

Regioreversed Nucleophilic Substitution of 2-(Allyloxy)benzothiazole by Allylic Grignard Reagents. A Regioselective Synthesis of 1,5-Dienes

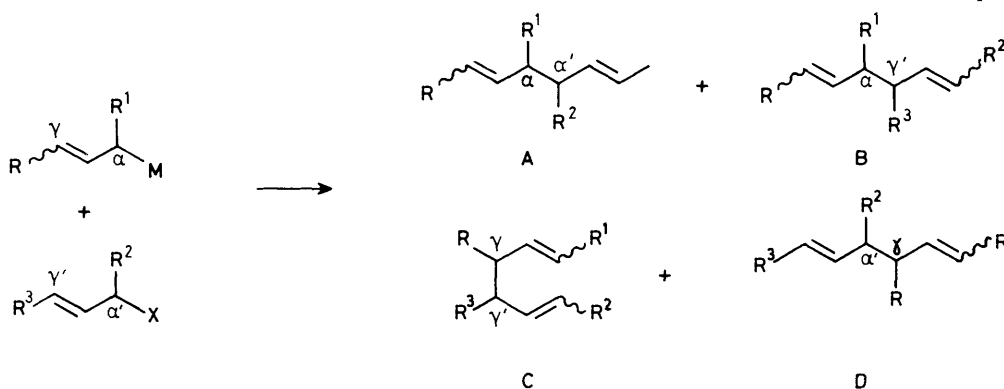
Vincenzo Calo,* Luigi Lopez, and Giannangelo Pesce

CNR Centro di Studio sulle Metodologie Innovative di Sintesi Organiche, c/o Dipartimento di Chimica, Via Amendola 173, 70126 Bari, Italy

2-(Allyloxy)benzothiazoles react with allylic organomagnesium compounds in the presence of copper bromide to give 1,5-dienes. The C–C coupling occurs almost exclusively in a head-to-tail fashion. Contrary to this the same electrophiles, when complexed with copper(I) bromide before the addition of the allylic Grignard reagents, give only 1,5-dienes derived from a head-to-head coupling process. The change in the selectivity is probably due to the co-ordinative effects of the substrates towards the organometallic species.

The coupling of allylic electrophiles with allylic carbon nucleophiles to give 1,5-dienes is very important since a number of terpenoids and other natural products contain the 1,5-diene unit. When ordinary allylmetal derivatives are used, regiochemical, stereochemical, and cross-homo scrambling reactions tend to accompany the desired reaction.¹ These difficulties arise because of the ambident character of allylic nucleophiles² and allylic electrophiles can react by S_N2 or S_N2' mechanisms³ (Scheme 1).

amounts of CuBr; the reaction rate strictly being related to the CuBr concentration. The Grignard reagent is added to a solution of (2) or (3) in THF immediately after the addition of the copper salt. In this manner prolonged contact between the allylic ether and CuBr is avoided. This procedure is crucial in dictating the regioselectivity of the process. In fact, depending on this contact time, before the addition of the Grignard reagent, we observed a variation in the regioselectivity with concomitant formation of head-to-head coupling products. For

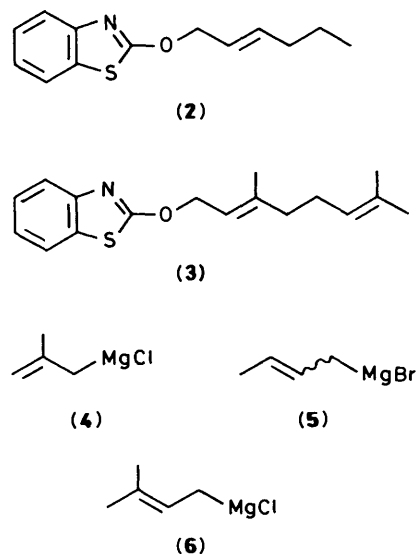


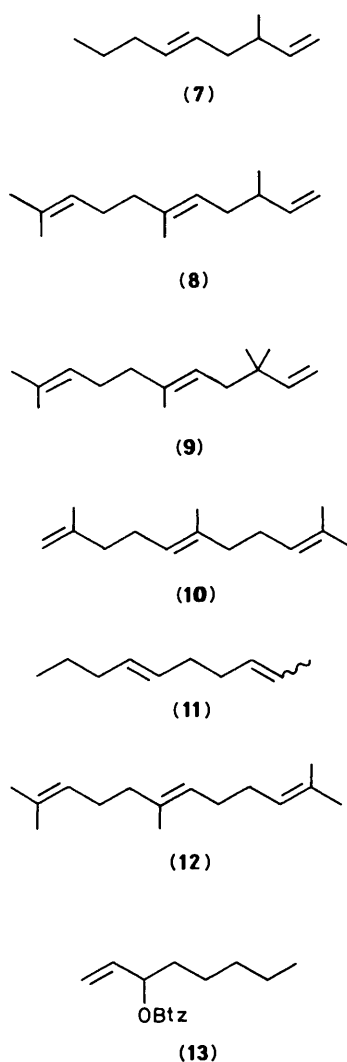
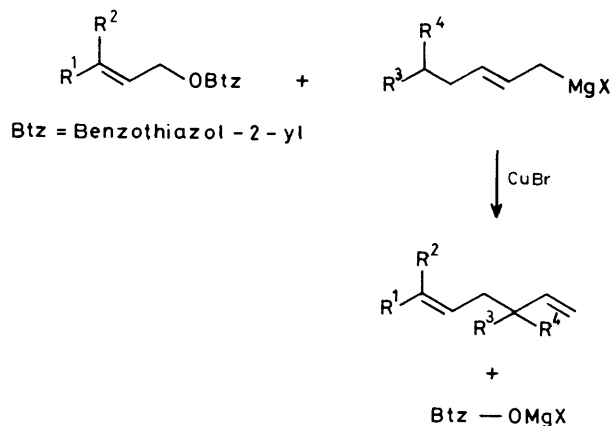
Scheme 1. X = Halogen, OAc, SO₂R, etc.; M = Mg, Li, Cu, B(R)₃, Zn, Sn

These difficulties can be circumvented in some cases by the use of α -thioallyl-lithium (Biellmann method)⁴ or metallated allylic sulphones reported by Grieco.⁵ Both methods require, however, reductive removal of the sulphide or sulphone moiety. The alternative use of α -alkoxyallyl-lithiums does not offer a better solution to the problem.⁶

In a preliminary paper,⁷ we showed that the synthesis of 1,5-dienes can be accomplished with a high degree of regioselectivity by using allylic ethers of benzothiazole as electrophiles.⁸ To avoid steric complications we chose, in the first instance, two primary allylic ethers (2) and (3), and three organomagnesium compounds (4)–(6).

Of these nucleophiles, (5) is known to react with electrophiles preferentially at the internal C- γ , whereas (6) reacts at C- α probably for steric reasons.⁹ Contrary to this, addition of (5) or (6) to the electrophiles (2) or (3) in the presence of CuBr in tetrahydrofuran (THF) at 0 °C, affords exclusively head-to-tail coupling products (Scheme 2). Thus the reaction of (2) and (3) with (5) gives (7) and (8), respectively, whereas that of (3) with (6) gives (9). Compound (10) arises from the reaction of (3) with (4). All reactions occur rapidly in the presence of stoichiometric





Scheme 3.

which proved to be a Cu(I)-complex of (2), similar to those of other different 2-(allyloxy)benzothiazoles already prepared by us.¹⁰ This complex reacts with (5) to give (11) almost exclusively. Similar behaviour is observed in the reaction of (3) with (6). A contact time of 2 h between (3) and CuBr prior to the addition of (6) afforded a mixture of (9) and (12), ratio 20:80, respectively.

We did not, however, succeed in isolating a CuBr-complex of (3) in order to obtain (12) exclusively *via* the reaction of this complex with (6). A less complicated picture is offered by the reaction of a secondary allylic ether such as (13). In fact, (13) reacts only in a tail-to-head fashion according to the Scheme 3.

Besides regioselectivity, these reactions show a high degree of stereoselectivity since (15) and (16) proved to be *trans* isomers. However, owing to the configurational instability of (5), compound (14) is obtained as a 1:1 mixture of *trans-trans* and *cis-trans* isomers. The secondary allylic ether (13) forms the copper complex easily but surprisingly, this complex reacts with (4)–(6) to give the same reaction products derived from the uncomplexed ethers. This peculiarity of secondary allylic ethers to give, upon reaction with Grignard reagent, only tail-to-head products, was used for the synthesis of farnesol benzyl ether (19). Thus the allylic ether (18) prepared from (17), in turn derived from geranyl benzyl ether, using known procedures,¹¹ afforded upon reaction with (6) in the presence of CuBr, the farnesyl ether (19) as a 1:1 *cis:trans* mixture.

Unlike the reaction of (13) with (6), migration of the terminal double bond in this case occurs without stereoselectivity and can be ascribed to the presence of the methyl group on the double bond. Interestingly, prolonged contact (20 h) of CuBr with (18) does not afford a complex, as occurs with (2) or (13), but the colour of the solution turns from pale yellow to deep green with partial disappearance of CuBr. The addition of the Grignard reagent (6) to this solution gives compound (20) in 40% yield in addition to (19).

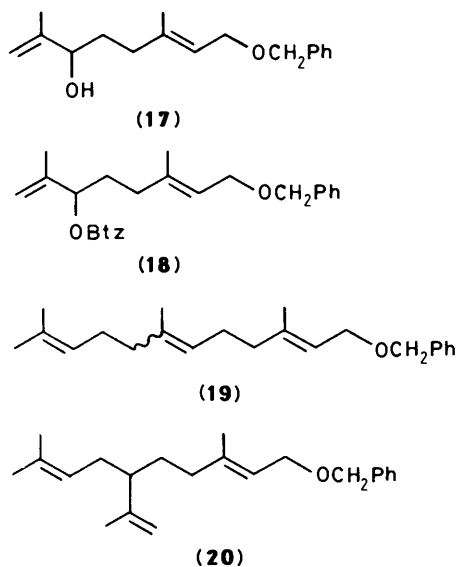
The benzothiazole nucleus linked to the allylic moiety must be present to obtain the observed regioselectivity in the C–C coupling process. In fact other allylic ethers^{12–14} react with poor regio- and stereo-selectivity with organomagnesium compounds in the presence of copper(I) halides, the $S_N2:S_N2'$ ratio being generally a sensitive function of steric effects in the ether.^{13,15} Therefore the high selectivity found by us could be ascribed to the co-ordination experienced by the substrates towards the organometallic species.

In conclusion, although some mechanistic aspects require further experiments, the use of these allylic ethers allows a regioselective synthesis of 1,5-dienes. Moreover, the same primary ether depending on the reaction conditions can lead to two regioisomeric dienes. The application of this methodology to the synthesis of biologically active terpenes is under investigation.

example, a reaction with a contact time of 20 min between CuBr and (2) prior to the addition of (5), affords a 20% of the linear product (11) in addition to compound (7). In an attempt to isolate the reaction intermediate responsible for this result, we found that on the mixing CuBr with (2) in THF, the copper salt slowly disappeared to give, upon filtration, a light green solid

Experimental

I.r. spectra were recorded on a Perkin-Elmer 681 spectrophotometer. ^1H N.m.r. spectra were recorded on Varian EM 360, HA 100, and XL 200 instruments. The regio- and stereochemical purity of the reaction products was tested by g.l.c. on HP 5830 A (10% SP 2100 on 100–120 Supelcoport 6 ft) and on



DANI 3800 HR instruments (SE30; 30 m; 0.25 i.d.). Yields refer to isolated products.

Preparation of 2-(Allyloxy)benzothiazoles.—The ethers (2), (3), (13), and (18) were synthesized starting from 2-chlorobenzothiazole and the appropriate potassium allyloxide in 70–90% yield as previously reported.^{7a}

(2E)-2-Hex-2-en-1-yloxybenzothiazole (2).—Colourless oil; $\delta(\text{CCl}_4)$ 0.85 (3 H, t), 1.10–1.40 (2 H, m), 1.80–2.20 (2 H, m), 4.85 (2 H, d), 5.55–5.75 (2 H, m), 6.90–7.24 (2 H, m, ArH), and 7.35–7.55 (2 H, m, ArH); $\nu_{\text{max}}(\text{neat})$ 1 672 and 974 cm^{-1} (Found: C, 66.9; H, 6.4; N, 5.9. $\text{C}_{13}\text{H}_{15}\text{NOS}$ requires C, 66.95; H, 6.43; N, 6.00%).

2-Oct-1-en-3-yloxybenzothiazole (13). Colourless oil; $\delta(\text{CCl}_4)$ 0.95 (3 H, t), 1.64–1.92 (6 H, m), 5.05–5.95 (4 H, m), 6.90–7.24 (2 H, m, ArH), and 7.35–7.55 (2 H, m, ArH); $\nu_{\text{max}}(\text{CCl}_4)$ 3 080, 990, and 910 cm^{-1} (Found: C, 68.95; H, 7.3; N, 5.3. $\text{C}_{15}\text{H}_{19}\text{NOS}$ requires C, 68.96; H, 7.27; N, 5.36%).

(2E)-2-(1-Benzoyloxy-3,7-dimethylocta-2,7-dien-6-yloxy)-benzothiazole (18). This ether was prepared by the usual procedure using the alcohol (17);¹¹ $\delta(\text{CCl}_4)$ 1.58 (3 H, s), 1.62 (3 H, s), 1.98 (2 H, br t), 3.80 (2 H, d), 4.25 (2 H, s), 4.80 and 4.90 (two s, 2 H, $\text{C}=\text{CH}_2$), 5.20 (1 H, br t), 5.42 (1 H, br t), 6.75–7.10 (7 H, m, ArH), and 7.20–7.40 (2 H, m, ArH). $\nu_{\text{max}}(\text{neat})$ 1 653 and 904 cm^{-1} (Found: C, 73.2; H, 6.8; N, 3.50. $\text{C}_{24}\text{H}_{27}\text{NO}_2\text{S}$ requires C, 73.28; H, 6.87; N, 3.55%); colourless oil; 80% yield starting from (17).

General Procedure for the Reaction of Allyl Grignard Reagents with Primary Benzothiazole Allylic Ethers to give Head-to-tail Products.—CuBr (0.01 mol) was added to the allylic ether (0.01 mol) dissolved in dry tetrahydrofuran (THF) at 0°C without stirring under nitrogen. To this suspension was added rapidly, with a syringe and with stirring, the Grignard reagent (0.02 mol) in THF. After 30 min, the resulting black solution was evaporated to a small volume and the residue was flash chromatographed (silica gel; eluant hexane) to give the diene followed by the unchanged allylic ether and 2-hydroxybenzothiazole. According to the above procedure the following compounds were prepared.

(5E)-3-Methylnona-1,5-diene (7). Colourless oil; 80%; $\delta_{\text{H}}(\text{CDCl}_3)$ 0.88 (3 H, t), 0.96 (2 H, d), 1.25–1.42 (2 H, m), 1.94–2.04 (4 H, m), 2.10–2.26 (2 H, m), 4.88–5.04 (2 H, m, $\text{CH}=\text{CH}_2$),

5.36–5.46 (2 H, m, $\text{CH}=\text{CH}$), and 5.68–5.86 (1 H, m, $\text{CH}=\text{CH}_2$); $\nu_{\text{max}}(\text{neat})$ 3 079, 1 641, 996, and 913 cm^{-1} (Found: C, 87.0; H, 13.0. $\text{C}_{10}\text{H}_{18}$ requires C, 86.96; H, 13.04%).

(5E)-3,6,10-Trimethylundeca-1,5,9-triene (8). Colourless oil; 70% yield obtained from the reaction of (3) with (5); $\delta(\text{CDCl}_3)$ 0.86 (3 H, d), 1.55 (6 H, s), 1.63 (3 H, s), 4.90–5.30 (4 H, m, $\text{C}=\text{CH}$ and $\text{CH}=\text{CH}_2$), and 5.78 (1 H, m). $\nu_{\text{max}}(\text{neat})$ 1 641, 996, and 913 cm^{-1} (Found: C, 87.5; H, 12.6. $\text{C}_{14}\text{H}_{24}$ requires C, 87.50; H, 12.50%).

(5E)-3,3,6,10-Tetramethylundeca-1,5,9-triene (9). 70% Yield from the reaction of (3) with (6); $\delta(\text{CDCl}_3)$ 0.90 (6 H, s), 1.52 (3 H, s), 1.80–2.20 (6 H, m), 4.60–5.20 (m, 4 H, $\text{C}=\text{CH}$ and $\text{CH}=\text{CH}_2$), and 5.40–5.90 (1 H, m, $\text{CH}=\text{CH}_2$); $\nu_{\text{max}}(\text{neat})$ 1 641, 996, and 913 cm^{-1} ($\text{CH}=\text{CH}_2$) (Found: C, 87.3; H, 12.6. $\text{C}_{15}\text{H}_{26}$ requires C, 87.38; H, 12.62%).

(5E)-2,6,10-Trimethylundeca-1,5,9-triene (10). 60% Yield from the reaction of (3) with (4); $\delta(\text{CDCl}_3)$ 1.60 (9 H, s), 1.68 (s, 3 H), 1.90–2.15 (8 H, m), 4.65 (2 H, s, $\text{C}=\text{CH}_2$) and 5.10 (2 H, br s); $\nu_{\text{max}}(\text{neat})$ 3 083, 1 671, 1 640, and 892 cm^{-1} (Found: C, 87.5; H, 12.6. $\text{C}_{14}\text{H}_{24}$ requires C, 87.50; H, 12.50%).

2-Hex-2-en-1-yloxybenzothiazole-CuBr Complex.—To 2-hex-2-en-1-yloxybenzothiazole (2) (0.46 g, 1 mol equiv.) dissolved in toluene or THF (25 ml) was added CuBr (0.28 g, 1 mol equiv.). This suspension was stirred at room temperature for 70 h until the disappearance of CuBr was complete. The light grey precipitate which was almost insoluble in organic solvents, was filtered off, washed with toluene, and dried under reduced pressure, m.p. 125–130°C (decomp.); $\nu_{\text{max}}(\text{KBr})$ 1 540, 1 505 ($\text{C}=\text{N}$), and 930 ($\text{C}=\text{C}$) cm^{-1} (Found: C, 41.0; H, 4.2; N, 3.8; Cu, 17.2. $\text{C}_{13}\text{H}_{15}\text{BrCuNOS}$ requires C, 41.44; H, 4.01; N, 3.71; Cu, 16.86%).

The free ligand (2) showed bands at 1 670, 1 560, 1 530, and 965 cm^{-1} . The i.r. spectrum of the complex compared with that of the free ligand shows both a lowering of $\text{C}=\text{C}$ and $\text{C}=\text{N}$ stretching frequencies. These data imply, although not adequately, that CuBr was complexed by the allylic ether.^{10,15}

(Z,E)- and (E,E)-Dodeca-2,6-diene (14). These compounds were obtained as 2:1 mixture of geometrical isomers by reaction of the organomagnesium (5) with (13) under the usual conditions (85% yield); $\delta(\text{CDCl}_3)$ 0.90 (3 H, t), 1.30–1.39 (6 H, m), 1.60 (3 H, d), 1.99–2.10 (6 H, m), and 5.38–5.42 (m, 4 H, $\text{CH}=\text{CH}$); $\nu_{\text{max}}(\text{neat})$ 968 and 702 cm^{-1} (Found: C, 86.7; H, 13.3. $\text{C}_{12}\text{H}_{22}$ requires C, 86.75; H, 13.25%).

(6E)-2-Methyldodeca-2,6-diene (15). 75% Yield; $\delta(\text{CCl}_4)$ 0.85 (3 H, t), 1.35 (6 H, br s), 1.55 (3 H, s), 1.65 (3 H, s), 1.95 (6 H, br s), 4.95 (1 H, br s), and 5.10–5.40 (2 H, m). $\nu_{\text{max}}(\text{neat})$ 1 672, 969, and 831 cm^{-1} (Found: C, 86.60; H, 13.4. $\text{C}_{13}\text{H}_{24}$ requires C, 86.70; H, 13.30%).

(5E)-2-Methylundeca-1,5-diene (16). The reaction of (4) with (13) gave (16) in 80% yield as a colourless oil; $\delta(\text{CDCl}_3)$ 0.82 (3 H, t), 1.22 (6 H, br s), 1.65 (3 H, s), 2.02 (6 H, br s), 4.65 (2 H, s), and 5.20–5.48 (2 H, m); $\nu_{\text{max}}(\text{neat})$ 1 650, 969, and 889 cm^{-1} (Found: C, 86.7; H, 13.3. $\text{C}_{12}\text{H}_{22}$ requires C, 86.75; H, 13.25%).

Farnesyl benzyl ether (19). From the reaction of (18) with (6), the ether (19) was isolated in 80% yield, after flash chromatography (eluant: hexane), as a 1:1 mixture of geometrical isomers at C-6. This product proved to be identical with a specimen prepared from commercial farnesol (Fluka); $\delta(\text{CDCl}_3)$ 1.58 (12 H, s), 2.00 (8 H, br s), 3.90 (2 H, d), 4.35 (2 H, s), 4.98 (2 H, br s), 5.30 (1 H, br t), and 7.15 (5 H, s).

The change in the regioselectivity of the C–C coupling process was due to the complexation of allylic ethers by CuBr.

Reaction of (2)·CuBr Complex with (5).—To a suspension of (2)·CuBr complex (0.97 g, 1 mol equiv.) in dry THF (15 ml) was added, at 0°C under nitrogen and with stirring, a solution of but-2-enylmagnesium bromide (5) (0.73M; 4 ml, 1 mol equiv.).

After 30 min, a gas chromatogram of the reaction mixture showed the formation of (7) and (11) in a ratio 7:93, respectively, the latter as a mixture of geometrical isomers (*Z,E:E,E* = 1:1); $\delta(\text{CDCl}_3)$ 0.88 (3 H, t), 1.60 (3 H, br d), and 5.30–5.58 (4 H, m); $\nu_{\text{max}}(\text{neat})$ 1 657, 968, and 702 cm^{-1} .

2,6,11-Trimethyldodeca-2,6,10-triene (12).—To compound (3) 0.6 g (1 mol equiv.) dissolved in dry THF (20 ml) was added CuBr (0.9 g, 3 mol equiv.). The resulting suspension was stirred at room temperature under nitrogen for 2 h during which time the colour of the suspension changed from light yellow to dark green. The addition of (6) (1 mol equiv.) in THF to this suspension, cooled to -30°C , gave, after the usual work-up, a mixture of (9) and (12), ratio 20:80, respectively, in an overall yield of 70%. The latter had the following spectral properties: $\delta(\text{CDCl}_3)$ 1.56 (12 H, s), 1.62 (3 H, s), 1.80–2.20 (8 H, m), and 5.10 (3 H, br s).

Benzyl Ether of 6-Isopropenyl-3,9-dimethyldeca-2,8-dien-1-ol (20).—To compound (18) (1 g, 1 mol equiv.) dissolved in THF (20 ml) was added CuBr (0.33 g, 3 mol equiv.). The resulting suspension was stirred at room temperature for 24 h. To the resulting dark green solution, cooled at -30°C , was added dropwise, the Grignard reagent (6) (1 mol equiv.). After 30 min, the usual work-up and flash chromatography gave a mixture of (20) and (19) in a 40:60 ratio (overall yield 70%). The ^1H n.m.r. spectrum of this mixture showed in addition to the frequencies of the farnesyl ether (19), lines ascribable to (20): $\delta(\text{CCl}_4)$ 5.18 (br t, 1 H, 2-H), 4.90 (br s, 1 H, 8-H), 4.55 (2 H, s, MeCCH_2), 3.80 (2 H, d, 1- H_2), and 2.55 (1 H, br s, 6-H).

Acknowledgements

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