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SINGLE ELECTRON TRANSFER IN MICHAEL INDUCED RING CLOSURE REACTIONS†

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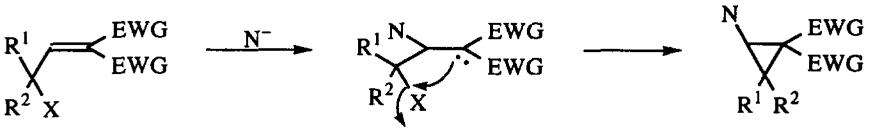
Abstract: Substituted cyclopropyl ether **3** is readily available from γ-bromoalkylidene malonate **2** via a Michael Induced Ring Closure (MIRC) reaction with sodium methoxide. Single Electron Transfer mechanism is suggested for the key cyclization step to account for the observed high reactivity of a tertiary halide, phosphonium salt and nitro compound.

In an ancillary study it was necessary to prepare an electrophilic cyclopropyl ether **3**. Of the methods available the most attractive seemed to be the Michael Initiated Ring Closure (MIRC) reaction,[1] which has frequently been used to prepare sterically crowded cyclopropanes. The generalized scheme for the MIRC reaction is presented below (**Scheme 1**).

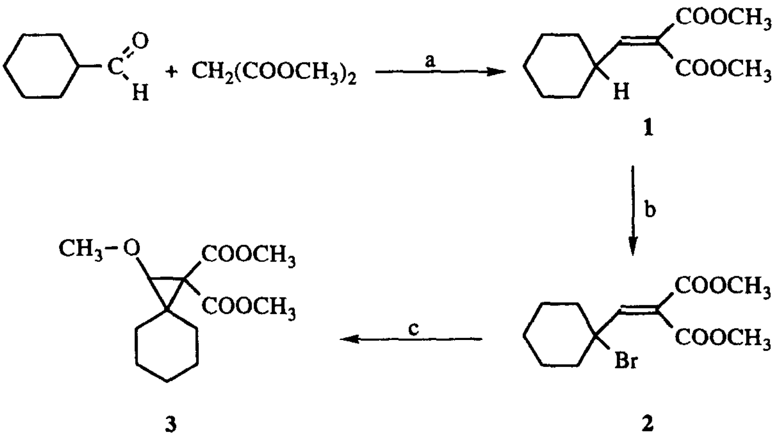
Scheme 1



As the name of the reaction indicates the process is started by a Michael addition of a nucleophile to an olefin which is doubly activated by electron withdrawing groups (EWG) in the α-position and bearing a leaving group (X) in the γ-position. The intermediate carbanion produced by addition of the nucleophile is thought to displace the leaving group to give the desired cyclopropane (**Scheme 2**).

†This paper is dedicated to the memory of Professor Nathan Kornblum.

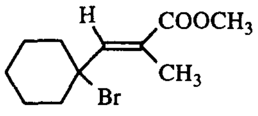
Scheme 2



a) piperidinium acetate, benzene, 80°C b) NBS, CCl_4, benzoyl peroxide c) MeONa/MeOH, r.t.

Cyclohexanecarboxaldehyde was condensed with dimethyl malonate using the standard Knoevenagel procedure[2] (piperidinium acetate, benzene, azeotropic removal of water) to yield **1** in 80% yield and the condensation product was brominated in the allylic position with N-bromosuccinimide in the presence of a catalytic amount of benzoyl peroxide. The crude bromide **2** (pure by NMR) was treated with one equivalent of sodium methoxide in methanol, at ambient temperature over-night, to yield **3** in 79% yield. Noteworthy is the yield and the ease with which this reaction proceeds even though a tertiary alkyl halide (which do not undergo S_N2 type reactions) is used. Moreover, no by-products could be detected by NMR.

It has been suggested that the mechanism of MIRC reactions of this type involves a nucleophilic displacement of the halide by the intermediate carbanion regardless of whether a primary, secondary or tertiary[3, 4] halide is used. Although an S_N2 displacement may be operating with primary[5] and possibly secondary halides it is highly unlikely for tertiary halides. Analysis of the literature leads to several important observations. Primary, secondary and tertiary systems can be used with apparently no significant differences among them, except for the fact that in the case of primary and secondary systems cyclopropanes are usually difficult to isolate due to the facile ring opening reactions.[1] A wide variety of nucleophiles can be used to initiate the reaction.[1] The reaction shows second order kinetics (first order in nucleophile and first order in the substrate).[3] Michael addition is the rate determining step. In most cases it is necessary to use doubly activated (2 EWG) substrates.[6] When only one group is present the reaction usually fails due to an unfavourable Michael equilibrium.[1] Indeed, two other systems which we have prepared (**4** and **5**) failed to give the corresponding cyclopropanes upon reaction with sodium methoxide.[7] In the case of the **4** the significantly lower stability of the intermediate carbanion prohibits the reaction, whereas the carbanion generated from **5** is too stable[8] and therefore completely unreactive.



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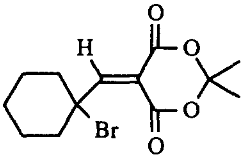

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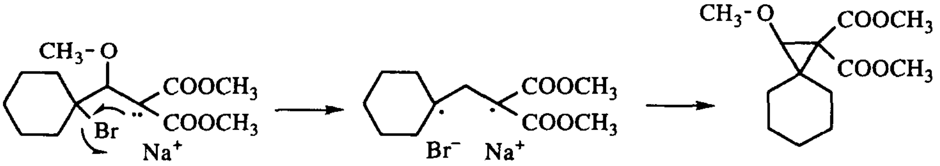
Instead, we would like to suggest an alternative explanation. In our view the substitution of tertiary bromide, in our and similar systems proceeds via a Single Electron Transfer mechanism (**Scheme 3**).

Scheme 3



According to this mechanism one electron is transfered from the malonate anion to C-Br antibonding orbital to produce a tertiary radical and bromide anion via anion radical transition state.[9] The 1,3-diradical formed then recombines quickly to give the desired cyclopropane. This mechanism finds wide support in the literature. Substitutions of tertiary halides by SET mechanism are well known.[10] Moreover, if in place of a tertiary halogen as a leaving group in the γ-position there is a triphenylphosphonium[11] or a nitro[12] group attached to the γ-tertiary carbon one still observes ring closure! These observations would be consistent with an SET[13] substitution mechanism.

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