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A General Approach to Conjugated (*E*, *E*)-Dienes through Sequential Coupling Reactions

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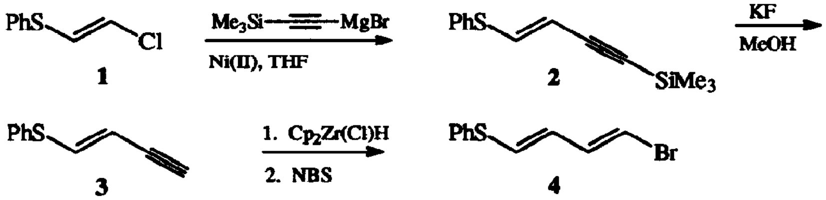
Abstract: a straightforward and useful procedure leading to a variety of conjugated (*E,E*)-dienes is reported. The method is based upon sequential coupling reactions of Grignard reagents with the readily available (1*E*,3*E*)-1-bromo-4-phenylthio-1,3-butadiene in the presence of $NiCl_2$(dppe).

The stereocontrolled synthesis of conjugated dienes is of considerable interest in organic chemistry since such dienes are often encountered in natural compounds, such as insect sex pheromones,[1] and are also valuable intermediates in the synthesis of more complex targets via Diels-Alder reactions.[2] A number of methods for preparing conjugated dienes[3-7] have appeared utilizing most frequently either a Wittig type approach[3] or coupling reactions of stereodefined vinyl halides with vinyl organometallic compounds, in the presence of transition metals as catalysts.[4] Furthermore, conjugated dienes can be obtained from 1,3-enynes, by selective reduction of the acetylenic unit,[5] or from aldehydes using organotitanium reagents.[6]

Our continued interest in the synthesis of stereodefined products has led us to devise new methodologies[8-10] for the preparation of such unsaturated systems. In particular, our procedure based upon sequential coupling reactions of Grignard reagents with (*Z*)- or (*E*)-1-bromo-2-phenylthioethene in the presence of Ni(II) or Pd(II) catalysts proved to be a versatile synthetic tool for obtaining alkenes[10a] or monoolefinic insect sex pheromones of *E*- or *Z*-configuration,[10b] *E,E*- or *E,Z*-1-silylated-1,3-dienes[10e] or pheromones with a conjugated (*Z,E* or *E,Z*) diene structure.[10f] Now, we wish to report a direct and general route to stereodefined conjugated dienes of *E,E*-configuration, based upon our sequential coupling approach.

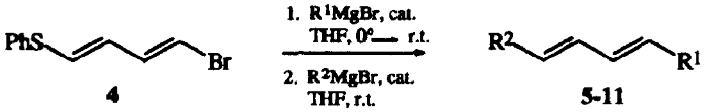
The methodology involves the preparation and the reactions of the new building block (1*E*,3*E*)-1-bromo-4-phenylthio-1,3-butadiene **4** which can be conveniently obtained according to Scheme 1:

Scheme 1



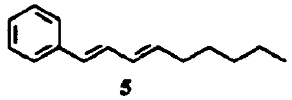
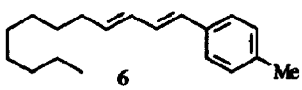
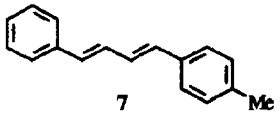
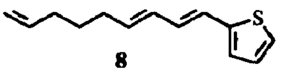
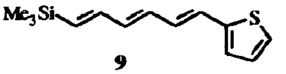
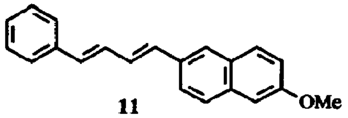
The reaction of the readily available (*E*)-1-chloro-2-phenylthioethene[11] **1** with the 2-trimethylsilylethynyl Grignard reagent in the presence of $NiCl_2$(dppe) leads to enyne **2**. After appropriate desilylation,[12] the hydrozirconation/bromination reactions[13] of compound **3** yield the desired conjugated diene **4** of *E,E* configuration[14] (97%, as ascertained by ^{1}H-NMR after purification by flash chromatography).

The two groups present on the terminal positions can be selectively substituted by sequential cross-coupling reactions, according to our procedure,[10b] with Grignard reagents in the presence of transition metals (eq. 1) leading to a variety of conjugated dienes (stereoisomeric purities in the range 95-97%):



4 **5-11** (1)

Table. Cross-coupling Reactions of (1 *E*,3*E*)-1-Bromo-4-phenylthio-1,3-butadiene with Grignard Reagents in the Presence of a Ni(II)-complex as Catalyst[a] (see equation 1)

Entry[b]	R^1	R^2	Reaction time (h)[c]	Products **5-11**	Overall yield%[d]
1	*n*-pentyl	phenyl	21	 **5**	52
2	*p*-tolyl	*n*-octyl	21	 **6**	45
3	*p*-tolyl	phenyl	22	 **7**	80
4	2-thienyl	4-pentenyl	19	 **8**	51
5	2-thienyl	2-(trimethylsilyl)-ethenyl	19	 **9**	50
6	4-pentenyl	4-pentenyl	15	 **10**	59
7	6-methoxy-2-naphthyl	phenyl	18	 **11**	67

a) 3 mol% of $NiCl_2(dppe)$ with respect to the Grignard reagent were used; b) all reactions were carried out with 1.1 equiv. of R^1MgBr and 2.2 equiv. of R^2MgBr; in entry 6 all Grignard reagent (3.3 equiv.) was added at the same time; c) times required for the second step; the first step was completed in less than 1 h; d) yields refer to products purified by flash chromatography (silica gel, eluted with petroleum ether or with petroleum ether/CH_2Cl_2 9/1 in the case of product **11**; satisfactory ^{1}H-NMR and mass spectra were obtained for all compounds.

The procedure has been applied to the synthesis of symmetrical (Table, entry 6) and non-symmetrical dienes. When the starting diene **4** was allowed to react with a Grignard reagent in the presence of the Ni(II) complex, substitution of the bromine occurred readily, and using an excess of Grignard reagent and longer reaction times the cross-coupling was followed by formation of the second C-C bond. In order to prepare the non-symmetrical dienes it was only necessary to add, after completion of the first reaction, a different Grignard reagent to the mixture containing the catalyst and the intermediate dienyl sulfide, without isolation of the latter. Aromatic, aliphatic and unsaturated Grignard reagents can be used, leading also to trienes (entries 4 and 5) or tetraene derivatives (entry 6), in fair to good overall isolated yields (45-80%). The stereochemistry of the double bonds was established from the ^{1}H-NMR coupling constants between the vinylic protons.[15]

The diene **4** was synthesized as follows: a 0.31 N THF solution of 2-trimethylsilylethynylmagnesium bromide (98 mL, 30.4 mmol) was slowly added at 0° C, under nitrogen, to a stirred suspension of $NiCl_2$(dppe) (0.49 g, 0.93 mmol) and *E*-1-chloro-2-phenylthioethene **1** (5.15 g, 30.2 mmol) in THF (40 mL). The mixture was slowly brought to room temperature and, after reaction completion (1 h), quenched with NH_4Cl and extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 and, after evaporation of the solvent, the residue was taken up in a minimum of petroleum ether and passed through a short Florisil column with petroleum ether as eluent, in order to remove the catalyst. The solvent was evaporated in vacuo and the residue was purified by distillation (b.p. 115-117° C, 1 mbar) affording 4.91 g (70% yield) of (*E*)-1-phenylthio-4-trimethylsilyl-1-buten-3-yne **2**.[14] Potassium fluoride[12] (12.2 g, 0.2 mol) was added to a methanol (45 mL) solution of compound **2** (4.91 g, 21 mmol) and the mixture was heated to reflux for 1 h and then concentrated. The residue was dissolved in ethyl acetate and washed with water. Concentration followed by flash chromatography (silica gel, petroleum ether) gave 3.13 g (93% yield) of enyne **3**.[14] A solution of this compound (3.13 g, 19.5 mmol) in dry benzene (40 mL) was added, under nitrogen, to a stirred suspension of $Cp_2Zr(Cl)H$ (5.28 g, 20.5 mmol) in benzene (40 mL). The white suspension turned to a yellow solution after stirring for 0.5 h in the dark. Additional 40 mL of benzene and N-bromo-succinimide (3.47 g, 19.5 mmol) were added and the reaction was completed after 0.3 h. The mixture was transferred to a separatory funnel with ethyl acetate and washed with water. The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was taken up in hexane, passed through a plug of alumina and evaporated in vacuo. The product **4** was isolated in 65% yield (3.05 g) after flash chromatography (silica gel, petroleum ether). Structural assignement was ascertained by ^{1}H-NMR spectroscopic data and GC/MS.[14]

In conclusion, our sequential coupling procedure should provide a highly stereospecific and general route to conjugated dienes, starting with readily available reagents and the new building block **4**. The mild reaction conditions and the simplicity of the operations involved are additional features making the methodology very promising.

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14. **2**, ^{1}H-NMR (200 MHz, CDCl$_3$): δ 0.2 (s, 9H), 5.57 (d, J = 15.5 Hz, 1H), 6.9 (d, J = 15.5 Hz, 1H), 7.24-7.48 (m, 5H) ppm. MS: m/e 232 (M$^+$, 100), 217 (89), 201 (79), 159 (3), 141 (11), 123 (4), 109 (7), 77 (12), 73 (6), 43 (8). **3**, ^{1}H-NMR (200 MHz, CDCl$_3$): δ 2.97 (dd, J = 2.4, 0.6 Hz, 1H), 5.51 (dd, J = 15.5, 2.4 Hz, 1H), 6.93 (dd, J = 15.5, 0.6 Hz, 1H), 7.25-7.49 (m, 5H) ppm. MS: m/e 160 (M$^+$, 100), 159 (29), 134 (24), 128 (23), 115 (88), 109 (7), 77 (16), 51 (37). **4**, ^{1}H-NMR (500 MHz, CDCl$_3$): δ 6.17 (ddd, J = 14.9, 10.9, 0.6 Hz, 1H), 6.23 (dt, J = 13.4, 0.6 Hz, 1H), 6.45 (dt, J = 14.9, 0.6 Hz, 1H), 6.73 (ddd, J = 13.4, 10.9, 0.6 Hz, 1H), 7.23-7.42 (m, 5H) ppm. MS: m/e 242 (M+2, 12), 240 (M$^+$, 12), 161 (100), 128 (79), 117 (11), 109 (8), 77 (14), 51 (23).
15. Spectroscopic data for compound **6**: (1*E*,3*E*)-1-(*p*-tolyl)-1,3-dodecadiene, ^{1}H-NMR (500 MHz, CDCl$_3$): δ 0.88 (t, J = 6.9 Hz, 3H), 1.21-1.62 (m, 12H), 2.15 (q, J = 7.2 Hz, 2H), 2.32 (s, 3H), 5.79 (dt, J = 15.1, 7.2 Hz, 1H), 6.18 (dd, J = 15.1, 10.4 Hz, 1H), 6.41 (d, J = 15.6 Hz, 1H), 6.7 (dd, J = 15.6, 10.4 Hz, 1H), 7.10 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H) ppm. MS: m/e 256 (M$^+$, 50), 157 (54), 143 (100), 129 (38), 118 (47), 105 (19), 91 (6), 41 (11).

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