

## Regioselective $\alpha$ -Addition of Organocopper Reagents to $\gamma$ -(Benzothiazole-2-thio)- $\alpha,\beta$ -enoates governed by Anchimeric Co-ordination. Synthesis of $\alpha$ -Alkylated- $\beta,\gamma$ -enoates

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The introduction of a leaving group, with co-ordination properties towards organocopper reagents, in the  $\gamma$ -position of  $\alpha,\beta$ -enoates, changes the regioselectivity of the nucleophilic addition process leading to  $\alpha$ -addition products.

Allylic electrophiles whose leaving groups have a co-ordination site for an organometallic nucleophile have been successfully utilized by us<sup>1</sup> to control the regioselectivity of the carbon-carbon cross-coupling reactions. The reagents of choice are allylic ethers or sulphides of benzothiazole whose heterocyclic nucleus acts both as leaving group and co-ordination centre.

To reverse the 'normal' regioselectivity found in the nucleophilic organocopper addition to  $\alpha,\beta$ -unsaturated enoates,<sup>2</sup> we synthesized  $\gamma$ -substituted- $\alpha,\beta$ -enoates of type (1), which have four positions suitable for attack by an

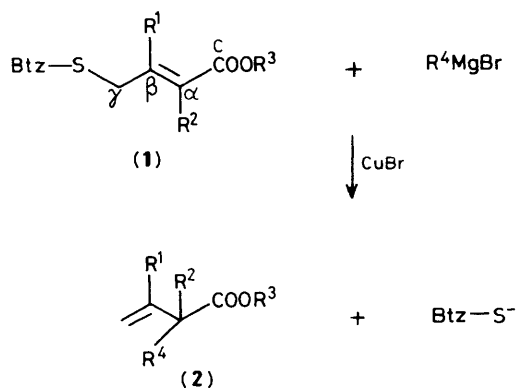
organometallic reagent. Two of these, ( $\alpha$  and  $\beta$ ), are subject to the directive effects exerted by the carbonyl group (normal addition), whereas attack at the  $\alpha$ - and  $\gamma$ -positions could be influenced by the leaving group linked to the  $\gamma$ -carbon. Previous reports show that  $\alpha,\beta$ -enones and enoates possessing a  $\gamma$ -oxygen or amide nitrogen, exhibit more complex reactivity towards cuprates than do simple  $\alpha,\beta$ -enones and enoates. The anionic leaving tendency for the  $\gamma$ -heteroatom is important. Either normal conjugate addition (with poorer  $\gamma$ -leaving groups) or reductive cleavage of the  $\gamma$ -heteroatom to form  $\beta,\gamma$ -unsaturated enones (with better  $\gamma$ -leaving groups) can

Table 1. Reaction<sup>a</sup> of benzothiazolyl sulphides with organocopper reagents.

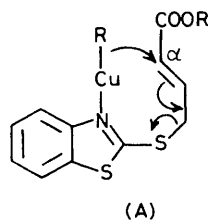
Entry	Sulphide <sup>b,c</sup>	Reagent	Product (% yield) <sup>d</sup>
1	(1a) R <sup>1</sup> = R <sup>2</sup> = H; R <sup>3</sup> = Me	Bu <sup>n</sup> MgBr	(2a) R <sup>4</sup> = Bu <sup>n</sup> (80)
2	(1b) R <sup>1</sup> = R <sup>2</sup> = H; R <sup>3</sup> = Et	„	(2b) R <sup>4</sup> = Bu <sup>n</sup> (83)
3	(1b)	C <sub>8</sub> H <sub>17</sub> MgBr	(2c) R <sup>4</sup> = C <sub>8</sub> H <sub>17</sub> (88)
4	(1d) R <sup>1</sup> = Me; R <sup>2</sup> = H; R <sup>3</sup> = Et	Bu <sup>n</sup> MgBr	(2d) R <sup>4</sup> = Bu <sup>n</sup> (78)
	Isomer ( <i>E</i> )	„	(2d) (82)
5	(1d) Isomer ( <i>Z</i> )	„	(2d) (82)
6	(1e) R <sup>1</sup> = R <sup>2</sup> = Me; R <sup>3</sup> = Et	„	(2e) R <sup>4</sup> = Bu <sup>n</sup> (85)

<sup>a</sup> Typical procedure: CuBr (0.03 mol) is added to (1) (0.01 mol) dissolved in dry tetrahydrofuran (THF) (20 ml) at  $-15^{\circ}\text{C}$ . To this suspension was added dropwise the Grignard reagent (0.02 mol) in THF. After 40–90 min, depending on the sulphide, the usual work up and silica gel flash chromatography (hexane-ether 5:1 as eluant) gives the pure  $\alpha$ -alkylated- $\beta,\gamma$ -unsaturated ester followed by 10–20% of the starting sulphide.

<sup>b</sup> Prepared by reaction of  $\gamma$ -bromounsaturated esters and 2-thiobenzothiazole. <sup>c</sup> Mixture of geometrical isomers. <sup>d</sup> Yields refer to isolated products and are unoptimized. Spectral data are consistent with the proposed structures.



Btz = Benzothiazol-2-yl



occur.<sup>2d,3</sup> We now report that allylic sulphides (1) undergo organocopper nucleophilic  $\alpha$ -addition<sup>†</sup> to give cleanly and in high yields  $\alpha$ -alkylated- $\beta,\gamma$ -unsaturated esters (2). The results are in Table 1.

This unprecedented reaction demonstrates that the directive effects exerted by the leaving group prevail over that exerted by the carbonyl group.  $\alpha$ -Alkylation (entry 6) or geometrical isomerism (entries 4 and 5) do not affect the regiochemistry of the reaction. A rationale which accounts for the observed selectivity should involve co-ordination

<sup>†</sup> This reaction can be considered a nucleophilic substitution ( $S_N2'$ ) which occurs on the  $\gamma$ -carbon with respect to the leaving group.

phenomena. For steric reasons, the copper reagent being co-ordinated by the sulphide, the nucleophilic attack should occur exclusively on the  $\alpha$ -carbon to the carbonyl as depicted in (A). This hypothesis is supported by the absence of reaction products due to  $\beta$ - or  $\gamma$ -attack. These reactions could be a useful alternative for alkylation of unsaturated esters, since the alkylation of enolate anions derived from  $\alpha,\beta$ -unsaturated esters is often contaminated by bis alkylation products.<sup>4</sup>

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