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A convenient synthesis of dialkyl 2-(2-haloethylidene)malonates, cyanoacetates and halocrotonates by one carbon extension

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ABSTRACT

2-Haloethylidenemalonates are highly reactive species and useful synthons for the synthesis of Famvir®, an antiviral drug. Simple methods for the preparation of 2-haloalkylidenemalonates are not available. We have developed a novel and non-cumbersome methodology for the synthesis of dialkyl 2-(2-haloethylidene)malonates, cyanoacetates and halocrotonates by one carbon extension of dialkyl (2-alkoxymethylene)malonates, cyanoacetates and 3-alkoxyacrylates with dimethylsulfoxonium methylide.

Introduction

2-Bromo and 2-chloroethylidenemalonates undergo interesting transformations with nucleophiles. Their substitution reactions have been extensively studied.[1] 2-Bromoethylidenemalonates have been converted to butenolides[1a] and have been used in the synthesis of substituted cyclopropanes[1d] and in the synthesis of Famvir®, an antiviral drug.[2] The literature on dialkyl 2-(2-haloethylidene)malonates is scanty except for an isolated patent report.[3] Herein, we describe a novel method for the synthesis of dialkyl 2-(2-iodoethylidene)malonates, cyanoacetates and iodocrtotonates identified during the course of cyclopropanation of dialkyl (2-alkoxymethylene) malonates, cyanoacetates and 3-alkoxy acrylates using dimethylsulfoxonium methylide (DIMSOY). This method has also been successfully extended to the synthesis of 2-bromoethylidenemalonates and 2-chloroethylidene malonates.

The sulfoxonium ylides are a class of organic compounds that have been extensively studied and reported.[4] The generation of sulfoxonium ylide and its reactivity with C=O, C=N, C=S and C=C systems were first reported by Corey et al.[5] In particular DIMSOY has proved to be a versatile nucleophilic reagent capable of reacting with a wide variety of olefinic systems.[4,5] Silicon assisted diversified reaction of β-silylmethylene malonates with DIMSOY has been reported by Pintu et. al.[6] Although the reaction of DIMSOY with diethyl ethoxymethylenemalonate and related substrates was applied for the synthesis of 4-ethoxycarbonyl-3-hydroxy-1-methylthia-benzene-1-oxide by Tamura et. al.,[7] the formation of 2-iodoethylidenemalonate in this reaction has been identified by us for the first time and reported here.

Results and discussion

Diethyl (2-ethoxymethylene)malonate **3a** was reacted with DIMSOY **2**, generated in situ by reacting trimethylsulfoxonium iodide **1** with sodium hydride in DMF at room temperature for about 30–45 min and the reaction mixture was quenched with 10% aqueous hydrochloric acid solution (Scheme 1) leading to the isolation of two products, a viscous liquid **5a** and a crystalline solid **4**, mp 112 °C.

Both these products were separated by column chromatography and characterized by mass spectrum and ^{1}H, ^{13}C NMR spectra. Based on its mass spectral and NMR spectral data, the product **4** was identified as 4-ethoxycarbonyl-3-hydroxy-1-methylthiabenzene-1-oxide, a known compound in the literature.[7a] The structure was further confirmed by single crystal X-ray crystallography as shown in Figure 1. (CCDC No: 1045871).

The other product **5a** has been identified as diethyl 2-(2-iodoethylidene)malonate based on its ^{1}H and ^{13}C NMR spectral data. While the synthesis of 1-methylthiabenzene-1-oxides by

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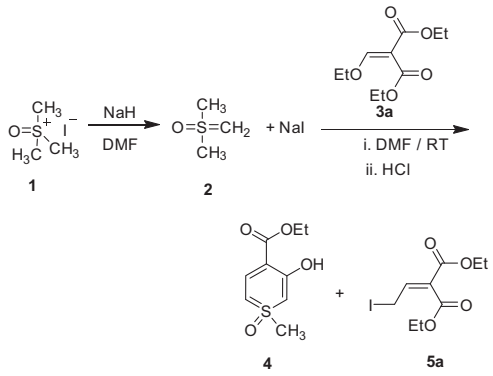
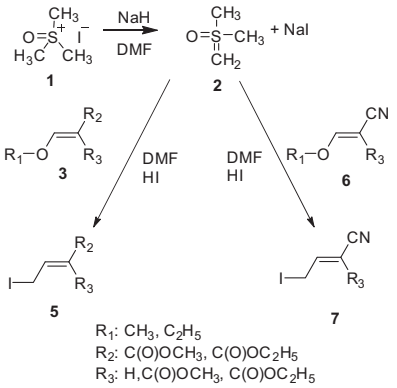


Scheme 1. Reaction of diethyl (2-ethoxyethylidene)malonate **3a** with dimethylsulfoxonium methylide **2**.



Scheme 2. Synthesis of 2-iodoethylidenemalonates **5** and cyanoacetates **7**.

the reaction of the ylide **2** is known,[7] formation of diethyl 2-(2-iodoethylidene)malonate **5a** in this reaction was a pleasant surprise to us. Inspired by this unexpected finding and the interesting chemistry associated with dialkyl 2-(2-haloalkylidene) malonates[1] and the paucity of methods for the preparation of 2-haloalkylidenemalonates, we endeavoured to optimize the reaction conditions so that this reaction could serve as a practical method for the synthesis of 2-iodoalkylidienemalonates.

Various solvents like DMF, DMSO, THF, acetonitrile, 1,2-dimethoxyethane and a few bases like sodium hydride, potassium t-butoxide and n-butyl lithium were screened. The optimized procedure consisted of stirring a mixture of dialkyl (2-alkoxymethylene)malonate **3** and DIMSOY **2** generated in situ from trimethylsulfoxonium iodide **1** with sodium hydride in dry DMF at 0 °C for 15 min and quenching the reaction mixture with aqueous hydroiodic acid (Scheme 2).

This reaction has been generalized by successfully applying on some of the dialkyl (2-alkoxymethylene)malonates **3**(**a**–**d**), cyanoacetates **6**(**a**–**b**) and 3-alkoxyacrylates **3**(**e**–**f**) (Table 1, entries 1–8). In the case of (2-alkoxymethylene) malononitriles **8a** and **8b**, the reaction was complex as evidenced from TLC and the desired iodoethylidene compound could not be obtained under this condition. (Table 1, entries 9 and 10). The proton NMR spectrum in the case of **7a** indicated it to be a single isomer. The olefinic proton of **7a** resonated at δ 7.70, more downfield compared to those of **5**(**a**–**c**) (δ 7.12), based on which a *Z* stereochemistry has been tentatively assigned to the iodocyanoacetates **7a**.

Adopting this optimized condition, a series of 2-alkoxymethylidene malonates, cyanoacetates, malononitriles and 3-alkoxyacrylates were reacted with DIMSOY and the resulting 2-iodoethylidene compounds were isolated and characterized. The results are tabulated in Table 1.

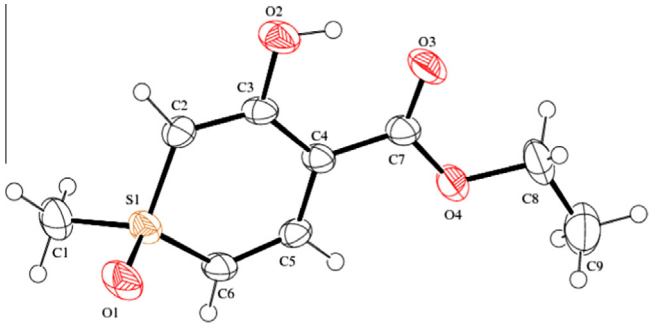
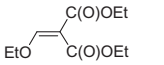
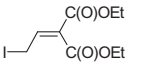
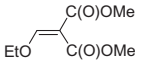
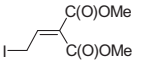
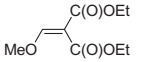
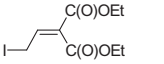
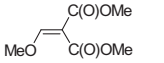
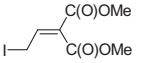
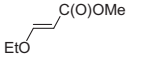
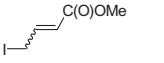
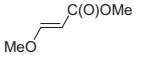
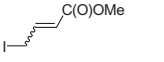
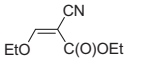
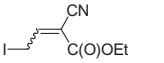
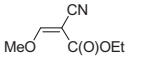
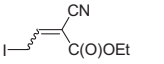
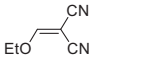
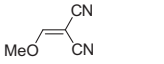


Figure 1. ORTEP diagram for 4-ethoxycarbonyl-3-hydroxy-1-methylthia-benzene-1-oxide **4**.

Table 1
Synthesis of dialkyl 2-(2-iodoethylidene)malonates **5** and cyanoacetates **7**

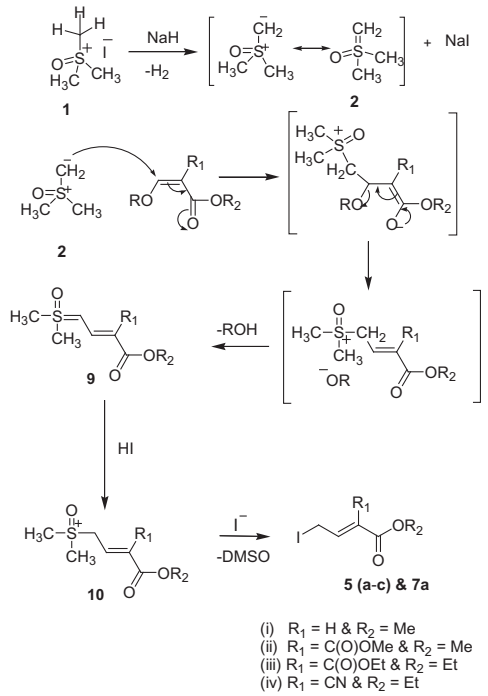
Entry	Substrate		Product		Yield (%)
1	**3a**		**5a**		60
2	**3b**		**5b**		58
3	**3c**		**5a**		55
4	**3d**		**5b**		60
5	**3e**		**5c**		54[a]
6	**3f**		**5c**		50[a]
7	**6a**		**7a**		58[b]
8	**6b**		**7a**		55[b]
9	**8a**		—	—	—
10	**8b**		—	—	—

[a] Isolated as *cis*, *trans* mixture.
[b] Based on NMR data, it is presumed to be *Z*-isomer.

The formation of dialkyl 2-(2-haloethylidene)malonates **5** and cyanoacetates **7** can be rationalized as shown in Scheme 3.

Our efforts to synthesize the dialkyl 2-(2-chloroethylidene) malonates **11** and dialkyl 2-(2-bromoethylidene)malonates **12** by quenching the reaction mixture with aqueous hydrochloric acid and aqueous hydrobromic acid respectively led only to the iodo compound **5**. However by a slight modification of the procedure, we were able to synthesize the chloro compounds **11** and bromo compounds **12**. By quenching the reaction mixture with water alone, it was possible to extract the ylide **9** which is reported in literature.[7a] Treatment of the ylide **9** with one equivalent of methanesulfonic acid and lithium chloride resulted in dialkyl 2-(2-chloroethylidene)malonate **11** in 70% yield.[8]

Though dimethyl sulfoxide is a good leaving group, the desired cyclopropyl compound was not formed in any of the reactions of DIMSOY with 2-alkoxymethylene malonates and 3-alkoxy acrylates. While the 1,3-elimination of dimethyl sulfoxide would lead to the formation of strained push-pull cyclopropane product,



Scheme 3. Mechanism for the formation of (2-iodoethylidene) malonates **5** and cyanoacetates **7**.

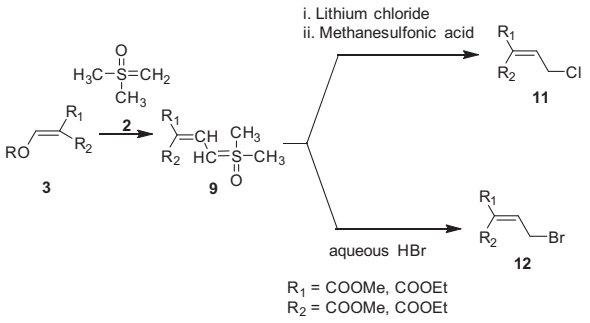
1,2-elimination of alkoxy anion would result in the formation of highly stable and conjugated allylide intermediate **9**. Thus the formation of allylide **9** could be the possible driving force for the product formed rather than the strained cyclopropane product.

Similarly treating the ylide **9** with one equivalent of aqueous hydrobromic acid afforded the dialkyl 2-(2-bromoethylidene)-malonate **12** in 40% yield (Scheme 4), (Table 2).

The formation of thiabenzene-1-oxide **4** can be explained as depicted in Scheme 5 based on earlier literature reports.[7] Reaction of diethyl (2-ethoxymethylene)malonate **3a** with excess of sulfoxonium ylide (2.0 mol equiv) yielded the thiabenzene-1-oxide **4** as the product in 60% yield.

While the reaction of DIMSOY with 2-(ethoxymethylene)-2,4-pentanedione, ethyl-2-(ethoxymethylene)acetoacetate, diethyl 2-(ethoxymethylene)malonate and 2-acetyl-3-methoxy-2-cyclohexen-1-one to give thiabenzene-1-oxide derivatives via an allylide **9** is known, there is no mention about the formation of the iodo compound in any of the reports.

In fact, Tamura et al., had investigated the very same reaction of DIMSOY with diethyl (2-ethoxymethylene)malonate **3a** and reported the formation of a mixture of the thiabenzene-1-oxide

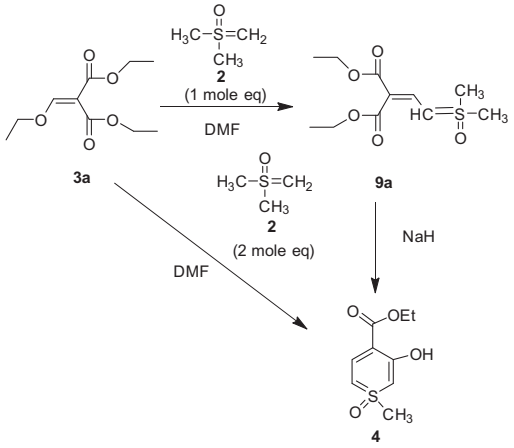


Scheme 4. Synthesis of 2-chloroethylidene and 2-bromoethylidenemalonate (**11**–**12**) from allylide **9** (**a**–**b**).

Table 2
Synthesis of 2-bromoethylidene and 2-chloroethylidenemalonate (**11**–**12**)

Entry	Substrate	Product	Yield (%)
1	**9a**	**11a**	60[a]
2	**9b**	**11b**	58[a]
3	**9a**	**12a**	55[b]
4	**9b**	**12b**	60[b]

Condition:
[a] Methane sulfonic acid and Lithium chloride in anhydrous THF at reflux temperature.
[b] Aqueous hydrobromic acid in dichloromethane at 0 °C.



Scheme 5. Synthesis of thiabenzene-1-oxide **4**.

4, dihydrofuran and furanone. However, they had not reported the formation of 2-iodoethylidenemalonate **5**. We have modified the procedure in such a way that the reaction mixture was first quenched with acid. This led to the protonation of the allylide and generating the sulfoxonium salt **10** which seems reactive enough to undergo substitution with iodide ion (Scheme 3). A variation of this procedure provides a convenient access for the synthesis of 2-bromoethylidenemalonates and 2-chloro-ethylidenemalonates which are useful extensions of the recently reported synthesis of α–chloro ketones.[8]

Conclusion

A simplified method for the synthesis of dialkyl 2-(2-haloethylidene)malonate, cyanoacetates and halocrotonates by one carbon extension has been identified. A wide variety of substrates were tested successfully with the above procedure.

Experimental section

General

The compound **3a**, **3d**, **3f**, **6a**, **8a** and the other reagents were purchased from commercial suppliers like Acros Organics, Sigma

Aldrich, Spectrochem, Alfa Aesar, TCI Chemicals, Qualigens, Lancaster and used without further purification. The compound **3b**, **3c**, **3e**, **6b**, **8b** were prepared by following the reported procedures.[9]

The ^{1}H & ^{13}C spectra for compounds **4**, **5**(**a**–**c**), **7a**, **9**(**a**–**b**), **11b**, **12b** were run in deuterated chloroform. For compound **9c**, they were run in deuterated dimethyl sulfoxide using 300 MHz & 75 MHz respectively on Bruker 300 MHz Avance NMR spectrometer. The ^{1}H and ^{13}C spectra for compounds **11a**, **12a** were taken in deuterated chloroform using Bruker 400 MHz Avance NMR spectrometer. Chemical shifts (δ) are reported as parts per million (ppm) with reference to tetramethylsilane (TMS) ($\delta H = 0.00$ ppm) unless otherwise stated. The coupling constants (J) are reported in Hz and signal multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (t), doublet of doublet (dd), multiplet (m). Melting points are uncorrected and were recorded on Veego Model VMP-PM melting point apparatus. IR spectra were recorded on Perkin Elmer FT-IR. Mass spectroscopy was recorded on Shimadzu QP2010 MS detector using EI technique. High-resolution mass spectra (HRMS) were recorded on a Micromass EI mass spectrometer. Single crystal XRD of compound **4** was taken in Bruker AXS Kappa APEXII CCD Diffractometer.

Procedure for the synthesis of 4-ethoxycarbonyl-3-hydroxy-2-methyl-thiabenzene-1-oxdie 4

Sodium hydride (60%), (1.88 g, 0.047 mol), washed twice with hexane to remove the paraffin oil, was added to a clean well dried RB flask. Traces of solvent were removed by applying nitrogen using evacuated carousel or ampoules. To the dried sodium hydride, dry DMF (20 mL) was added under nitrogen atmosphere, followed by trimethylsulfoxonium iodide, (2.07 g, 0.0094 mol) in single lot. The contents were stirred for 60 min at 40–45 °C. The ylide solution was cooled to 0 °C under nitrogen atmosphere. A solution of **3a** (1.0 g, 0.0046 mol) in DMF (5 mL) was added into the ylide solution in single lot at 0 °C. The reaction mixture was maintained at 0 °C for a period of 2 h and quenched with water at 5 °C. The aqueous mixture was extracted with chloroform and the organic layer was washed with brine solution. The organic layer was concentrated and the crude product purified using column chromatography on silica gel (hexane/EtOAc) to afford **4** as pale yellow colour solid. (mp 112 °C, $\lambda_{max} = 273$ nm). (Lit.[7a] mp 111–112 °C).

General procedure for the synthesis of (2-iodoethylidene)-malonates and cyanoacetates 5 and 7 (5a as an example)

Sodium hydride (60%), (1.88 g, 0.047 mol), washed twice with hexane to remove the paraffin oil, was added to a clean well dried RB flask. Traces of solvent were removed by applying nitrogen using evacuated carousel or ampoules. To the dried sodium hydride, dry DMF (30 mL) was added under nitrogen atmosphere, followed by trimethylsulfoxonium iodide (10.35 g, 0.047 mol) in single lot and the contents were stirred for 60 min at 40–45 °C. This solution was added to a mixture of the compound **3a** (10 g, 0.046 mol) in DMF (5 mL) at 0 °C under nitrogen atmosphere over a period of 15 min. The completion of reaction was checked by TLC. Then the reaction mixture was maintained for a period of 1–2 h at room temperature and quenched by adding the reaction mixture into a solution of aqueous hydroiodic acid (10%) solution at 0 °C. The aqueous mixture was extracted with chloroform and the organic layer was washed with 10% sodium thiosulfate solution to remove the excess iodine. The organic layer was concentrated and purified using column chromatography on silica gel (hexane/EtOAc) to afford the iodo compound **5a**, as pale yellow colour oily liquid.

General procedure for the synthesis of allylide 9 (9a as an example)

Sodium hydride (60%), (1.88 g, 0.047 mol), washed twice with hexane to remove the paraffin oil, was added to a clean well dried RB flask. Traces of solvent were removed by applying nitrogen using evacuated carousel or ampoules. To the dried sodium hydride, dry DMF (30 mL) was added under nitrogen atmosphere, followed by trimethylsulfoxonium iodide (10.35 g, 0.047 mol) in single lot and the contents were stirred for 60 min at 40–45 °C. This solution was added to a mixture of the compound **3a** (10 g, 0.046 mol) in DMF (5 mL) at 0 °C under nitrogen atmosphere over a period of 15 min. The completion of reaction was checked by TLC. Then the reaction mixture was maintained for a period of 1–2 h at room temperature and quenched by adding the reaction mixture into ice cold water. The aqueous mixture was extracted with chloroform and the organic layer was washed with brine solution. The organic layer was concentrated and purified using column chromatography on silica gel (hexane/EtOAc) to afford the allylide **9a** as colourless solid (mp 123 °C).

General procedure for the synthesis of dialkyl 2-(2-chloroethylidene)malonate 11 (11a as an example)

The allylide **9a**, (3.00 g, 0.012 mol) was taken in THF (10 mL), treated with anhydrous Lithium chloride, (0.51 g, 0.012 mol) and methanesulfonic acid, (1.15 g, 0.012 mol). The reaction mixture was refluxed for 4–5 h. The completion of reaction was checked by TLC. The reaction mixture was quenched by adding the mixture into ice cold water. The aqueous mixture was extracted with Diethyl ether and the organic layer was washed with brine solution. The organic layer was concentrated and purified using column chromatography on silica gel (hexane/EtOAc) to afford the dialkyl 2-(2-chloroethylidene)malonate **11a** as pale yellow colour oily liquid.

General procedure for the synthesis of dialkyl 2-(2-bromoethylide-ne)malonate 12 (12a as an example)

The allylide **9a**, (3.00 g, 0.012 mol) was taken in dichloromethane (10 mL) and treated with aqueous hydrobromic acid, (2.06 g, 0.012 mol) at 0 °C. The reaction mixture was stirred for about 30–45 min at 0 °C. The completion of reaction was checked by TLC. The reaction mixture was quenched with ice cold water. The organic layer was washed with brine solution, concentrated and purified using column chromatography on silica gel (hexane/EtOAc) to afford the dialkyl 2-(2-bromoethylidene)- malonate **12a** as pale yellow colour oily liquid.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.05.015.

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