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(1*E*,3*E*,5*Z*)-1,6-Dibromohexa-1,3,5-triene: regio- and stereocontrolled mono pallado-catalysed cross-coupling reactions

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Abstract

We describe the regio- and stereocontrolled synthesis of (*Z*,*E*,*E*)-α-bromo-ω-substituted hexatrienes. The synthesis is based on a mono pallado-catalysed cross-coupling reaction between (1*E*,3*E*,5*Z*) isomer of 1,6-dibromohexa-1,3,5-triene and various organozinc reagents. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Keywords: trienes; coupling reactions; palladium; palladium compounds; zinc; zinc compounds.

Numerous natural products, with generally interesting biological properties, have in their structure a stereodefined trienic conjugated chain. The halogenotrienes could be excellent precursors for the synthesis of these natural compounds, via transition metal catalysed reactions.[1] In the literature, few routes have been described allowing to accede rapidly to halogenotrienes, but most of them display low stereoselectivity. They were prepared, for example, by stereoselective hydrogenolysis of 1,1-dibromo-1-alkenes,[2] substitution of (*E*)-metalloalkenes with halogen groups,[3] haloalkenylation of aldehydes using Wittig type reagents[4,5] or stereoselective reduction of homopropargylic alcohols into (*E*)-homoallylic alcohols followed by an elimination reaction.[6]

A great difference of reactivity of vinylic halogeno compounds depending on the *E* or *Z* configuration of the double bond has been mentioned. For example, Carpita et al. have described a high stereoselectivity for pallado-catalysed cross-coupling reactions involving (*E*)- and (*Z*)-1-bromoalkenes[7a,b,d] or (*E*)- and (*Z*)-1,2-dibromoethylene.[7c] Moreover, recently we have reported the exclusive exchange of the bromine atom substituting the double bond with an *E* configuration of (1*E*,3*E*,5*Z*)-1,6-dibromohexa-1,3,5-triene **1** according to a stereoselective bromine–lithium exchange reaction.[5a,c] These last results led us to anticipate that our strategy should give way to monocoupling compounds selectively.

We propose a new route to accede to (*Z*,*E*,*E*)-α-bromo-ω-substituted hexatrienes **2** in a one step procedure by a mono pallado-catalysed cross-coupling reaction between the (1*E*,3*E*,5*Z*)-1,6-dibromohexa-1,3,5-triene **1** and various organozinc reagents **3**. The 1,6-dibromohexa-1,3,5-triene **1** has been recently

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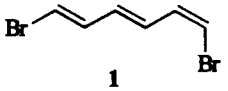
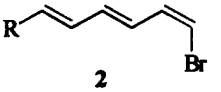
Table 1
Monocoupling reaction results from **1**

	Organozinc reagent R	Organozinc reagent preparation	X	Monocoupling product : %	Dicoupling product : %
1	**3a** phenyl	Mg/Zn	Br	**2a** : 66	*traces*
2	**3b** p-MeO-C_6H_4	"	"	**2b** : 63	"
3	**3c** 2-furyl	Li/Zn	"	**2c** : 63	"
4	**3d** benzyl	Zn*	"	**2d** : 65	-
5	**3e** *n*-pentyl	Mg/Zn	"	**2e** : 55	-
6	**3f** AcO-$(CH_2)_3$-CH_2	Zn*	I	**2f** : 61	-
7	**3g** Cl-$(CH_2)_3$-CH_2	"	"	**2g** : 47	-
8	**3h** $MeOOCCH_2$	"	Br	**2h** : 22	-
9	**3i** C_5H_{11}-C≡C	Li/Zn	"	**2i** : 62	**5i** : 7
10	**3j** Me_3Si-C≡C	"	"	**2j** : 22	**5j** : 57

prepared by us[5a,c] according to a Wittig reaction with the (2*E*,4*E*)-5-bromopenta-2,4-dienal **4**, also synthesised by our group,[5a–c,8] and used in pallado-catalysed cross-coupling reactions.[8] It was obtained as a mixture of 1*E*,3*E*,5*Z* and 1*E*,3*E*,5*E* stereomers (1*E*,3*E*,5*Z*:1*E*,3*E*,5*E* 70:30). After easy and quantitative separation, the pure isomer (1*E*,3*E*,5*Z*)-**1** has been implicated in mono pallado-catalysed cross-coupling reactions.



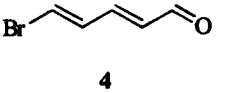
1



2

RZnX

3

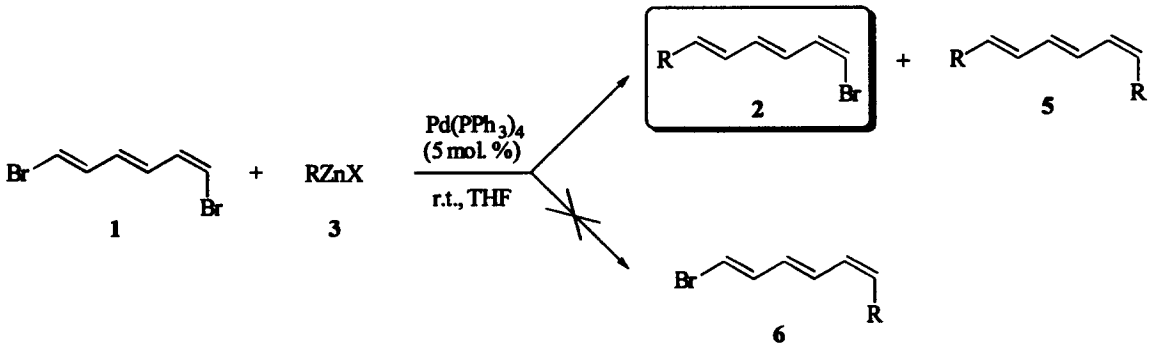


4

Organozinc reagents **3** in tetrahydrofuran (THF) were prepared by a transmetallation reaction from organomagnesium (commercially available or prepared in Grignard conditions, Mg/Zn, Table 1) or organolithium (prepared by action of *n*-butyllithium, Li/Zn, Table 1) reagents and zinc dibromide, or by direct insertion of zinc metal into a carbon–halide bond, using zinc dust activated successively by 1,2-dibromoethane and chlorotrimethylsilane[9] (*Z**, Table 1).

To optimise the monocoupling reaction and to prevent any dicoupling reaction, the 1,6-dibromohexa-1,3,5-triene **1** reagent should always be locally in excess with regard to the organozinc reagent **3**. Then, all our experiments were carried out using a syringe pump to perform a very slow addition of the organozinc reagent **3** solution to the stirred mixture of 1,6-dibromohexa-1,3,5-triene **1** and $Pd(PPh_3)_4$ (5 mol%) in THF at room temperature, until total consumption of **1** (Scheme 1).[10]

We have never observed any product resulting from a monocoupling reaction on the *Z* double bond (i.e. product **6**) (Scheme 1). With aromatic, heteroaromatic, benzylic, aliphatic and functionalised aliphatic organozinc reagents **3**, the reaction occurred regioselectively on the *E* double bond and the monocoupling products **2** were obtained with moderate to good yields (22 to 66%) (Table 1, entries 1–8). In some cases we observed some traces of dicoupling product **5** by TLC, which could not be isolated (Table 1, entries 1, 2 and 3). Moreover, the poor yield observed for the formation of the monocoupling product **2h** (Table 1,



Scheme 1.

entry 8) could be explained by the weak reactivity of the Reformatsky reagent on account of a 1–3 equilibrium migration of the zinc atom from carbon to oxygen (enolate character).[11]

The cross-coupling reaction with acetylenic zinc reagents **3i** and **3j** (Table 1, entries 9 and 10) led to a mixture of monocoupling **2i** and **2j** and non-negligible amounts of dicoupling **5i** and **5j** products, this last could be the major one (Table 1, entry 10). Similarly, absence of selectivity with acetylenic zinc reagents has been previously observed in the literature.[7,12] Studies are currently under active progress in our laboratory to explain and limit the dicoupling product formation.

In conclusion, we have synthesised selectively various monocoupling products **2** (except for the use of acetylenic organozinc reagents) and particularly functionalised bromotrienes starting from the pure isomer (1*E*,3*E*,5*Z*)-1,6-dibromohexa-1,3,5-triene **1**. All these products are new and gave satisfactory structural analyses. The monocoupling reaction is stereospecific; there is a total retention of the configuration of the double bonds of the dibromide starting material. Also, this reaction is regioselective, according to an exclusive coupling reaction with the bromine atom substituting the *E* double bond.

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10. Typical procedure for the preparation of (1*Z*,3*E*,5*E*)-1-bromo-6-phenylhexa-1,3,5-triene **2a**: a solution of phenylzinc bromide **3a** (0.5 M) was added dropwise, using a syringe pump, at room temperature and under argon, to a stirred solution of 92 mg of **1** and 35 mg of $Pd(PPh_3)_4$ in 5 ml anhydrous THF. The reaction was monitored by TLC (SiO_2, pentane as eluant, UV and phosphomolybdic acid in EtOH as revelators). After addition of 1.5 equiv. of organozinc reagent **3a**, the reaction was complete, as indicated by the total consumption of **1**. The solution was hydrolysed by 5 ml of 5% aqueous $NaHCO_3$ and extracted with pentane (3×15 ml). The organic layers were combined, dried over $MgSO_4$ and evaporated. Compound **2a** (60 mg) was isolated after flash chromatography (SiO_2, pentane) as a yellow solid. Yield: 66%. Mp: 64°C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm): 6.14 (d, 1H, H^1, *J*=6.7 Hz), 6.52 (dd, 1H, H^4, *J*=14.2, 10.2 Hz), 6.60 (dd, 1H, H^3, *J*=14.2, 9.8 Hz), 6.61 (d, 1H, H^6, *J*=15.6 Hz), 6.67 (dd, 1H, H^2, *J*=9.8, 6.7 Hz), 6.84 (dd, 1H, H^5, *J*=15.6, 10.2 Hz), 7.16 to 7.39 (m, 5H, phenyl). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm): 108.40 (C^1), 126.56 (2C, phenyl), 127.94, 128.29, 128.58, 128.68 (2C, phenyl), 132.60, 134.61, 136.52, 136.94 (1C, phenyl). MS (EI, 70 eV) m/z (rel. int.): 236–234 (M^+, 15%); 155 (M–Br, 100%). IR (KBr, neat): 688, 996, 1446, 1606, 1734, 1882, 1954, 3020–3072 cm^{-1}. Anal. calcd for $C_{12}H_{11}Br$: C, 61.30; H, 4.72. Found: C, 61.36; H, 4.84.
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