A simple three-step synthesis of β,β-disubstituted acrylates *

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Abstract

β,β-Disubstituted acrylates, not available through the known procedures, are simply prepared by reaction of allylic sulphides of benzothiazole with organocopper reagents.

In recent years much attention has been devoted to the synthesis of α-substituted acrylic acids and derivatives, which are important sub-units in a variety of natural products and also owing to their acceptor and dienophile properties, useful synthons for the synthesis of complex organic species [1].
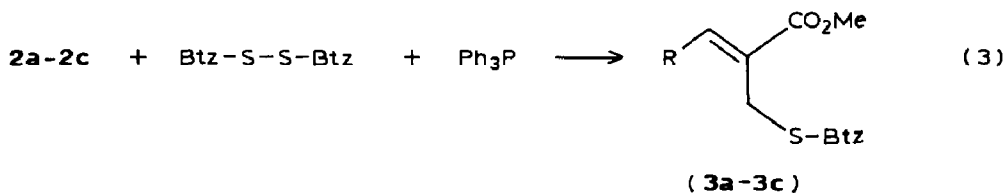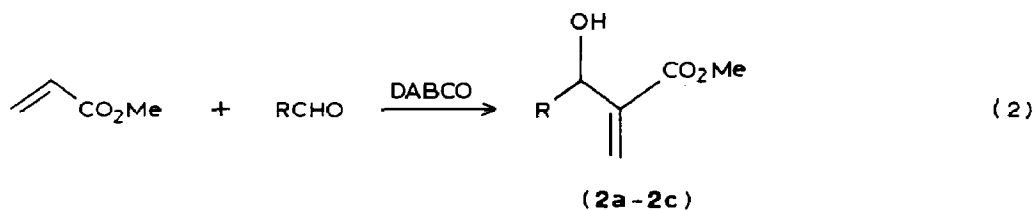
We previously [2] reported that the benzothiazole-2-thio group when in the γ-position of α,β-unsaturated esters, is not only a good leaving group, but also, interestingly, leads to reversal of the "normal" regioselectivity found in the nucleophilic organocopper addition to α,β-unsaturated esters to give α-alkylated-β,γ-enoates (eq. 1).
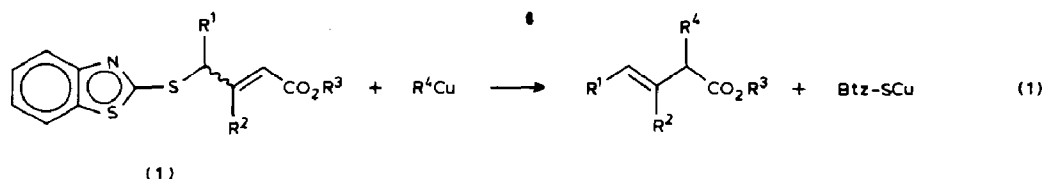
(Btz = benzothiazol-2-yl)

The observed selectivity can be accounted for by assuming that there is coordination of the sulphide **1** to the copper reagent, and that in consequence, the nucleophilic attack occurs exclusively at the α-carbon to the carbonyl. This paper reports a new synthesis of β,β-disubstituted acrylates involving reaction of allylic sulphides **3** with organocopper reagents.

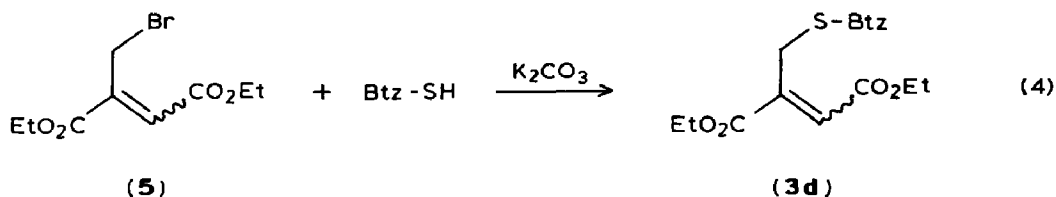* This paper was presented in part at the VESOC, August 1987, Jerusalem (Israel).

$$
\text{CH}_2=\text{CH-CO}_2\text{Me} \quad + \quad \text{RCHO} \quad \xrightarrow{\text{DABCO}} \quad
\begin{array}{c}
\text{OH} \\
\text{R} \overset{|}{\underset{}{\text{—}}} \text{C} \overset{\text{CO}_2\text{Me}}{\underset{\|}{}}
\end{array}
\qquad (2)
$$

(2a-2c)

$$
\textbf{2a-2c} \quad + \quad \text{Btz-S-S-Btz} \quad + \quad \text{Ph}_3\text{P} \quad \longrightarrow \quad
\begin{array}{c}
\text{CO}_2\text{Me} \\
\text{R} \\
\text{S-Btz}
\end{array}
\qquad (3)
$$

(3a-3c)

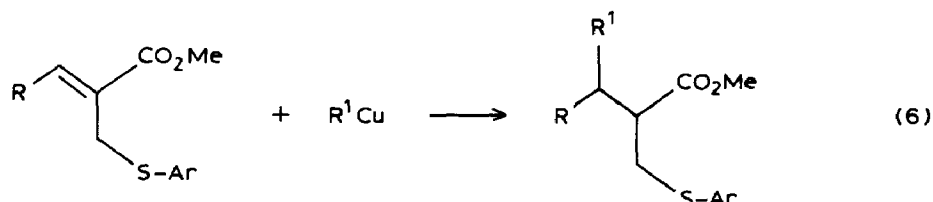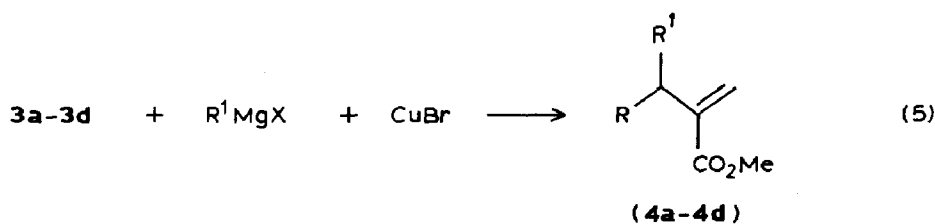(a : R = Me ; b : R = Me$_2$CH ; c : R = n-C$_8$H$_{17}$)

Results and discussion

For the synthesis of β,β-disubstituted acrylates, which are not available by the known procedures [1] we needed some new allylic sulphides of benzothiazole (3a–3c), and these were prepared from β-hydroxy esters 2, which were readily synthesized by Hoffmann's procedure [1g] by reaction of an aldeyde with methyl acrylate in the presence of 1,4-diazabicyclo[2,2,2]octane (DABCO) (eq. 2).

The subsequent reaction (eq. 3) of the β-hydroxy esters with benzothiazole disulphide and triphenylphosphine, involving an allylic rearrangement, afforded the corresponding allylic sulphides 3a–3c as (Z)-isomers in almost quantitative yield. A different procedure was followed for the synthesis of 3d, which was prepared by reaction of the diethyl ester of bromomesaconic acid with benzothiazol-2-thiol in the presence of potassium carbonate (eq. 4). The sulphides 3a–3d react cleanly with organomagnesium compounds in the presence of CuBr or CuI in tetrahydrofuran (THF) at $-25°$C to give the substituted acrylates 4a–4f (eq. 5). The presence of the benzothiazole group is essential. Thus, esters of type 3, in which the Btz–S group is replaced by alkyl–S or phenyl–S groups, react under the same conditions to give (along with other products) products of 1,4-addition without loss of the RS moiety. The best results were obtained when for each equivalent of 3, two equivalents of Grignard reagent and four equivalents of CuBr or CuI were used. Use of lower Cu salt concentrations decreased the reaction rate. The presence of other functional groups (2 g, entry 6) is well tolerated. The results are shown in Table 1.

The results demonstrate that the presence of benzothiazole group in the β'-position of the esters is important, since as mentioned above, other RS groups in the same position behave as poor leaving groups and react with organocopper reagents to give saturated esters (eq. 6). On the other hand it is known [3,4] that the allylic

$$
\begin{array}{c}
\text{Br} \\
\text{EtO}_2\text{C} \overset{}{\underset{}{}} \text{CO}_2\text{Et}
\end{array}
\quad + \quad \text{Btz-SH} \quad \xrightarrow{\text{K}_2\text{CO}_3} \quad
\begin{array}{c}
\text{S-Btz} \\
\text{EtO}_2\text{C} \overset{}{\underset{}{}} \text{CO}_2\text{Et}
\end{array}
\qquad (4)
$$

(5) \qquad\qquad (3d)

$$3a-3d \quad + \quad R^1MgX \quad + \quad CuBr \quad \longrightarrow \quad \underset{CO_2Me}{\overset{R^1}{R}} \qquad (5)$$

(4a-4d)

$$\underset{S-Ar}{\overset{CO_2Me}{R}} \quad + \quad R^1Cu \quad \longrightarrow \quad \underset{S-Ar}{\overset{R^1}{R}}\overset{CO_2Me}{} \qquad (6)$$

sulphides of benzothiazole can coordinate with copper(I) halides and organocopper reagents, and as a result of coordination with organocopper reagents the sulphides react exclusively by an S_N2' mechanism. We thus believe that our observations cannot be attributed only to the better nucleofugal power of the Btz–S moiety or to the directive effects exerted by the ester group, but must also involve the coordinating ability of the leaving group. Thus cuprates, which are less "electrophilic" than the organocopper reagents, and therefore less susceptible to coordination by 3, upon reaction with these sulphides give a complex mixture of products derived from attack of the nucleophile on all the possible electrophilic centres of the sulphide ester. We conclude that the coordination effects exerted by the leaving group play an important role in dictating the regiochemistry of the reactions.

Experimental

IR spectra were recorded on a Perkin–Elmer 681 spectrophotometer. ^{1}H NMR spectra were recorded on Varian EM 360 and XL 200 instruments.

Preparation of methyl 2-(1-hydroxyalkyl)acrylate (2a–2c)

These intermediates were synthesized as described in ref. 1g, and isolated as colourless oils in 70–85% yield. In the ^{1}H NMR spectra of 2a–2c the two olefinic

Table 1

Reaction of sulphides 3 with organocopper reagents

Entry	Sulphide (R)	Grignard reagent (R^1)	Product (yield, %) [a]
1	3a (Me)	n-C_4H_9MgBr	4a (88)
2	3a	n-C_8H_{17}MgBr	4b (86)
3	3b (Me_2CH)	n-C_4H_9MgBr	4c (90)
4	3c (n-C_8H_{17})	n-C_4H_9MgBr	4d (95)
5	3c	Me_3SiCH$_2$MgCl	4e (85) [b]
6	3d (COOEt)	n-C_4H_9MgBr	4f (95)

[a] Yield of isolated products. [b] This reaction required 24 h of stirring at r.t. for completion.

protons give signals at δ (CDCl$_3$) 6.15 and 5.78 ppm as two singlets. ν_{max} (neat) 3485, 1723 and 1631 cm^{-1}.

General procedure for the preparation of methyl 3-alkyl-2'-(2-benzothiazolthio)acrylate (3a–3c)

To a stirred solution of benzothiazole disulphide (0.015 mol) and triphenylphosphine (0.015 mol) in 30 ml of toluene at room temperature was added the hydroxy ester (**2a–2c**) (0.015 mol); stirring was continued until the phosphine had disappeared (as shown by TLC, ether, 5/1, v/v). After the solvent had been evaporated off, the residue was chromatographed on a short column of silica gel (hexane/ether, 5/1, v/v) to give the sulphide esters in 75–90% yield as pale yellow liquids which show the following spectroscopic data:

CH$_3$CH=C(CH$_2$SBtz)CO$_2$Me (3a). δ (CDCl$_3$): 1.95 (d, 3H), 3.75 (s, 3H), 4.35 (s, 2H), 6.98 (q, 1H), 7.20–7.35 (m, 2H, ArH) and 7.58–7.92 (2H, m, ArH). ν_{max} (neat) 1724 and 1651 cm^{-1}. (Found: C, 55.8; H, 4.7; N, 4.9. C$_{13}$H$_{13}$NO$_2$S$_2$ calcd.: C, 55.89; H, 4.69; N, 5.01%).

(CH$_3$)$_2$CHCH=C(CH$_2$SBtz)CO$_2$Me (3b). δ (CDCl$_3$): 0.95 (d, 6H), 3.60 (s, 3H), 4.20 (s, 2H), 6.55 (d, 1H), 7.20–7.35 (m, 2H, ArH), 7.58–7.92 (m, 2H, ArH). ν_{max} (neat) 1719 and 1645 cm^{-1}. (Found: C, 58.5; H, 5.5; N, 4.5. C$_{15}$H$_{17}$NO$_2$S$_2$ calcd.: C, 58.60; H, 5.57; N, 4.55%).

C$_8$H$_{17}$CH=C(CH$_2$SBtz)CO$_2$Me (3c). δ (CDCl$_3$): 3.82 (s, 3H), 4.40 (s, 2H), 6.90 (t, 1H), 7.10–7.32 (m, 2H, ArH), 7.40–7.82 (m, 2H, ArH). (Found: C, 63.0; H, 7.3; N, 3.7. C$_{20}$H$_{27}$NO$_2$S$_2$ calcd.: C, 63.62; H, 7.20; N, 3.70%).

Synthesis of diethyl ester of bromomesaconic acid (5)

A solution of the diethyl ester of mesaconic acid (Aldrich) (0.026 mol), N-bromosuccinimide (0.026 mol) and a crystal of 2,2'-azobis(2-methylpropionitril) in 50 ml of dry carbon tetrachloride was refluxed for 4 h. The usual work-up ending in evaporation of the solvent left the crude bromoester (90% yield), which was used directly for the synthesis of **3d**. δ(CCl$_4$): 1.30 (t × t, 6H), 4.30 (q × q, 4H), 4.72 (s, 2H), 6.70 (s, 1H).

EtO$_2$CCH=C(CH$_2$S − Btz)CO$_2$Et (3d). To a stirred solution of the diethyl ester of bromomesaconic acid (0.03 mol) and 2-thiobenzothiazole (0.03 mol) in 30 ml of tetrahydrofuran (THF) at room temperature was added anhydrous potassium carbonate (0.03 mol). Stirring was continued until the bromoester had disappeared (as shown by TLC, hexane/ether, 5/2, v/v). The suspension was filtered and the solid washed with THF. The combined filtrate and washings were evaporated to a small volume and diluted with water. After acidification of the solution to pH at 4–5 the product was extracted twice with ether and flash-chromatographed on silica gel (hexane/ether, 3/1, v/v) to give **3d** in a 80% yield. M.p. 58°C. δ (CCl$_4$): 1.30 (t × t, 6H), 4.25 (q, 4H), 4.78 (s, 2H), 6.65 (s, 1H), 7.0–7.30 (m, 2H, ArH), 7.40–7.75 (m, 2H, ArH). (Found: C, 5.46; H, 4.8; N, 3.9. C$_{16}$H$_{17}$NO$_4$S$_2$ calcd.: C, 54.68; H, 4.87; N, 3.98%).

*General procedure for the preparation of acrylates **4a–4f** by reaction of **3a–3d** with organocopper reagents*

The Grignard reagent (0.02 mol) in THF was added dropwise at −25°C under nitrogen, to a suspension of 0.04 mol of CuBr in 15 ml of THF. After 30 min. the

sulphide (**3a**–**3d**) (0.01 mol) was added dropwise. During the addition a yellow precipitate of copper(I) benzothiazole-2-thiolate (Btz–SCu) was formed. After 30–60 min., depending on the sulphide, the suspension was filtered through a pad of silica gel, and evaporated to give the almost pure acrylate (**4a**–**4f**). Alternatively the suspension was chromatographed on a short column of silica gel (eluant hexane) to give pure acrylates, which were characterized by ^{1}H NMR spectroscopy.

Methyl 2-methylene-3-methylheptanoate (4a). δ (CDCl$_3$): 3.75 (s, 3H); 5.54 (s, 1H) and 6.20 (s, 1H). (Found: C, 70.4; H, 10.6. C$_{10}$H$_{18}$O$_2$ calcd.: C, 70.54; H, 10.65%).

Methyl 2-methylene-3-methylundecanoate (4b). δ (CDCl$_3$): 3.75 (s, 3H); 5.55 (s, 1H) and 6.20 (s, 1H). (Found: C, 74.2; H, 11.5. C$_{14}$H$_{26}$O$_2$ calcd.: C, 74.28; H, 11.58%).

Methyl 2-methylene-3-isopropylheptanoate (4c). δ (CCl$_4$): 3.55 (s, 3H); 5.20 (s, 1H); 5.95 (s, 1H). ν_{max} (CCl$_4$): 1723 and 1626 cm^{-1}. (Found: C, 72.6; H, 11.2. C$_{12}$H$_{22}$O$_2$ calcd.: C, 72.67; H, 11.20%).

Methyl 2-methylene-3-butylundecanoate (4d). δ (CDCl$_3$): 3.80 (s, 3H); 5.37 (s, 1H); 6.10 (s, 1H). (Found: C, 75.4; H, 12.6. C$_{17}$H$_{34}$O$_2$ calcd.: C, 75.50; H, 12.67%).

Methyl-2-methylene-3-(methylenetrimethylsilyl)heptanoate (4e) δ (CDCl$_3$, CHCl$_3$ as reference standard): −0.70 (d, 9H); 3.35 (bs, 3H); 5.04 (bs, 1H); 5.65 (bs, 1H). (Found: C, 68.3; H, 11.4. C$_{17}$H$_{34}$O$_2$Si calcd.: C, 68.39; H, 11.48%). ν_{max} (neat): 1724 and 1625 cm^{-1}.

Ethyl 2-methylene-3-carboxyethylheptanoate (4f). δ (CDCl$_3$): 3.30 (t, 1H); 4.10 (q × q, 4H); 5.68 (s, 1H); 6.32 (s, 1H). (Found: C, 64.3; H, 9.1. C$_{13}$H$_{22}$O$_4$ calcd.: C, 64.43; H, 9.15%).

Acknowledgement

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