JOC*Note*

Facile Synthesis of 2-Alkynyl Buta-1,3-dienes via Sonogashira Cross-Coupling Methodology

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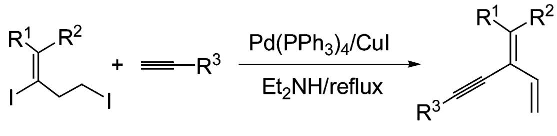

2-Alkynyl buta-1,3-dienes **4** can be synthesized in moderate to high yields by the reactions of the corresponding diiodides **1** derived from methylenecyclopropanes with substituted alkynes **2** via Sonogashira cross-coupling in the catalysis of $Pd(PPh_3)_4$/CuI.

Introduction

The palladium-catalyzed coupling of terminal alkynes with aryl and vinyl halides in the presence of catalytic CuI and an amino base (the Sonogashira reaction) is one of the important and widely used carbon−carbon bond-forming reactions in organic synthesis.[1,2] This method has been successfully applied in the synthesis of natural compounds,[3] biologically active molecules,[4] new organic materials for optical and microelectronic application,[5] dendrimeric, oligomeric, polymeric materials,[6] macrocycles with acetylene links,[7] polyalkynylated molecules, and, generally, as a route to new intriguing molecular architectures.[8] Previously, we synthesized some interesting molecules with a buta-1,3-diene structure by various coupling reactions with 1,1-disubstituted 2,4-diiodo-but-1-enes **1** derived from methylenecyclopropanes (MCPs) and substituted alkenes, boronic acids, or Grignard reagents as the substrates since buta-1,3-dienes and its derivatives are important in organic synthesis, especially as starting materials in Diels−Alder reactions.[9] These interesting results led us to a further detailed study of the synthesis of 2-alkynyl buta-1,3-dienes[10−12] by a Sonogashira-type reaction because enynes are also interesting compounds that can be found in many naturally occurring and biologically active compounds.[13] Herein, we report the synthesis of 2-alkynyl buta-1,3-dienes from 1,1-disubstituted 2,4-diiodo-but-1-dienes and alkynes via a Sonogashira-type reaction in the catalysis of $Pd(PPh_3)_4$/CuI.

Results and Discussion

As a first try, we searched for a protocol for the cross-coupling reaction of 1,1-diphenyl-2,4-diiodo-but-1-ene **1a**

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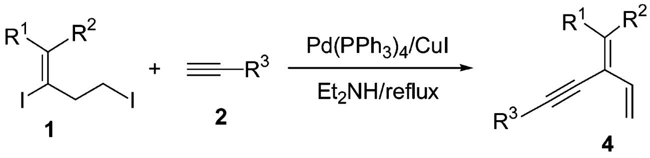
TABLE 1. Sonogashira Coupling Reaction of Diiodide 1a and Phenylacetylene 2a under Various Reaction Conditions



entry[a]	catalyst	base[b]	temp (°C)	yield (%)[c] 3	yield (%)[c] 4a
1	Pd(PPh$_3$)$_4$/CuI	^{i}Pr$_2$NH	reflux	–	60
2	Pd(PPh$_3$)$_4$/CuI	Et$_2$NH	reflux	–	90
3	Pd(PPh$_3$)$_4$/CuI	Et$_3$N	reflux	–	85
4	Pd(PPh$_3$)$_4$/CuI	pyridine	100	–	trace
5	Pd(PPh$_3$)$_4$/CuI	morpholine	100	–	24
6	Pd(OAc)$_2$/CuI/PPh$_3$[d]	Et$_2$NH	reflux	–	64
7	PdCl$_2$(PPh)$_3$/CuI	Et$_2$NH	reflux	–	76
8	Pd(OAc)$_2$/CuI	Et$_2$NH	reflux	–	51
9	CuI[e]	Et$_2$NH	reflux	40	30
10	NiCl$_2$(PPh$_3$)$_2$/CuI	Et$_2$NH	reflux	60	22

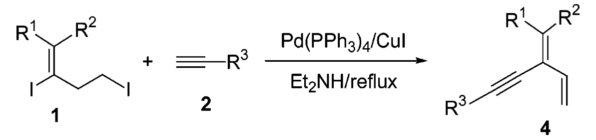
[a] Unless otherwise specified, all the reactions were carried out using **1a** (0.25 mmol), **2a** (0.3 mmol) in the catalysis of Pd(PPh$_3$)$_4$ (0.1 equiv) or NiCl$_2$(PPh$_3$)$_2$ and CuI (0.2 equiv) at the appropriate temperatute for 24 h. [b] As the base and solvent. [c] Isolated yields. [d] A quantity of 0.4 equiv of PPh$_3$ was used. [e] A quantity of 0.2 equiv of CuI was used.

(0.25 mmol) with phenylacetylene **2a** (0.30 mmol). We were pleased to find that diiodide **1a** could react with phenylacetylene **2a** in the presence of 10 mol % of Pd(PPh$_3$)$_4$, 20 mol % of CuI and ^{i}Pr$_2$NH as the base and solvent under reflux temperature to give the desired product **4a** within 24 h with a 60% yield as the sole product (Table 1, entry 1).

The structure of **4a** was determined by ^{1}H and ^{13}C NMR spectroscopic data and X-ray diffraction (Supporting Information).[14]

The reaction conditions were further optimized, and some typical results are listed in Table 1. In a second experiment, we found that when Et$_2$NH was used as the base and solvent, the coupling product **4a** was obtained with a 90% yield also as a sole product (Table 1, entry 2). When Et$_2$NH was replaced by Et$_3$N or morpholine, **4a** was similarly obtained as the sole product as well but in somewhat lower yields (Table 1, entries 3 and 5). When pyridine was used as the base and solvent, no desired product was obtained (Table 1, entry 4). In addition, the coupling product **4a** was obtained in lower yields using mixed palladium(II) catalysts such as Pd(OAc)$_2$/CuI/PPh$_3$, PdCl$_2$(PPh$_3$)$_2$/CuI, and Pd(OAc)$_2$/CuI (Table 1, entries 6–8). In the case of some other catalysts such as CuI or NiCl$_2$(PPh$_3$)$_2$, the coupling product **4a** was obtained in much lower yields along with the elimination product **3** (Table 1, entries 9 and 10). Thus, the optimized reaction conditions for this Sonogashira-type reaction are Pd(PPh$_3$)$_4$/CuI as the catalyst and Et$_2$NH as the base and solvent under reflux temperature (Table 1, entry 2).

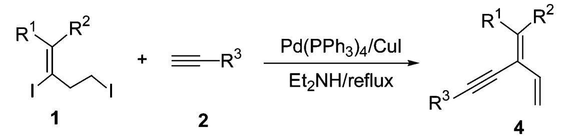
TABLE 2. Sonogashira-type Reaction of Diiodides 1 (0.25 mmol) and Aryl-Substituted Alkynes 2 (0.30 mmol) under the Optimized Reaction Conditions



entry	**1** (R^1/R^2)	**2** (R^3)	yield (%)[a]
1	**1b** (*p*-MeOC$_6$H$_4$/*p*-MeOC$_6$H$_4$)	**2a** (C$_6$H$_5$)	**4b**, 91
2	**1c** (*p*-MeC$_6$H$_4$/*p*-MeC$_6$H$_4$)	**2a**	**4c**, 87
3	**1d** (*p*-ClC$_6$H$_4$/*p*-ClC$_6$H$_4$)	**2a**	**4d**, 97
4	**1e** (Me/*p*-EtOC$_6$H$_4$)	**2a**	**4e**, 71
5	**1b**	**2b** (*p*-MeOC$_6$H$_4$)	**4f**, 82
6	**1a** (C$_6$H$_5$/C$_6$H$_5$)	**2b**	**4g**, 99
7	**1d**	**2b**	**4h**, 99
8	**1b**	**2c** (*p*-ClC$_6$H$_4$)	**4i**, 78
9	**1a**	**2c**	**4j**, 56
10	**1d**	**2c**	**4k**, 60
11	**1e**	**2c**	**4l**, 76

[a] Isolated yields.

TABLE 3. Sonogashira-type Reaction of Diiodides 1 (0.25 mmol) and Alkyl-Substituted 2 (0.30 mmol) under the Optimized Reaction Conditions



entry	**1** (R^1/R^2)	**2** (R^3)	yield (%)[a]
1	**1b** (*p*-MeOC$_6$H$_4$/*p*-MeOC$_6$H$_4$)	**2d** (CH$_2$OH)	**4m**, 30
2	**1c** (*p*-MeC$_6$H$_4$/*p*-MeC$_6$H$_4$)	**2d**	**4n**, 49
3	**1a** (C$_6$H$_5$/C$_6$H$_5$)	**2d**	**4o**, 28
4	**1b**	**2e** (CH$_2$OBn)	**4p**, 92
5	**1c**	**2e**	**4q**, 78
6	**1a**	**2e**	**4r**, 57
7	**1b**	**2f** (*n*-C$_4$H$_9$)	**4s**, 51
8	**1c**	**2f**	**4t**, 47
9	**1a**	**2f**	**4u**, 29

[a] Isolated yields.

To survey the generality of this Sonogashira-type reaction, we next investigated the reactions using some other diiodides **1** with **2a** or other aryl-substituted alkynes **2b** and **2c** as the substrates under the optimized conditions. The results are shown in Table 2. As can be seen from Table 2, the corresponding 2-alkynyl buta-1,3-dienes **4** were obtained in moderate to excellent yields in most cases (Table 2). For substrates **1** in which both R^1 and R^2 are aromatic groups such as **1a**, **1b**, **1c**, and **1d**, the cross-coupling reactions with alkynes **2a** and **2b** proceeded very well to give the desired products **4** in good to excellent yields (Table 2, entries 1–3, 5–7). For aryl-substituted alkyne **2c** with an electron-withdrawing group (Cl-) on the benzene ring, the corresponding products **4** were obtained in relatively lower yields (Table 2, entries 8–10). For substrate **1e** in which R^1 is a methyl group and R^2 is an aryl group, the reactions also proceeded smoothly to give the desired products in good yields (Table 2, entries 4 and 11).

We next explored some alkyl group substituted alkynes **2d**–**f** for this transformation. The results are summarized in Table 3. The reactions proceeded smoothly

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(14) The X-ray data of **4a** have been deposited in CCDC with the number 227450. Empirical formula: C$_{24}$H$_{18}$; formula weight: 306.38; crystal color, habit: colorless, prismatic; crystal system: triclinic; lattice type: primitive; lattice parameters: a = 9.8838(18) Å, b = 10.5056(18) Å, c = 10.8938(19) Å, α = 117.681(3)°, β = 99.163(4)°, γ = 108.395(4)°, V = 885.3(3) Å^3; Space group: $P\bar{1}$; Z = 2; D_{calcd} = 1.149 g/cm^3; F_{000} = 324; diffractometer: Rigaku AFC7R; residuals: R; Rw = 0.0480, 0.0881.

but gave the desired products in somewhat lower yields in contrast to the aryl-substituted alkynes **2a**−**c** (Table 3). For substrate **1**, in which both R^1 and R^2 are aromatic groups such as **1a**, **1b**, and **1c**, the Sonogashira cross-coupling reactions with alkyne **2d** furnished the corresponding products **4** in 28−49% yields (Table 3, entries 1−3). For alkyl-substituted alkyne **2e** in which the hydroxyl group was protected by a benzyl group, the yields of the corresponding products **4** were raised dramatically for the reactions with diiodides **1a**−**c** to 57−92% (Table 3, entries 4−6). For alkyne **2f**, the Sonogashira cross-coupling products **4** were obtained in moderate yields (Table 3, entries 7−9).

Thus, the novel Sonogashira-type reaction of diiodides **1** and alkynes **2** to give 2-alkynyl buta-1,3-dienes **4** in moderate to high yields has been developed.

Conclusions

Some 2-alkynyl buta-1,3-dienes were synthesized by the Sonogashira-type reaction of diiodides **1**, derived from the ring-opening reaction of MCPs with iodine, with some substituted alkynes **2** in the catalysis of $Pd(PPh_3)_4$/CuI. A range of alkynes has been examined. Efforts are in progress to investigate the reaction mechanism and the subsequent transformation thereof.

Experimental Section

General Reaction Procedure for the Sonogashira-type Reaction. Under an argon atmosphere, diiodide **1** (0.25 mmol), alkyne **2** (0.30 mmol), $Pd(PPh_3)_4$ (0.025 mmol), and CuI (0.05 mmol) were added into a Schlenk tube with degassed Et_2NH (1.0 mL). The reaction mixture was stirred under reflux for about 24 h. The solvent was removed under reduced pressure, and then the residue was purified by a flash column chromatography.

Product 4a: A yellow solid, mp 117−120 °C; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 5.31 (dd, 1H, $J = 1.8$, 10.5 Hz), 5.95 (dd, 1H, $J = 1.8$, 16.8 Hz), 6.59 (dd, 1H, $J = 10.5$, 16.8 Hz), 7.19−7.36 (m, 13H, Ar), 7.49−7.53 (m, 2H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 87.8, 94.8, 117.2, 119.9, 123.6, 127.5, 127.8, 127. 9, 128.0, 128.1, 128.3, 130.5, 130.6, 131.4, 134.6, 140.6, 141.90, 149.13. IR (CH_2Cl_2) ν 3058, 3055, 2911, 2837, 1948, 1819, 1596, 1485, 1441 cm^{-1}. MS (%) *m/e* 306 (M^+, 100). Anal. Calcd for $C_{24}H_{18}$: C, 94.08%; H, 5.92%. Found: C, 93.98%; H, 5.91%.

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Supporting Information Available: Spectroscopic data of the compounds shown in Tables 1−3, X-ray crystal data of **4a**, and detailed descriptions of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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