

STEREOSPECIFIC SYNTHESIS OF ALKENYL SULPHIDES BY CROSS-COUPLING REACTIONS OF SECONDARY ALKYL GRIGNARD REAGENTS WITH *Z*- OR *E*-1-BROMO-2-PHENYLTHIOETHENE IN THE PRESENCE OF TRANSITION METAL CATALYSTS

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Summary

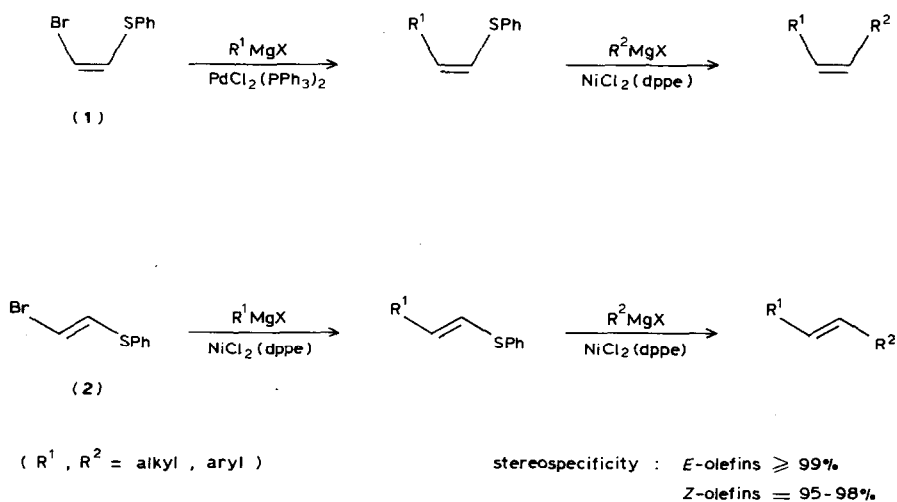
Z- and *E*-1-bromo-2-phenylthioethenes were cross-coupled stereospecifically with *s*-alkyl Grignard reagents in the presence of a series of Ni^{II} , Pd^{II} or Fe^{III} catalysts with the aim of finding a catalyst which would not cause *s*-alkyl $\rightarrow$ *n*-alkyl isomerization. With $\text{PdCl}_2(\text{dppf})$ (dppf = 1,1'-bis(diphenylphosphino)ferrocene) and $\text{NiCl}_2(\text{dppe})$ (dppe = 1,2-bis(diphenylphosphino)ethane) there was still some isomerization contribution, but it was completely suppressed by using iron(III) catalysts.

Introduction

We have described a stereospecific procedure leading to *Z*- or *E*-1,2-disubstituted ethenes [1]. The method is based on sequential coupling reactions of Grignard reagents with the readily available *Z*- or *E*-1-bromo-2-phenylthioethene [2] in the presence of Ni^{II} or Pd^{II} catalysts, as in the following scheme (Scheme 1).

The procedure was also applied to the synthesis of a series of mono-olefinic pheromones (1,2-dialkylethenes or alkenyl acetates) or of their precursors [3]. As a result, a comparison with classical methodologies for olefin synthesis (i.e. Wittig reaction and acetylenes hydrogenation) led us to the conclusion that the sequential cross-coupling procedure can be regarded as one of the most useful methods for the synthesis of alkyl- or aryl-substituted ethenes. The approach is limited by the availability of Grignard reagents, but this is a relatively minor limitation in view of the rapidly expanding range of such reagents [4].

In previous investigations [1,3] we used Grignard reagents derived from *n*-alkyl halides, aryl halides or protected ω -halohydrins. In one case [1] a secondary group was used (i.e. 1-phenylethyl) without significant secondary $\rightarrow$ primary group isomerization. However, this kind of isomerization is known to occur frequently in



SCHEME 1

cross-coupling reactions involving simple *s*-alkyl group such as isopropyl or *s*-butyl groups [5] and so in order to extend the potential of our olefin synthesis we decided to investigate the isomerization in the cross-coupling reactions. In particular, since a variety of catalysts can be used for cross-coupling reactions with alkenyl halides (the first step of our procedure, see Scheme 1), whereas cross-coupling with alkenyl sulphides (the second step of our procedure, see Scheme 1) appears to require the use of nickel catalysts, we focused our attention on the first cross-coupling reaction. It is noteworthy that this reaction, besides representing a crucial step of our procedure, is also important in itself since it provides a convenient route to alkenyl sulphides, a class of synthetically important compounds [6]. We now present the results of our investigation of the cross-coupling reactions of *Z*- or *E*-1-bromo-2-phenylthioethene with Grignard reagents involving two typical *s*-alkyl groups (*i.e.* isopropyl and *s*-butyl) in the presence of various transition metal catalysts.

Results and discussion

The $\text{PdCl}_2(\text{PPh}_3)_2$ catalyzed reactions of *Z*-1-bromo-2-phenylthioethene (1) with isopropylmagnesium chloride in THF or ether (see Table 1, entries 1–3) gave a relatively large amount of product 4 derived from *s*-alkyl $\rightarrow$ *n*-alkyl isomerization together with the product of reduction 5. The use of $\text{PdCl}_2(\text{dppf})$ as a catalyst in the reactions in ether was found to reduce the extent of isomerization to 6% (entry 4). This catalyst has been reported by Kumada and coworkers [7] to be the most selective catalyst in cross-coupling reactions. In our system it appears that $\text{NiCl}_2(\text{dppe})$ can give comparable results (entry 6). The *E*-isomer 2 gave a small amount of *n*-propyl product with $\text{PdCl}_2(\text{dppf})$, whereas such a product was not detected in the reactions catalyzed by $\text{NiCl}_2(\text{dppe})$ (entries 7 and 8). For both isomers the cross-coupling leading to the isopropyl product was found to occur with the usual [1,3] high degree of retention of configuration.

The reactions of the *Z*-isomer with *s*-butylmagnesium chloride (entries 9–11) were found to be less influenced by the *s*-alkyl $\rightarrow$ *n*-alkyl group isomerization, the

n-butyl product being a 4–6% of the total. This product was completely absent when $\text{PdCl}_2(\text{dppf})$ in ether was used as a catalyst. The isomerization was also completely absent in the reactions of the *E*-isomer (entries 12 and 13). The stereospecificity of the cross-coupling leading to the s-butyl product was higher in the reactions of the latter isomer than in the reactions of the *Z*-counterpart.

It is also noteworthy that the isomerization led to n-alkyl products with retained configuration and that the process was frequently accompanied by reductive dehalogenation. These results are in agreement with the mechanistic scheme suggested to account for the side reactions accompanying the cross-coupling of secondary alkyl reagents [7,8].

The reactions of compounds **1** and **2** with n-alkyl Grignard reagents (n-propyl and n-butyl) were found to be effectively catalyzed by iron(III) compounds such as FeCl_3 , $\text{Fe}(\text{acac})_3$ (acac = acetylacetonide), $\text{Fe}(\text{DBM})_3$ (DBM = dibenzoylmethide) and $\text{Fe}(\text{DPM})_3$ (DPM = dipivaloylmethide). Isolated yields of 70–80% for both isomers were obtained using the last catalyst. Therefore, since in investigations with other substrates these catalysts gave good selectivities in the cross-coupling process [9], we used them in the reactions of compounds **1** and **2** with isopropyl- and s-butyl-Grignard reagents. The isomerization was completely suppressed by using $\text{Fe}(\text{DBM})_3$ and $\text{Fe}(\text{DPM})_3$ as catalysts with both isomers (**1** or **2**) and both reagents (isopropyl or s-butyl) (entries 14–21). Furthermore, there was a quite high retention of configuration (see entries 15, 17, and 20).

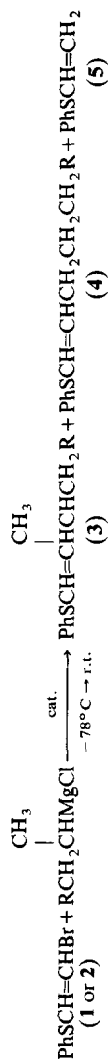
In conclusion, the present investigation has shown that with a suitable choice of the catalyst it is possible to perform stereospecific cross-coupling reactions using compounds **1** or **2** as substrates and secondary alkyl Grignard reagents in THF or ether, without problems arising from the isomerization process. In view of the possibility of converting the alkenyl sulphides **3** into a variety of 1,2-disubstituted ethenes, the results further confirm the value of our approach to the stereospecific synthesis of such compounds.

Experimental

All reactions and transfers involving organometallic compounds were carried out under nitrogen. Tetrahydrofuran (THF) and diethyl ether were purified by two distillations from Na wire under nitrogen. *Z*- and *E*-1-bromo-2-phenylthioethene were prepared by known procedures [2,3]. The purified reaction products were characterized by their ^1H NMR spectra, recorded on Varian EM 390 (90 MHz) spectrometer in CCl_4 with tetramethylsilane as an internal standard, and their mass spectra determined with a Kratos M60 (70 eV) spectrometer. Boiling points are uncorrected. The composition of the isomeric products of the reaction mixture was performed by GLC analysis on a Dani 3800 capillary column apparatus, using a fused silica capillary column (30 m $\times$ 0.25 mm i.d., carrier He, 0.6 bar) coated with SE 30 as a stationary phase. $\text{NiCl}_2(\text{dppe})$, $\text{PdCl}_2(\text{PPh}_3)_2$, $\text{Fe}(\text{acac})_3$, $\text{Fe}(\text{DPM})_3$ and FeCl_3 were commercial products, but $\text{Fe}(\text{DBM})_3$ [9b] and $\text{PdCl}_2(\text{dppf})$ [7b] were made by literature procedures.

Coupling reactions

The usual procedure [1,3] was followed in the Ni^{II} and Pd^{II} catalyzed cross-coupling reactions in THF or in ether, i.e. addition of Grignard reagent to a stirred

TABLE 1. CROSS-COUPLING REACTIONS OF *s*-ALKYL GRIGNARD REAGENTS WITH *Z*- OR *E*-1-BROMO-2-PHENYLTHIOETHENE^a

Entry	Substrate configuration	Catalyst	Solvent	R	Reaction time (h)	Yield of 3 ^b %	Composition of the product mixture ^c				
							3	4		5	
							Z	E	Z	E	
1	Z	PdCl ₂ (PPh ₃) ₂	THF	H	14	—	48.2	6.9	31.4	—	13.5
2	Z	PdCl ₂ (PPh ₃) ₂	ether	H	6	—	29.7	—	65.7	—	4.6
3	Z	PdCl ₂ (PPh ₃) ₂ ^d	THF	H	14	—	38.9	6.4	38.0	—	16.7
4	Z	PdCl ₂ (dppf)	ether	H	12	(57)	94	—	6	—	—
5	Z	PdCl ₂ (dppf)	THF	H	3	—	18	—	18	—	64
6	Z	NiCl ₂ (dppe)	THF	H	12	(67)	89.8	3.2	2.5	—	4.5
7	E	PdCl ₂ (dppf)	ether	H	12	(74)	—	94	—	6	—
8	E	NiCl ₂ (dppe)	THF	H	5	(86)	1.8	98.2	—	—	—
9	Z	PdCl ₂ (PPh ₃) ₂	THF	CH ₃	14	—	84.4	9.4	6.2	—	—
10	Z	PdCl ₂ (dppf)	ether	CH ₃	12	(31)	84.4	9.4	—	—	6.2
11	Z	NiCl ₂ (dppe)	THF	CH ₃	14	(47)	84.5	10.1	4.1	—	1.3
12	E	PdCl ₂ (dppf)	ether	CH ₃	12	(79)	1.4	98.6	—	—	—
13	E	NiCl ₂ (dppe)	THF	CH ₃	5	(84)	3	97	—	—	—
14	Z	Fe(DBM) ₃	THF	H	8	50	91	3	—	—	6
15	Z	Fe(DPM) ₃	THF	H	8	(65) 55	100	—	—	—	—
16	E	Fe(DBM) ₃	THF	H	12	60	5.7	94.3	—	—	—
17	E	Fe(DPM) ₃	THF	H	12	80	—	100	—	—	—
18	Z	Fe(DBM) ₃	THF	CH ₃	9	45	96.2	2.6	—	—	1.2
19	Z	Fe(DPM) ₃	THF	CH ₃	9	(51) 46	95.5	3.3	—	—	1.2
20	E	Fe(DBM) ₃	THF	CH ₃	12	76	—	100	—	—	—
21	E	Fe(DPM) ₃	THF	CH ₃	12	71	5	95	—	—	—

^a A 2/1 molar ratio of Grignard reagent to substrate was used (but a 1.1/1 ratio for entries 6, 8, 11 and 13). 0.66 mol% of iron(III), 3 mol% of Ni^{II} or Pd^{II} catalysts with respect to the substrate were used. ^b Yields of isolated purified products; yields determined by GLC analysis are given in parentheses. ^c The product distribution refers to the composition of the reaction mixture as determined by GLC on capillary columns. ^d Reaction carried out by the procedure used with the Fe catalyst (see text).

suspension of catalyst and substrate. In one experiment (entry 3) we adopted the procedure used for the Fe^{III} catalyzed reactions and described below.

The iron complex (0.033 mmol) was placed in a dry, nitrogen-flushed, 100 ml flask equipped with a magnetic stirrer, then dissolved in 5 ml of dry THF. The solution was cooled to -78°C and a THF solution of the Grignard reagent (primary or secondary) (10 mmol) was added. After 15 min a solution of the halide (1.08 g, 5 mmol) in 35 ml of THF was slowly added dropwise. The mixture was stirred at -78°C for 0.5 h, and then allowed to warm to room temperature. After being stirred for the time specified in the Table the mixture was quenched with dilute HCl and extracted with ether. The combined organic extracts were washed with water, dried (Na_2SO_4), and concentrated. The residue was taken up in a minimum of petroleum ether and passed through a Florisil column, with petroleum ether as eluant, in order to remove the iron salts. The solvent was removed in vacuo and the products were purified by distillation.

The following products were identified from published spectral and physical data: *Z*- and *E*-3-methyl-but-1-en-1-yl phenyl sulphide [10], *Z*-hex-1-en-1-yl phenyl sulphide [11], *E*-hex-1-en-1-yl phenyl sulphide [12], and phenyl vinyl sulphide [13].

Spectral data (MS and ^1H NMR) of other coupling products are given below.

Z-pent-1-en-1-yl phenyl sulphide [14]. b.p. $77-78^\circ\text{C}/0.1$ Torr; MS (70 eV): 178 (M^+) (100%), 149 (81), 110 (5), 109 (14). ^1H NMR: δ 7.4–6.9 (m, 5H); 6.25–5.50 (m, 2H); 2.4–2.0 (m, 2H); 1.7–1.2 (m, 2H) and 1.2–0.8 (m, 3H) ppm.

E-pent-1-en-1-yl phenyl sulphide [14]. b.p. $80-81^\circ\text{C}/0.1$ Torr; MS (70 eV): 178 (M^+) (73%), 149 (100), 110 (30), 109 (22). ^1H NMR: δ 7.5–6.9 (m, 5H); 6.3–5.5 (m, 2H); 2.35–1.8 (m, 2H); 1.7–1.2 (m, 2H) and 1.15–0.80 (m, 3H) ppm.

Z-3-methyl-pent-1-en-1-yl phenyl sulphide. b.p. $74-75^\circ\text{C}/0.1$ Torr; MS (70 eV): 192 (M^+) (58%), 163 (100), 135 (25), 110 (11), 109 (15). ^1H NMR: δ 7.35–6.95 (m, 5H); 6.08 (d, J 9 Hz, 1H); 5.50 (t, J 9 Hz, 1H); 1.65–1.15 (m, 1H); 1.7–1.2 (m, 2H) and 1.2–0.8 (m, 6H) ppm.

E-3-methyl-pent-1-en-1-yl phenyl sulphide. b.p. $81-82^\circ\text{C}/0.1$ Torr; MS (70 eV): 192 (M^+) (87%), 163 (100), 135 (28), 110 (10), 109 (17). ^1H NMR: δ 7.5–7.0 (m, 5H); 6.05 (d, J 15 Hz, 1H); 5.75 (dd, J 15, J 9 Hz, 1H); 2.4–1.9 (m, 1H); 1.65–1.15 (m, 2H) and 1.15–0.8 (m, 6H) ppm.

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