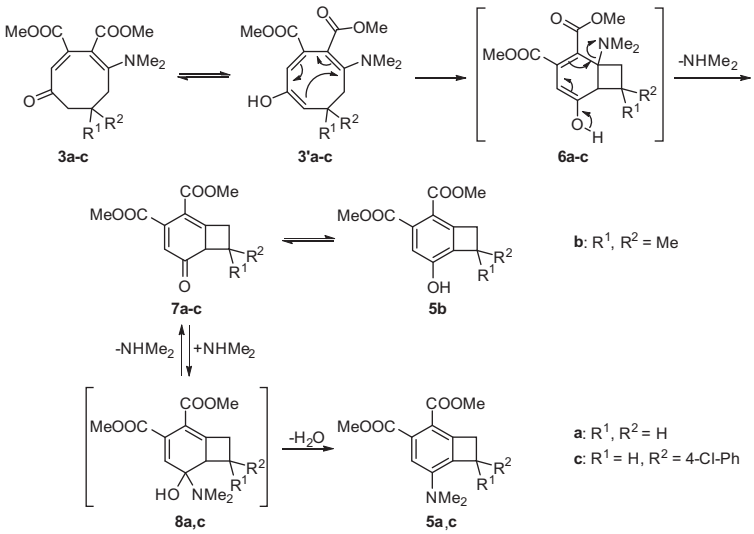


Figure 1. ORTEP view of compound **5c**.

increased. For example, in the case of enaminone **2c**, longer reaction times were required and besides the main product, a considerable amount of **5c** was formed. This was postulated to have originated from **3c**, since the molecular formula indicated that only a molecule of water had been eliminated from the cycloadduct **3c** (Scheme 1).

Having made this connection, we elected to heat cycloadducts **3a–c** in acetonitrile in the presence of 4-dimethylaminopyridine under microwave irradiation (300 W). The benzocyclobutenes



Scheme 2. Proposed mechanism for the formation of benzocyclobutenes **5a–c**.