S,S'-Diethyl Dithiomalonate as Ethanol Carbanion Equivalent in Annelation Reactions

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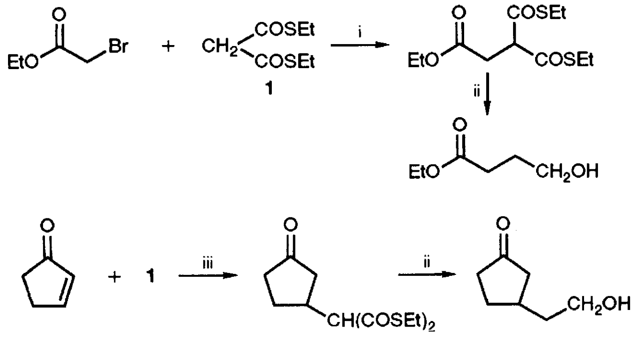
S,S'-Diethyl dithiomalonate **1** undergoes concomitant alkylation reaction and Michael addition with ω-iodo-α,β-unsaturated ketones; the dithiomalonate group present in the cyclization products can be easily reduced by Raney nickel to the ethanol level.

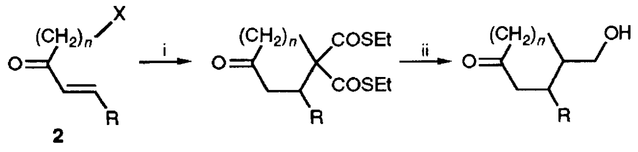
S,S'-Diethyl dithiomalonate **1** has been shown previously in these laboratories to undergo facile alkylation with a variety of alkyl halides[1] and Michael addition with α,β-unsaturated carbonyl compounds of structural diversity.[2] Interestingly, when the products were subjected to treatment with Raney nickel, the dithioester group was invariably reduced to the ethanol level[1,2] as exemplified in Scheme 1.

An extrapolation of these results suggested an interesting and potentially useful application of dithiomalonate **1** as a convenient source of ethanol carbanion to facilitate the synthesis of functionalized cyclic compounds. As shown in Scheme 2, using a combination of alkylation and Michael reactions, **1** could serve as a masked ethanol carbanion in annelation reaction with an α,β-unsaturated ketone **2** possessing a suitable leaving group. This new annelation process has now been recognized experimentally and the preliminary results are described in this communication.

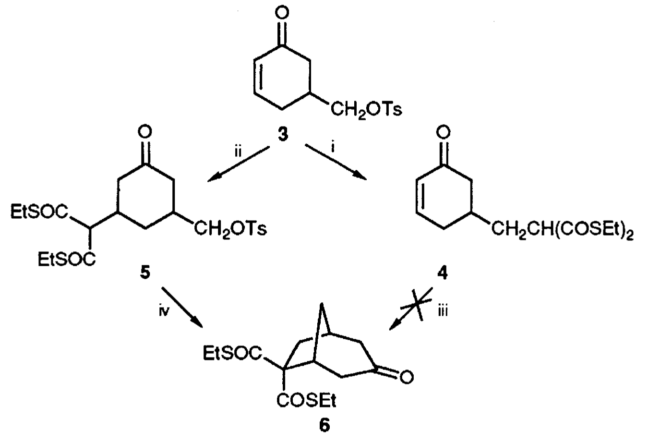
In early experiments, cyclohexenone **3**[3] was treated with dithiomalonate **1** in 1,2-dimethoxyethane (DME) in the presence of sodium hydride or 1,4-diazabicyclo[2.2.2]octane (DABCO) which were successfully used previously to effect alkylation and Michael addition, respectively.[1,2] Neither of these bases was found to be effective for the desired cyclization. With sodium hydride, only the substitution product **4** was obtained, while DABCO induced only Michael addition giving adduct **5** as the exclusive product. Compound **4**



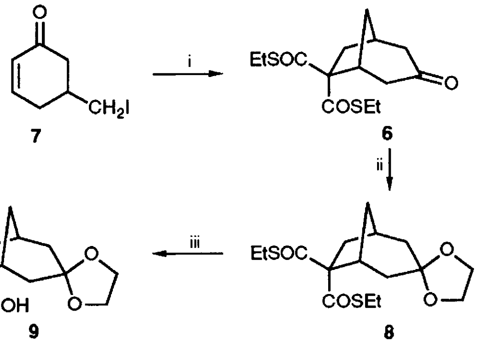
Scheme 1 *Reagents*: i, NaH, DME; ii, Raney-Ni, benzene; iii, DABCO, DME



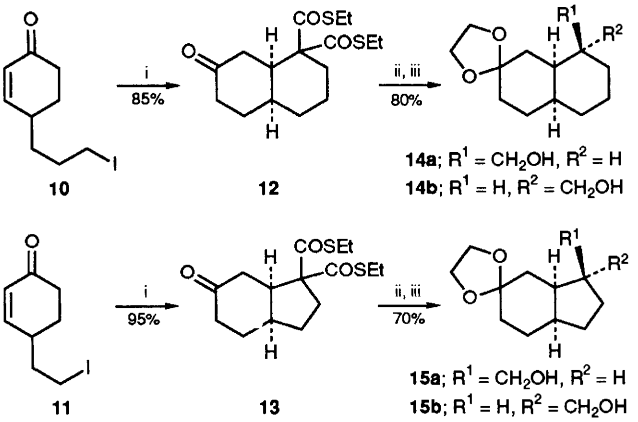
Scheme 2 *Reagents*: i, **1**, base; ii, Raney-Ni



Scheme 3 *Reagents*: i, **1**, NaH, THF; ii, **1**, DABCO, DME; iii, DABCO, DME; iv, NaH, THF, NaI (0.2 equiv.)



Scheme 4 *Reagents and conditions*: i, **1**, K_2CO_3, acetone, 65%; ii, 2-ethyl-2-methyl-1,3-dioxolane, *p*-TsOH, benzene, reflux, 100%; iii, Raney-Ni, benzene, 70%



Scheme 5 *Reagents and conditions*: i, **1**, K_2CO_3, acetone; ii, 2-ethyl-2-methyl-1,3-dioxolane, *p*-TsOH, benzene, reflux; iii, Raney-Ni, benzene

could not be further cyclized with DABCO in DME. On the other hand, when Michael adduct **5** was treated with sodium hydride in tetrahydrofuran (THF) in the presence of a catalytic amount (0.2 equiv.) of sodium iodide, the desired cyclization product **6** was formed, albeit in low yield (Scheme 3).

In order to improve the yield as well as to effect the annelation directly, other reaction conditions were explored. Among the bases examined, potassium carbonate was found to be superior. When iodoenone **7**† was treated with **1** (1.5 equiv.) in acetone at room temperature in the presence of potassium carbonate (2.5 equiv.) the desired cyclization product **6** was formed in 65% yield after 43 h. Initial attempts to convert the dithioester moiety of compound **6** to the ethanol unit by treatment with acid-washed W-2 Raney nickel[2] gave unsatisfactory yields (<25%) of the desired product. A considerable improvement was realized after the ketone carbonyl was protected in the form of a ketal (**6**→**8**) *via* a transketalization process using an excess of 2-ethyl-2-methyl-1,3-dioxolane and *p*-toluenesulphonic acid (0.1 equiv.) in refluxing benzene. Treatment of ketal **8** with Raney nickel gave an inseparable mixture of two epimeric alcohols **9** in 3:1 ratio and a total yield of 70% (Scheme 4). Thus, the use of dithiomalonate **1** as a latent ethanol carbanion in annelation reaction has been experimentally proven to be feasible.

To examine the generality of the above annelation procedure, iodoenones **10**‡ and **11**§ were individually treated with dithiomalonate **1** and potassium carbonate at room temperature. The corresponding annelation products **12** and **13** were formed in good yields. Subsequent ketalization of **12** followed by reduction of the resulting ketal with Raney-Ni afforded the desired alcohols **14a** and **14b** (1:1, 80% overall yield) which were readily separated by flash chromatography on silica gel (10% ethyl acetate, 85% hexane and 5% ethanol). Similarly, keto dithiolester **13** was transformed into ketal alcohols **15a** and **15b** (3:1, 70% overall yield) by ketalization and reduction. These results are summarized in Scheme 5.

As demonstrated above, dithiomalonate **1** can be applied effectively as a masked ethanol carbanion in annelation reactions. Its reaction with appropriate iodoenones allows cyclization with overall incorporation of an ethanol unit to give bridged and fused bicyclic compounds possessing functionalities suitable for further transformations.

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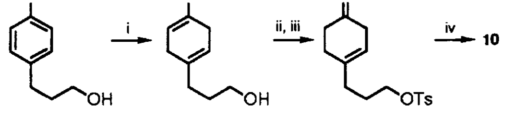
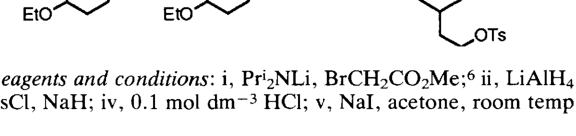
† Compound **7** was prepared from **3** by substitution with sodium iodide under Finkelstein reaction conditions.[4]

‡ Iodo enone **10** was prepared from 3-(4-methoxyphenyl)propan-1-ol according to the following scheme:



Reagents and conditions: i, Na, NH_3(l);[5] ii, TsCl, pyridine; iii, 0.1 mol dm^{-3} HCl; iv, NaI, acetone, reflux

§ The following scheme was used to prepare iodo enone **11**.



Reagents and conditions: i, Pr^i_2NLi, $BrCH_2CO_2Me$;[6] ii, $LiAlH_4$;[7] iii, TsCl, NaH; iv, 0.1 mol dm^{-3} HCl; v, NaI, acetone, room temp.