Facile Synthesis of Cross-Conjugated *gem*-Disubstituted Trienes via Palladium-Catalyzed Cross-Coupling Protocol of 1,1-Disubstituted 2,4-Diiodo-But-1-ene With Alkenes

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Received 4 February 2004

Abstract: Cross-conjugated coupling products described in the title are obtained in moderate to high yields by the reactions of the corresponding 1,1-disubstituted 2,4-diiodo-but-1-enes, which are derived from the ring-opening reaction of methylenecyclopropanes with iodine, with substituted alkenes in the presence of palladium(II) catalyst under simple Heck-type reaction conditions.

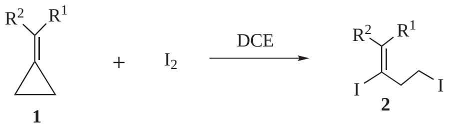
Key words: methylenecyclopropanes, cross-conjugated trienes, cross-coupling reaction, palladium catalyst, alkenes, diiodides

In recent years acyclic polyenes of the so-called dendralene-type[1] are beginning to receive steadily increasing attention[2] because of their unusual cross-conjugated properties and emerging synthetic potential. The cross-conjugated triene is of particular interest because its two conjugated dienes systems can form polymeric Diels–Alder adduct with bifunctional dienophile. In addition, the trienes **5** (cross-conjugated *gem*-disubstituted trienes), for the same reason, should be of interest as a cross-linking agent for vinyl polymers. Moreover, cross-conjugation is a commonly encountered phenomenon in natural product and dyestuff chemistry, although in the majority of cases the various π-systems are polarized either by heteroatoms and/or by electron-donating or -accepting substituents.[3] Since the preparation of the parent 3-methylene-penta-1,4-diene was first reported by Bloomquist and Verdol in 1955[4] and also by Bailey and Economy[5] shortly thereafter, various synthetic methods have been developed for the preparation of the parent trienes and its derivatives.[1] But to the best of our knowledge, there are no more mild conditions were reported for the synthesis of cross-conjugated trienes[6] though Yamaguchi reported an efficient synthesis of trienes by catalytic dimerization of monosubstituted allenes in the presence of P(*o*-Tol)$_3$.[7]

Palladium-catalyzed reactions are versatile methods for carbon-carbon bond formations as a result of their generality and ability to tolerate a wide range of important organic functional groups.[8] Among them, the Heck-type[9–11] and related chemistry occupy a special place. Recently, we reported that the ring-opening reactions of methylenecyclopropanes (MCPs) **1** promoted by metal halides (Lewis acids) to give the homoallylic halides in high yields in CH_2Cl_2 under mild conditions. In that paper, we also found that in the presence of TiI_4 or iodine (I_2), the ring-opening reaction of 1,1-diphenylmethylenecyclopropane (**1d**) produced 1,1-diphenyl-2,4-diiodo-but-1-ene (**2d**) in high yield.[12] Herein we wish to report a facile method for the synthesis of cross-conjugated *gem*-disubstituted trienes **5** by a one-step palladium-catalyzed coupling reaction of diiodides **2** with substituted alkenes.

The corresponding 1,1-disubstituted 2,4-diiodo-but-1-enes **2** were prepared from the reactions of various MCPs **1** with iodine in moderate to high yields in 1,2-dichloroethane (DCE).[13] The results are summarized in Table 1. For MCPs **1a**, **1c**–**e** (both R^1 and R^2 are aromatic groups), the reaction proceeded smoothly to give the corresponding diiodinated products **2a** and **2c**–**e** in good to excellent yields (Table 1, entries 1, 3–5). For the unsymmetric MCP **1b** (R^1 is an aromatic group and R^2 is an aliphatic group), the reaction produced the product **2b** in 27% yield under the same conditions exclusively as *E*-configuration (Table 1, entry 2). The *E*-configuration of **2b** was determined by ^1H NMR NOESY spectroscopic data (Supporting Information). The stereospecificity of **2b** can be explained by the steric effect between iodine atom and phenyl ring. Therefore, the *E*-**2b** is thermodynamically more stable.

Table 1 The Ring-opening of MCPs **1** by Iodine in 1,2-Dichloroethane (DCE)



1a: $R^1 = R^2 = p\text{-}CH_3OC_6H_4$; **1b**: $R^1 = p\text{-}EtOC_6H_4$, $R^2 = CH_3$; **1c**: $R^1 = R^2 = p\text{-}CH_3C_6H_4$; **1d**: $R^1 = R^2 = C_6H_5$; **1e**: $R^1 = R^2 = p\text{-}ClC_6H_4$.

Entry	Substrate	Yield[a] (%)
1	**1a**	**2a** (90)
2	**1b**	**2b** (27)
3	**1c**	**2c** (90)
4	**1d**	**2d** (88)
5	**1e**	**2e** (92)

[a] Isolated yields.

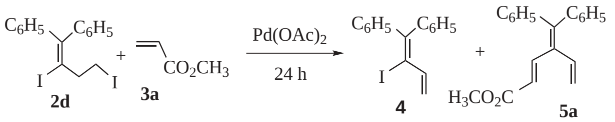
SYNLETT 2004, No. 5, pp 0807–0810

DOI: 10.1055/s-2004-820017; Art ID: U03404ST

Next, we carried out the typical Heck-type reactions of diiodides **2** with some alkenes. Using 1,1-diphenyl-2,4-diiodo-but-1-ene (**2d**) (0.25 mmol) and methyl acrylate (0.3 mmol) as the substrates, we attempted to develop the optimized reaction conditions for this Heck-type reaction. The results are shown in Table 2. The configuration of **5a** was determined as 1*E*,4*E* by ^{1}H NMR NOESY spectroscopic data (Supporting Information). The original set of reaction conditions is 20 mol% of $Pd(OAc)_2$, 2.0 equivalents of $NaHCO_3$, 1.0 equivalent of Bu_4NCl (TBAC) at 60–70 °C in DMF. This Heck-type reaction was completed within 24 hours to give the corresponding product **5a** in 55% yield along with the uncross-coupled product **4** in 17% yield (Table 2, entry 1). In a second experiment, we found that when the temperature was raised to 100 °C, the cross-conjugated triene **5a** was obtained exclusively in 80% yield (Table 2, entry 2). When the base $NaHCO_3$ was replaced by Et_3N, KOAc or NaOH at 100 °C, **5a** was also obtained as a sole product but in slightly lower yields (Table 2, entries 3, 5 and 8). In addition, when Na_2CO_3 was used as the base, only the uncross-coupled product **4** was given in 59% yield (Table 2, entry 4). The addition of PPh_3 (40 mol%) did not significantly improve the yields of the reaction product (Table 2, entries 2–9, 3–10 and 5–11). Using CH_3CN or Et_3N as the solvent under the similar reaction conditions, the yields of **5a** were not significantly improved as well (Table 2, entries 6, 7, 12 and 13). Therefore, the optimized conditions for this Heck-type reaction are using DMF as a solvent, $NaHCO_3$ as a base in the presence of additive TBAC (Table 2, entry 2).[14]

To survey the generality of this Heck-type reaction, we next investigated the reaction using other diiodides **2** with some substituted alkenes such as methyl acrylate **3a**, methyl vinyl sulfone **3b** and styrene **3c** under the optimized conditions. The results are summarized in Table 3. As can be seen from Table 3, the corresponding trienes **5** were obtained in moderate to excellent yields in most cases (Table 3). For substrates **2** in which both R^1 and R^2 are aromatic groups such as **2a**, **2c** and **2d**, the cross-coupling reactions proceeded very well to give the normal Heck-type reaction products **5b**, **5c**, **5e**, **5f** and **5h** in good to high yields (Table 3, entries 1, 2, 4, 5, and 7). Only for substrate **2b** (R^1 is an aryl group and R^2 is a methyl group), this Heck-type reaction produced the isomerized product **6** in 30% yield, which is presumably derived from the normal coupling product (Table 3, entry 3). For styrene **3c**, the corresponding Heck-type reaction product was obtained in moderate yields (Table 3, entries 6, 8). The product **5g** was obtained as a mixture of (*trans*,*trans*)-**5g** and (*cis*,*trans*)-**5g** and the relative configuration was determined by ^{1}H NMR (Supporting Information).

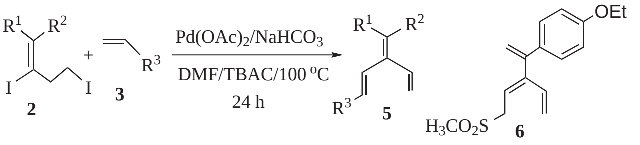
Table 2 The Optimization Reaction Conditions of the Heck-Type Reaction



Entry	Solvent	Base	Additive[a]	Temp. (°C)	Yield[b] (%)	
					4	**5a**
1	DMF	$NaHCO_3$	TBAC	60–70	17	55
2	DMF	$NaHCO_3$	TBAC	100	–	80
3	DMF	Et_3N	–	100	–	77
4	DMF	Na_2CO_3	TBAC	100	59	–
5	DMF	AcOK	–	100	–	75
6	CH_3CN	Et_3N	–	100	20	51
7	CH_3CN	$NaHCO_3$	TBAC	100	37	47
8	DMF	NaOH	TBAC	100	Trace	64
9	DMF	$NaHCO_3$	TBAC–PPh_3	100	–	75
10	DMF	Et_3N	TBAC–PPh_3	100	–	65
11	DMF	AcOK	TBAC–PPh_3	100	–	50
12	Et_3N	–	–	Reflux	–	66
13	Et_3N	–	PPh_3	Reflux	69	–

[a] TBAC = Tetrabutylammonium chloride.
[b] Isolated yields.

Table 3 The Heck-Type Reaction of Diiodides **2** (0.25 mmol) with Substituted Alkenes **3** (0.3 mmol) under the Optimized Conditions



2a: $R^1 = R^2 = p\text{-}CH_3OC_6H_4$; **2b**: $R^1 = p\text{-}EtOC_6H_4$, $R^2 = CH_3$;
2c: $R^1 = R^2 = p\text{-}ClC_6H_4$; **2d**: $R^1 = R^2 = C_6H_5$.
3a: $R^3 = CO_2CH_3$; **3b**: $R^3 = SO_2CH_3$; **3c**: $R^3 = C_6H_5$.

Entry	Substrates		Product	Yield[a] (%)
1	**2a**	**3a**	**5b**	81
2	**2a**	**3b**	**5c**	80
3	**2b**	**3b**	**6**	30
4	**2c**	**3a**	**5e**	99
5	**2c**	**3b**	**5f**	61
6	**2c**	**3c**	**5g**	53 (6:1)[b]
7	**2d**	**3b**	**5h**	72
8	**2d**	**3c**	**5i**	44

[a] Isolated yields.
[b] (*trans*,*trans*)/(*cis*,*trans*) (Supporting Information).[15]

In conclusion, we have synthesized some cross-conjugated *gem*-disubstituted trienes **5** via a simple Heck-type reaction of diiodides **2**, derived from MCPs **1** with iodine under mild conditions, with some alkenes. A range of substituted alkenes has been examined. This process provides a novel and efficient route for the synthesis of cross-conjugated *gem*-disubstituted trienes **5** under simple Heck-type conditions without special phosphine ligand. Efforts are in progress to elucidate the mechanistic details of this reaction and to disclose its scope and limitations.

Acknowledgment

We thank the State Key Project of Basic Research (Project 973) (No. G2000048007), Chinese Academy of Sciences (KGCX2-210-01), Shanghai Municipal Committee of Science and Technology, and the National Natural Science Foundation of China for financial support (203900502, 20025206 and 20272069).

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(13) **Typical Procedure for the Ring-Opening of MCPs 1 by I_2 in 1,2-Dichloroethane (DCE)**: Under an ambient atmosphere, MCP **1a** (10 mmol), I_2 (10 mmol) and 1,2-dichloroethane (2.5 mL) were added into a Schlenk tube. The mixture was stirred at r.t. for 8 h. The solvent was removed under reduced pressure and the residue was then purified by a flash column chromatography to give product **2a** as a yellow solid; mp 112–114 °C. ^1H NMR (300 MHz, $CDCl_3$) $\delta = 3.08$ (t, $J = 7.2$ Hz, 2 H), 3.37 (t, $J = 7.2$ Hz, 2 H), 3.80 (s, 3 H, CH_3O), 3.84 (s, 3 H, CH_3O), 6.84 (d, $J = 9.0$ Hz, 4 H, Ar), 7.07 (d, $J = 6.9$ Hz, 2 H, Ar), 7.16 (d, $J = 6.9$ Hz, 2 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 6.58$, 44.53, 55.13, 55.19, 105.46, 113.31, 113.75, 129.91, 130.11, 132.54, 138.99, 149.71, 158.73, 158.79. IR (CH_2Cl_2): 3046, 2954, 2833, 2676, 2299, 2050, 1605, 1508, 1265, 1247, 741, 705 cm^{-1}. MS: m/z (%) = 520 (84.92) [M^+], 393 (28.23), 266 (100). HRMS: m/z calcd for $C_{18}H_{18}I_2O_2$: 519.9396; found: 519.9406.

(14) **Typical Procedure for the Heck-Type Reaction:** Under an ambient atmosphere, **2a** (0.25 mmol), **3a** (0.30 mmol), $Pd(OAc)_2$ (0.05 mmol), tetrabutylammonium chloride (TBAC) (0.25 mmol), $NaHCO_3$ (0.5 mmol) and *N*,*N*-dimethylformamide (DMF) (1.0 mL) were added into a Schlenk tube. The reaction mixture was stirred at 100 °C for about 24 h. The reaction solution was washed with saturated brine, dried over anhyd $MgSO_4$, and then purified by a flash column chromatography to give **5a** as a pale yellow solid. Mp: 85–88 °C. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 3.72$ (s, 3 H), 5.36 (dd, $J = 1.2$, 11.4 Hz, 1 H), 5.39 (dd, $J = 1.2$, 17.7 Hz, 1 H), 6.21 (d, $J = 15.9$ Hz, 1 H), 6.39 (dd, $J = 11.4$, 17.7 Hz, 1 H), 7.09–7.18 (m, 5 H, Ar), 7.27–7.33 (m, 5 H, Ar), 7.47 (d, $J = 15.9$ Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 51.49$, 119.71, 121.65, 127.73, 127.81, 127.89, 128.13, 131.06, 131.11, 132.61, 135.14, 141.10, 141.48, 144.32, 147.80, 167.82. IR (CH_2Cl_2): 3067, 2978, 2304, 115, 1605, 1265, 739 cm^{-1}. MS *m*/*z* (%) = 290 (35.94) [M$^+$], 258 (32.98), 215 (100). HRMS: *m*/*z* calcd for $C_{20}H_{18}O_2$: 290.1301; found: 290.1290.

(15) To clarify the selectivity of the reaction, an experimental run was carried out on a larger scale of **2d** (2.0 mmol) and **3a** (2.4 mmol) as the substrates. We found that no other isomer was obtained based on the ^{1}H NMR spectroscopic data of the reaction mixtures. At present stage, we are not sure of the reason on the selectivity of the reaction of **2c** and **3c** yet. We have determined the relative configuration of **5g** by ^{1}H NMR as the corresponding coupling constant of the former is 16.5 Hz and 8.7 Hz for the latter (Supporting Information).