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The Iodination and Iodocyclisation of Some Alkenylmalonates[1]

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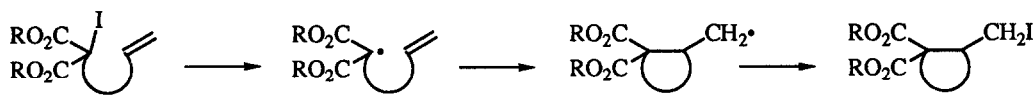
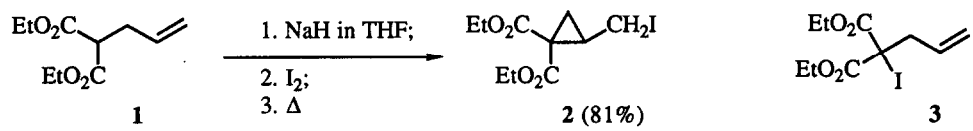
Abstract: Consecutive treatment of various allylmalonates with sodium hydride and iodine in THF affords cyclopropane derivatives via intermediate formation of iodomalonates; iodocyclisation under similar conditions affords cyclopentane and cyclohexane derivatives from appropriate alkenylmalonates

The development, principally by Curran and his co-workers,[2] of iodine atom transfer annulations has made an important addition to synthetic radical chemistry. Iodomalonates have proven to be particularly useful iodine atom donors and their application to inter- and intra-molecular carbon-carbon bond forming reactions has been thoroughly investigated.[3,4] The general principle is illustrated below for an intramolecular reaction wherein radical formation and cyclisation is followed by atom transfer. It has the advantage over standard tin hydride mediated reactions that only a catalytic quantity of tin compound is required, an asset for product purification, and it is additionally attractive to the synthetic chemist because the iodine present in the iodomalonate is preserved in the product, allowing further elaboration if desired; the halide or its equivalent is frequently reduced in other approaches. Like other radical cyclisations this approach is most effective for five and six membered rings. There appears to have been no report of its use for the formation of three membered rings.



Herein we wish to describe an approach which is both an alternative and a complement to Curran's radical atom transfer procedure and which can be applied to the parent malonates without their prior conversion to iodomalonates. Thus, when allylmalonate **1** was treated sequentially with sodium hydride and then with iodine at reflux in THF, the cyclopropylcarbinyl iodide **2** was isolated in a yield of 81%.[5]

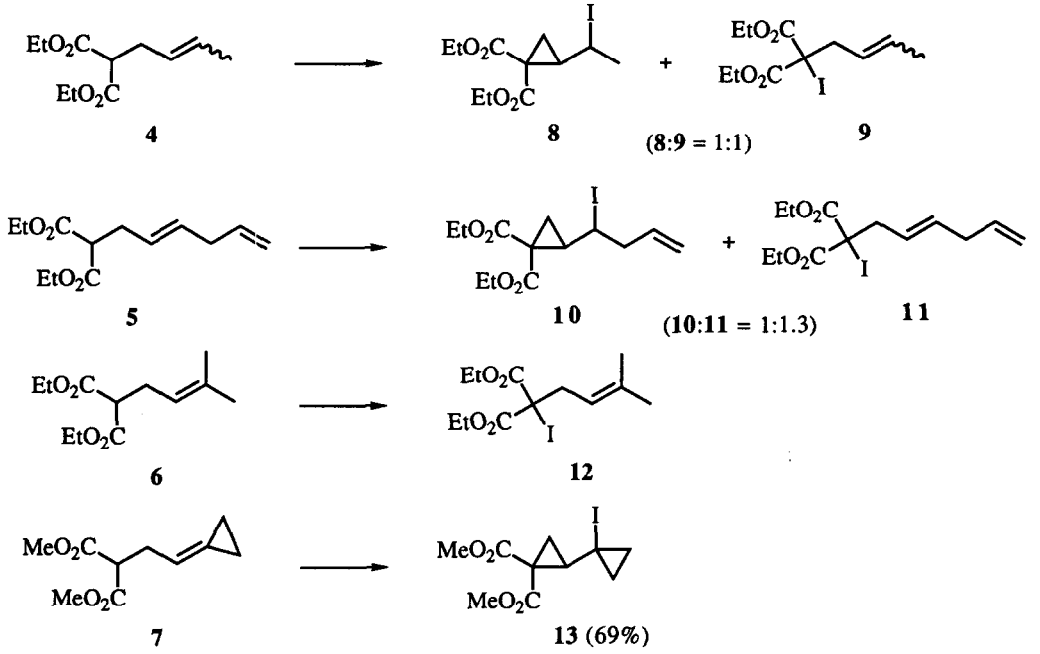


1 **2** (81%) **3**

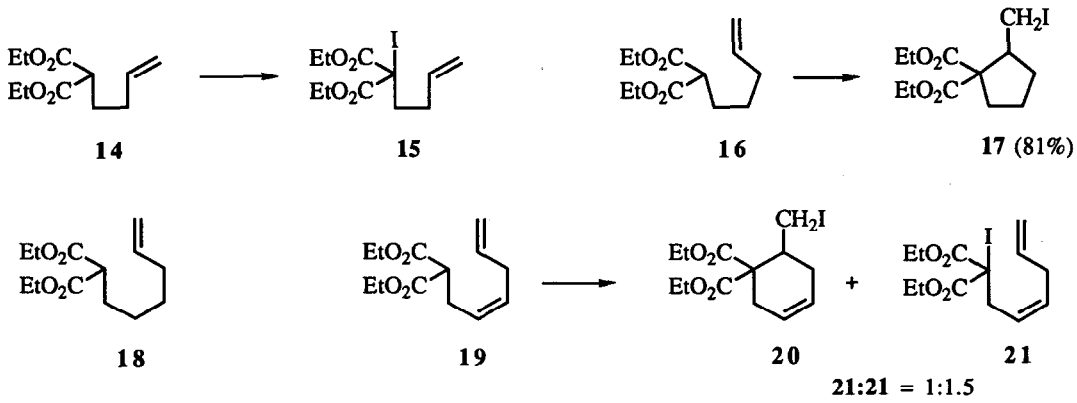
Investigation by thin layer chromatography and ^1H nmr spectroscopy during the course of the reaction revealed that the iodomalonate **3** was formed initially when iodine was added to the allylmalonate. However, when the mixture was heated **3** underwent rearrangement to **2**. We have found that the the key to the rearrangement is the sodium iodide formed *in situ* concomitantly with **3**. Treatment of **3** with dry sodium iodide in THF followed by heating at reflux gave **2**, whereas in the absence of iodide ion **3** underwent slow partial reversion to the parent malonate **1**. Addition of sodium iodide to a THF solution of an iodomalonate results in an immediate yellow colouration which rapidly darkens to the characteristic brown colour of iodine in THF. In the light of these results we have developed two experimental protocols: method A is a one-pot procedure involving

treatment of the malonate with NaH/I_2 in THF; method B is a two step process involving the prior conversion of the malonate into the corresponding iodomalonate.

Method A has been employed to investigate the scope of this route to cyclopropane derivatives. Unlike **1** which gave exclusively the cyclised product **2**, the malonates **4** and **5** containing a 1,2-disubstituted double bond gave cyclopropylcarbinyl iodides **8** and **10** respectively and the corresponding iodomalonates **9** and **11** in approximately equal quantities. Small amounts of starting material were also recovered, whether as a result of incomplete reaction or iodide decomposition is not known. Iterative chromatography was required for the complete separation of the two iodides in each mixture, with a significant loss of material on each successive column. However, the mixtures of iodides were initially isolated with a mass balance comparable to that of **2** (i.e. >80%). The products were identified by appropriate spectral (^1H nmr, ^{13}C nmr, mass spectroscopy) and microanalytical methods. Malonate **6** did not give any cyclopropylcarbinyl iodide: **12** was isolated together with some starting material. In contrast to the progressive suppression of cyclopropane formation with increasing substitution of the double bond, malonate **7**[6] resulted exclusively in bicyclopropyl iodide **13** in good isolated yield (69%). This is in keeping with the view that the thermodynamic stability of the cyclopropylcarbinyl iodide and the iodomalonate determines their relative proportions in the product mixture.



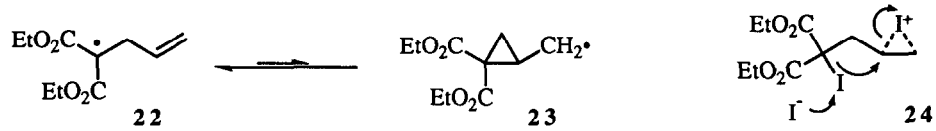
We have also conducted a preliminary survey of the formation of larger rings from the malonates **14**, **16**, **18**, and **19**. The butenylmalonate **14** gave only the corresponding iodomalonate **15** and cyclic products could not be detected. However, the pentenylmalonate **16** gave exclusively the iodide **17** in 81% isolated yield, the result of 5-*exo* cyclisation. The reaction of the hexenylmalonate **18** gave a very complex mixture and it was impossible to discern whether or not cyclisation had occurred. The *cis*-hexadienylmalonate **19** also gave a mixture of products but in this case it was possible to identify the iodide **20**, the result of 6-*exo* cyclisation, and the iodomalonate **21** in the ^1H nmr spectrum of the mixture. Both **20** and **21** have been prepared by alternative routes.[1] The other components of the mixture could not be identified.



It is noteworthy that during his work on the preparation of iodomalonates Curran[4] reported a similar cyclisation of pentenylmalonate. The corresponding iodomalonate was also formed but the predominant product was a dimer, the consequence of oxidative coupling.[7] The differences between his results and ours may be attributable to the reaction temperature and time. Curran did not examine the mechanism for the cyclisation but commented that either a free radical or an ionic mechanism could be envisaged: radicals could be formed either by oxidation of the anion or by initiation of the initially formed iodomalonate. The high 5-*exo* selectivity for the cyclisation was noted and, in the light of the 5-*exo*/6-*endo* ratio of 90/10 for the pentenyliodomalonate under radical atom transfer conditions, was attributed to a potential temperature effect. Our observation of a very high 5-*exo* selectivity for cyclisation of **16** in THF at reflux indicates that this may be a consequence of the mechanism or solvent rather than temperature.

The contrasts between the method used here and radical atom transfer systems were most evident in the case of cyclopropane formation. The iodomalonate **3** gave a complex and intractable mixture of products when subjected to the standard conditions for radical atom transfer (irradiation at 60°C in a benzene solution with 10mol% hexabutylditin). The iodomalonates **11** and **21** also behaved very differently under Curran's conditions.[1]

A simple radical mechanism for the reactions described here seems unlikely since the equilibrium between **22** and **23** lies highly in favour of the acyclic form.[8] Successful radical strategies for 3-membered ring closure have overcome the inherent problems by incorporating at the cyclopropylcarbinyl centre either a radical stabilizing group [9] or a leaving group.[10] However, it is conceivable that the equilibrium between **22** and **23**, although unfavourable, gives a sufficient concentration of **23** under atom transfer conditions to allow **2** to be formed.



Nevertheless, the available evidence favours the view that the mechanism does not involve radicals. For example, the high stereoselectivity of the reaction of the *trans*-hexadienylmalonate **5** which gave only one detectable diastereomer of the product **10** seems inconsistent with a radical mechanism but would be consistent with an ionic mechanism involving an intermediate iodonium species (or a vicinal diiodide from the addition of iodine to the double bond). In order to confirm this observation it would have been desirable to have in hand the other diastereomer of **10**, which should be accessible from the *cis*-hexadienyl malonate **19** if the reaction is stereoselective. Unfortunately in this regard, malonate **19** underwent preferential 6-*exo* rather than 3-*exo* cyclisation.

In another experiment designed to probe the mechanism a sample of the cyclopropylcarbinyl iodide **10** was heated in THF at reflux with sodium iodide.. The resultant mixture contained **10** and iodomalonate **11** in a ratio of 1:1.3, the same as that for the initial conversion of **5** to **10** and **11**. Since the *trans*-hexadienyliodomalonate **11** can be distinguished from its *cis* isomer **21** by ^{1}H and ^{13}C nmr spectroscopy it was possible to determine that **10** gave exclusively **11**. According to the ^{1}H and ^{13}C nmr spectral data, the stereochemistry of **10** was unchanged after the reaction. It thus appears that the iodomalonates and cyclopropylcarbinyl iodides are in equilibrium while the stereospecific opening of the cyclopropane ring is indicative of a concerted process.

In summary the available experimental evidence is consistent with the view that the reaction requires both iodine and iodide ion and involves iodide ion promoted cyclisation of a bridged iodonium species **24**. There is literature precedence both for cyclopropane formation with malonate anions[11-13] and for iodine activation of double bonds in the conversion of allyl stannane to cyclopropylcarbinyl iodide.[14]

Although it is still impossible at present to decide conclusively whether the reactions reported here are ionic or radical in nature, the comparison between the results of standard radical conditions and methods A and B has revealed important differences, most notably the formation of otherwise inaccessible cyclopropylcarbinyl iodides. A more detailed investigation of the mechanistic and synthetic implications of these iodocyclisations is in hand.

References and Notes

1. This work and related unpublished results were reported at the Royal Australian Chemical Institute one-day symposium, University of Wollongong, November 1992.
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5. A typical procedure: Sodium hydride (105 mg, 60% dispersion in oil, 2.62 mmol) was added to a solution of diethyl allylmalonate (436 mg, 2.18 mmol) in THF (7 ml) and stirred at room temperature for 20 min. A solution of iodide (664 mg, 2.62 mmol) in THF (7 ml) was added. The mixture was heated at reflux for 4 hr, then poured into ether and washed with aqueous sodium thiosulphate. The aqueous phase was extracted twice with ether. The combined ethereal solutions were washed with water and brine, and dried over sodium sulphate. Filtration and removal of the solvent *in vacuo*, followed by chromatography of the crude product on silica gel with petrol (40-60°)/Et_2O/CH_2Cl_2 (90:5:5) as the eluent, gave *diethyl 2-iodomethylcyclopropane-1,1-dicarboxylate* **2** (573 mg, 81%) as a colourless liquid (Found: C, 37.02; H, 4.79. $C_{10}H_{15}O_4I$ requires C, 36.81; H, 4.64; υ_{max}(film)/cm^{-1} 2980, 1725, 1370, 1320, 1280, 1213, 1180, 1135, 1100 and 1020; δ_H (300 MHz; $CDCl_3$) 4.21(4H, m), 3.24 (1H, dd), 3.10 (1H, dd), 2.44 (1H, dd), 1.56 (1H, dd), 1.47 (1H, dd), 1.30 (3H, t), 1.26 (3H, t); δ_C (75 MHz; $CDCl_3$) 168.92, 167.21, 61.81, 61.73, 38.69, 30.62, 23.73, 14.13, 13.98, 2.09; *m/z* 326 (M^+), 261, 199, 171, 153, 125, 99, 53; calc for $C_{10}H_{15}O_4I$: 326.0015, found 326.0013.
6. We gratefully acknowledge a gift of a sample of the malonate **7** from Professor Armin de Meijere, Göttingen University.
7. We have occasionally observed a small amount (2%) of a similar dimer in the reaction of allylmalonate.
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12. While this manuscript was being prepared we became aware of the work of Taguchi[14] on the $Ti(OMe)_4$ promoted iodocyclisation of alkenylmalonates which appears to be mechanistically related to the work described here.
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