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# A new one-pot, solvent free synthesis of diethyl 3,3-thiodipropenoate

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COMMUNICATION

# A new one-pot, solvent free synthesis of diethyl 3,3-thiodipropenoate

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Three isomers of diethyl 3,3-thiodipropenoate (DETDP) have been prepared as new compounds by the solvent free reaction of ethyl propiolate and thioamides or sodium sulfide in a short time and high yields.

*Keywords*: Thioamide; Ethyl acetylene carboxylate; Diethyl 3,3-thiodipropenoate; Montmorillonite K10; Solvent free



## 1. Introduction

The Michael addition plays an important role in organic synthesis and bio-organic reactions [1]. The Michael reaction [2] is the addition of an enolate to a C=C conjugated double bond bearing an electron-withdrawing group. Condensation takes place in basic media, typically alkali metal alkoxides. $\alpha$, $\beta$-unsaturated aldehydes, ketones and carboxylic acid derivatives usually act as acceptors. Occasionally, the alkoxide employed to create the enolate competes with the carbanion and adds to the acceptor.

The definition of the Michael addition has grown in some circles to include other nucleophiles – the sulfide anion is one such agent since it acts as a Michael donor in some important bioorganic reactions. For example, cysteine proteases are proteolytic enzymes involved in the degradation of proteins. These proteases play vital roles in mammalian cell turnover [3] and apoptosis [4,5] and they are very important in the life cycle of many parasites [6]. Some of the most important of these proteases are cruzain, which has been isolated from *Trypanosome cruzi* and is the etiologic agent of Chagas' disease, and falcipain, which is essential for the life cycle of the *Plasmodium falciparum* parasite (responsible for malaria) and for the degradation of hemoglobin. The proposed mechanism of action of the cysteine protease inhibitors consists of the addition of the sulfur anion of the active-site to the $\beta$-carbon of a double bond with formation of a covalent bond [7].

Indeed, thiol or sulfide addition to Michael acceptors has now become commonplace for organic chemists. Several variations now exist, including the use of magnesium thiolates to

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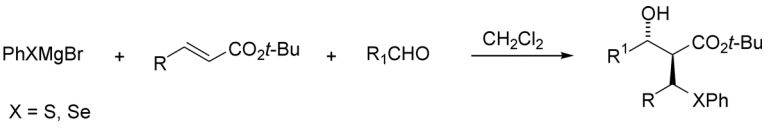


Figure 1. Anti-aldol selective synthesis by magnesium thiolates.

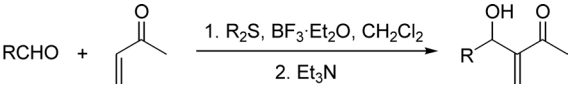


Figure 2. Baylis–Hillman reaction in the presence of sulfides.

generate an enolate for subsequent anti-selective aldol condensation chemistry (figure 1) [8]. Also, a sulfide-$BF_3 \cdot OEt_2$ mediated Baylis–Hillman reaction has been developed in which the sulfide acts *via* nucleophilic attack onto the activated alkene (figure 2) [9]. A recent application of a thiol adding to quinone may serve in assessing the depletion of endogenous thiols within plasma and whole blood [10].

The nucleophilic Michael-type reaction addition of $H_2S$ to methyl acrylate (MA, figure 3) over solid basic catalysts yields methyl 3-mercaptopropionate (MMP). The reaction has been reported in the patent literature [11, 12] and it was noted that methyl 3-mercaptopropionate reacts further with methyl acrylate to form dimethyl 3,3-thiodipropionate (DMTDP, figure 3). Moreover, other side-reactions may take place, namely the condensation of two molecules of methyl 3-mercaptopropionate to give the corresponding disulfide and the polymerization of methyl acrylate. The activity of the catalyst can be related to its ability to form reactive nucleophilic species $HS^-$.

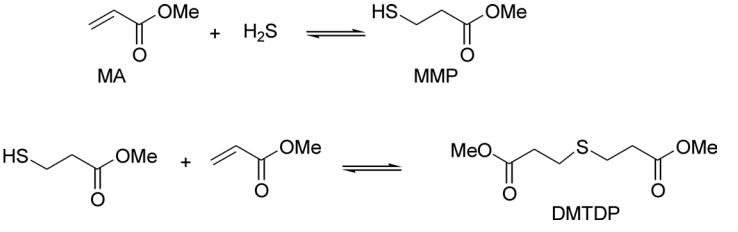


Figure 3. Reaction scheme for base-catalyzed addition of $H_2S$ to methyl acrylate.

Selective preparation of MMP is generally achieved in the presence of a large excess of $H_2S$ with magnesium oxide anionic-exchanged resins as catalyst. The formation of MMP occurs through the reaction between MA and $HS^-$ resulting from $H_2S$ dissociative adsorption on MgO [13] (figure 4).

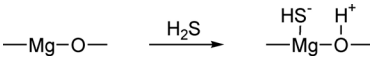


Figure 4. Dissociative adsorption of $H_2S$ over MgO.

The use of $H_2S$ in the reported methods is difficult, requires special conditions and necessitates a tedious work up [13]. To improve the synthetic protocol, we decided to use solid supported reagents such as thioamides or sodium sulfide instead of $H_2S$ and MgO. Further, we employed microwave irradiation to probe its value in promoting the chemistry. Microwave assistance often renders experimentally and industrially important organic syntheses more

effective and more eco-friendly [14–17]. Based on our efforts, we report a novel rapid reaction between montmorillonite K10 supported sulfide anion or thioamides and ethyl propiolate for the preparation of diethyl 3,3-thiodipropenoate isomers.

## 2. Results and discussion

The acidity of the solid support surfaces is useful in activating the carbonyl group, and facilitates the Michael attack to the $\beta$-carbon, forming three DETDP isomers (figure 5, tables 1 and 2). The isomers were distinguished by coupling constant differences between alkenyl hydrogens in the $^1$H NMR spectrum.

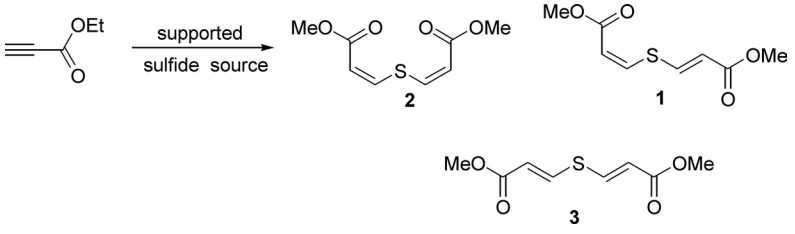


Figure 5. Preparation of diethyl 3,3-thiodipropenoate using ethyl acetylene carboxylate.



Table 1. Preparation of DETDP isomers under microwave irradiation.

| Sulfide source | Time (min) | %**1** | %**2** | %**3** | Overall yield (%) |
|---|---|---|---|---|---|
| $PhCSNH_2$ | 4 | 38 | 36 | 26 | 90 |
| $CH_3CSNH_2$ | 4 | 42 | 37 | 21 | 84 |
| $NH_2CSNH_2$ | 3 | 35 | 35 | 30 | 93 |
| $Na_2S$ | 3 | 13 | 29 | 58 | 97 |

Table 2. Preparation of DETDP isomers by thiobenzamide.

| Temp (°C) | Time (min) | %**1** | %**2** | %**3** | Overall yield (%) |
|---|---|---|---|---|---|
| 0 | 60 | 42 | 30 | 28 | 67 |
| 26 | 48 | 35 | 24 | 41 | 75 |
| 60 | 30 | 23 | 35 | 42 | 71 |

No reaction takes place when sulfur element ($S_8$) is used as a sulfur source instead of thioamides or sodium sulfide, suggesting that no sulfide radicals are involved when thioamides are used as the sulfur source. Though the polarity of the substrates makes them good candidates for efficient reaction under microwave irradiation (table 1), yields are nevertheless reasonable in the absence of microwaves (table 2).

The reaction between ethyl propiolate and thioamides has not yet been reported. We report here an example of such a reaction, our protocol listing mild conditions, short reaction times, solvent-free conditions and no side-products among its advantages.

We suggest that the *trans–trans* (**3**) and *cis–cis* (**1**) isomers are the most and least stable isomers, respectively. Moreover, isomer **1** is formed first as it is kinetically favored, but during

the work-up and purification it is converted into **2** and **3**. If a mixture of the isomers is boiled under reflux for 2.5 h at 60 °C in $CHCl_3$ isomer **3** is the only product.

When this reaction was performed in ethanol or toluene, under reflux conditions without montmorillonite K10, only starting materials were observed on the TLC plate after 8 h. In general, in the absence of solid support, yields are very low and the reaction times longer.

In conclusion, we have established a new efficient and facile one-pot reaction for coupling two unsaturated compounds with a sulfur bridge. The procedure involves a simple set-up and work-up, high yields and short reaction times while incorporating an environmentally friendly method. There were no side-products.

## 3. Experimental

Chemicals were purchased from Merck and Fluka. Products were separated and purified by column chromatography. All products were identified by their mp and IR, NMR and GC-MS spectroscopic properties.

### 3.1 *General procedure*

Thioamide or dry sodium sulfide (2 mmol), montmorillonite K10 (2 g, surface area 200 $m^2\ g^{-1}$, Fluka) and ethyl propiolate (6 mmol) were crushed together using a mortal and pestle. The resultant mixture was exposed to microwave irradiation for the indicated time (table 1). In a similar experiment the reaction mixture was placed in a flask and stirred at room temperature (26 °C) (or 0 or 60 °C) for the indicated time (table 2). The progress of the reaction was followed by TLC using ethyl acetate–light petroleum ether (3:7) until the starting material was no longer visible. The mixture was extracted with methanol, the solvent was evaporated and the three produced isomers were purified by column chromatography over silica gel, and then identified by their mp, IR, $^1H$ and $^{13}C$ NMR and GC-MS spectroscopic properties.



### 3.2 *Z,Z-diethyl 3,3-thiodipropenoate (1)*

Mp: 94–96 °C; IR (KBr): $\nu$ ($cm^{-1}$): 1185 (s, C−O), 1580 (m, C=C), 1700 (s, C=O) $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$ (ppm): 1.33 (t, 3H), 4.26 (q, 2H), 5.99 (d, $J = 10.3$ Hz, 1H), 7.12 (d, $J = 10.3$ Hz, 1H); $^{13}C$ NMR ($CDCl_3$): $\delta$ (ppm): 14.76, 61.05, 116.12, 147.88, 166.17 GC-MS: retention time 7.59 min, $M^{+\cdot} = 230$.

### 3.3 *E,Z-diethyl 3,3-thiodipropenoate (2)*

Mp 105–106 °C; IR (KBr): $\nu$ ($cm^{-1}$): 1190 (s, C−O), 1570 (m, C=C), 1694 (s, C=O); $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$ (ppm): 1.33 (m, 6H), 4.23 (q, 2H), 4.26 (q, 2H), 6.05 (d, $J = 10.0$ Hz, 1H), 6.10 (d, $J = 15.5$ Hz, 1H), (d, $J = 10.0$ Hz, 1H), 7.73 (d, $J = 15.5$ Hz, 1H); $^{13}C$ NMR ($CDCl_3$): $\delta$ (ppm): 16.06, 17.80, 68.22, 72.21, 122.10, 129.00, 155.19, 161.89, 175.17, 184.01; GC-MS: retention time 9.83 min, $M^{+\cdot} = 230$.

### 3.4 *E,E-diethyl 3,3-thiodipropenoate (3)*

Mp 102–103 °C; IR (KBr): $\nu$ ($cm^{-1}$): 1191 (s, C−O), 1565 (m, C=C), 1690 (s, C=O); $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$ (ppm): 1.32 (t, 3H), 4.24 (q, 2H), 6.10 (d, $J = 15.4$ Hz, 1H), 7.69–7.72 (d, $J = 15.4$ Hz, 1H); $^{13}C$ NMR ($CDCl_3$): $\delta$ (ppm): 18.14, 74.05, 130.10, 163.58, 184.23; GC-MS: retention time 9.59 min, $M^{+\cdot} = 230$.

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