One-Pot Synthesis of Conjugated (*E*)-Enynones via Two Types of Cross-Coupling Reaction

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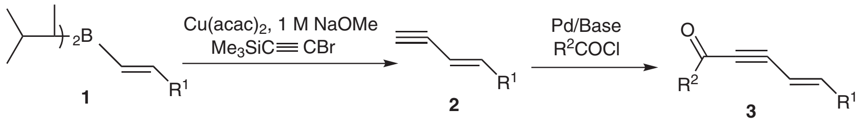
Abstract: (Trimethylsilyl)ethynyl bromide can be easily transformed into conjugated (*E*)-enynones, whose skeleton consists of consecutive carbonyl, ethynyl, and (*E*)-ethenyl units, via a one-pot multicomponent Suzuki-type reaction–Sonogashira reaction sequence. Thus, a three-component coupling of (trimethylsilyl)ethynyl bromide, (*E*)-alk-1-enyldisiamylborane and acid chloride is achieved in a two-step, one-pot procedure, in which (*E*)-alk-1-enyl group is installed as nucleophile in the sp-carbon atom attached to bromine atom and acyl group is installed as electrophile in the other sp-carbon atom.

Key words: (trimethylsilyl)ethynyl bromide, conjugated enynone, cross-coupling, alkenylborane, acid chloride

Conjugated ynones have found a wide range of applications as intermediates in the synthesis of natural products[1] and heterocycles,[2] as well as substrates in organic synthesis through organometallic compounds.[3] A great number of methods have been reported for their preparation, and the methodology can be divided into three categories: (1) the palladium and/or copper-catalyzed coupling reaction of terminal alkynes with acid chlorides (Sonogashira reaction),[4] (2) the cross-coupling reaction between alkynyl organometallic reagents and acid chlorides,[5–15] and (3) the palladium and/or copper-catalyzed carbonylative coupling reaction of terminal alkynes with aryl hahides (carbonylative Sonogashira reaction).[16] Each of them has a characteristic feature. The cross-coupling reaction using alkynyl organometallic reagents can proceed well without employing any base which may give rise to undesired side reaction with acid chloride. Carbonylative Sonogashira coupling can be performed even in protic solvent or ionic liquid. Thus it is possible to choose among many methods according to circumstances.

On the other hand, conjugated enynones, in which the sp-carbon atom of conjugated ynone connects with an alkenyl carbon atom, also play key roles in the synthesis of natural products[17] and [2+2]-photocycloadducts.[18] However, the method for preparing such conjugated enynones is rare,[19] and there are no reports, to our knowledge, on synthesizing conjugated enynones with definite geometry. As part of our ongoing research aimed at assembling π-extended conjugation,[20] we herein report one-pot synthesis of conjugated (*E*)-enynones, (*E*)-1-arylalk-4-en-2-yn-1-ones **3**, under mild reaction conditions. Based on the copper-catalyzed cross-coupling reaction of (*E*)-alk-1-enyldisiamylboranes **1** with (trimethylsilyl)ethynyl bromide leading to the formation of terminal conjugated (*E*)-enynes **2** (Suzuki-type reaction),[21] we envisioned that the desired compounds **3** could be obtained by reaction of compounds **2** with aroyl chlorides (Sonogashira reaction) in a two-step, one-pot manner as illustrated in Scheme 1. Therefore, the main challenge in this one-pot reaction was to investigate the reaction conditions for the Sonogashira reaction.

Optimization of the reaction conditions was explored using (*E*)-dec-3-en-1-yne (**2a**) and benzoyl chloride as model substrates. Thus, the cross-coupling reaction of (*E*)-oct-1-enyldisiamylborane (**1a**) (1 mmol) with (trimethylsilyl)ethynyl bromide (0.67 mmol) was carried out in the presence of $Cu(acac)_2$ (0.05 mmol) and 1 M NaOMe (0.75 mmol) at –15 °C to room temperature overnight to generate compound **2a** (ca. 0.5 mmol).[22] After removal of methanol under reduced pressure, the reaction with benzoyl chloride (1 mmol)[23] was conducted in the presence of palladium source, ligand, and Et_3N (1 mmol)[24] in anhydrous THF at room temperature for two hours. Addition of CuI was unnecessary because $Cu(acac)_2$ had already been used for the cross-coupling reaction of **1a** with (trimethylsilyl)ethynyl bromide. The results are summarized in Table 1. Use of $PdCl_2(PPh_3)_2$ (2 mol% relative to compound **2a**) as a palladium source gave the desired product, (*E*)-1-phenylundec-4-en-2-yn-1-one (**3aa**), albeit in mod-



Scheme 1 The proposed two-step, three-component coupling process

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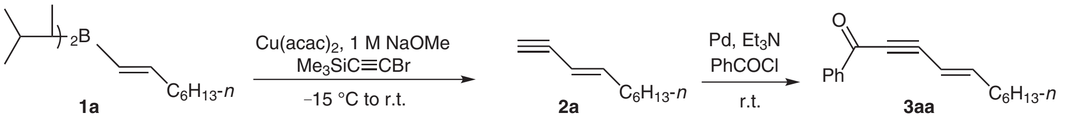
Table 1 Effect of Pd Sources and Ligands on the Cross-Coupling with Benzoyl Chloride[a]



Entry	Pd source	(mmol)	Ligand	(mmol)	Yield of **3aa** (%)[b]
1	$PdCl_2(PPh_3)_2$	0.01	–	–	47
2	$Pd(PPh_3)_4$	0.01	–	–	70
3	$PdCl_2$	0.01	–	–	0
4	$Pd_2(dba)_3{\cdot}CHCl_3$	0.005	–	–	0
5	$Pd(OAc)_2$	0.01	–	–	0
6	$PdCl_2$	0.01	Ph_3P	0.02	80
7	$Pd_2(dba)_3{\cdot}CHCl_3$	0.005	Ph_3P	0.02	86
8	$Pd(OAc)_2$	0.01	Ph_3P	0.02	86
9	$Pd(OAc)_2$	0.01	$(2\text{-furyl})_3P$	0.02	82
10	$Pd(OAc)_2$	0.01	$(4\text{-MeOPh})_3P$	0.02	78
11	$Pd(OAc)_2$	0.005	Ph_3P	0.01	84

[a] Reaction conditions: (1) **1a** (1 mmol), $Me_3SiC{\equiv}CBr$ (0.67 mmol), $Cu(acac)_2$ (0.05 mmol), 1 M NaOMe (0.75 mmol), –15 °C to r.t., overnight; (2) PhCOCl (1 mmol), Pd source, ligand, Et_3N (1 mmol), r.t., 2 h.

[b] Isolated yields based on the amount of **2a** (0.5 mmol) formed.

erate yield (Table 1, entry 1). When $Pd(PPh_3)_4$ (2 mol%) was used in place of $PdCl_2(PPh_3)_2$, the yield of product **3aa** improved considerably (Table 1, entry 2). Ligand-free palladium sources, such as $PdCl_2$, $Pd(OAc)_2$, and $Pd_2(dba)_3{\cdot}CHCl_3$, did not lead to any desired product at all (Table 1, entries 3–5). But, in contrast, the palladium source in combination with Ph_3P (4 mol%) led to high yields of product **3aa** (Table 1, entries 6–8), indicating that phosphine ligand is crucial to the success of this coupling reaction. For our further studies, $Pd(OAc)_2$ is preferable to $PdCl_2$ and $Pd_2(dba)_3{\cdot}CHCl_3$ in terms of the yield and cost. Among phosphine ligands screened, Ph_3P proved to be the best ligand (Table 1, entry 8).[25] Reducing the loading of $Pd(OAc)_2/Ph_3P$ showed a decreasing tendency in the yield of product **3aa** (Table 1, entry 11).

Having established our optimized conditions for the sequential coupling reaction, we examined the scope of the one-pot synthesis of (*E*)-1-arylalk-4-en-2-yn-1-ones **3**. The results are shown in Table 2. Different types of compounds **2** underwent smooth cross-coupling with a variety of aroyl chlorides to afford products **3** in good to high yields. This coupling reaction was successfully applied to compound **2** with a structurally and electronically diverse substituent R^1 (Table 2, entries 1–4). The cross-coupling reaction with various aroyl chlorides was carried out using both (*E*)-dec-3-en-1-yne (**2a**) and (*E*)-4-phenylbut-3-en-1-yne (**2b**). It is noteworthy that the use of compound **2b** provides π-conjugated molecules (Table 2, entries 2, 6, 8, 10, 12, 14, and 16). Electron-donating as well as electron-withdrawing aroyl chlorides could be used as coupling partner (Table 2, entries 5–10). Using condensed aroyl chloride such as 2-naphthoyl chloride, the cross-coupling reaction could also proceed smoothly (Table 2, entries 11 and 12). In addition, heteroaroyl chlorides such as 2-furoyl and 2-thiophenecarbonyl chlorides were good substrates for this coupling reaction (Table 2, entries 13–16).

In summary, we have developed a two-step, one-pot, three-component synthesis of (*E*)-1-arylalk-4-en-2-yn-1-ones **3** using a Suzuki-type reaction–Sonogashira reaction sequence. This protocol is the first method for preparing compounds **3** in good to high yields. The extended scope of this transformation will be reported in due course.

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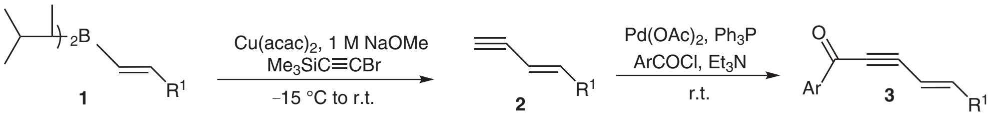
Table 2 Synthesis of (*E*)-1-Arylalk-4-en-2-yn-1-ones[a]



Entry	R^1	Ar	Product	Yield (%)[b]
1	n-C_6H_{13}	Ph	**3aa**	86
2	Ph	Ph	**3ba**	90
3	cyclohex-1-enyl	Ph	**3ca**	92
4	$Cl(CH_2)_3$	Ph	**3da**	88
5	n-C_6H_{13}	2-Tol	**3ab**	90
6	Ph	2-Tol	**3bb**	85
7	n-C_6H_{13}	4-Tol	**3ac**	79
8	Ph	4-Tol	**3bc**	77
9	n-C_6H_{13}	4-ClC_6H_5	**3ad**	78
10	Ph	4-ClC_6H_5	**3bd**	82
11	n-C_6H_{13}	2-naphthyl	**3ae**	87
12	Ph	2-naphthyl	**3be**	77
13	n-C_6H_{13}	2-furyl	**3af**	76
14	Ph	2-furyl	**3bf**	86
15	n-C_6H_{13}	2-thienyl	**3ag**	79
16	Ph	2-thienyl	**3bg**	79

[a] Reaction conditions: (1) **1** (1 mmol), $Me_3SiC{\equiv}CBr$ (0.67 mmol), $Cu(acac)_2$ (0.05 mmol), 1 M NaOMe (0.75 mmol), –15 °C to r.t., overnight; (2) ArCOCl (1 mmol), $Pd(OAc)_2$ (0.01 mmol), Ph_3P (0.02 mmol), Et_3N (1 mmol), r.t., 2 h.

[b] Isolated yields based on the amount of **2** (0.5 mmol) formed.[26]

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(22) Compound **2a** was formed in about 75% GC yield based on $Me_3SiC{\equiv}CBr$ employed, see ref. 21.

(23) Considering that acid chloride would be consumed by reaction with residual both NaOMe and MeOH, an excess amount of benzoyl chloride was employed in this one-pot reaction. Indeed, using a stoichiometric amount of benzoyl chloride (0.5 mmol), a decrease in the yield of product **3aa** was observed.

(24) Among amine bases including *i*-Pr_2NEt, Et_3N was the base of choice for the cross-coupling reaction with benzoyl chloride.

(25) To a solution of BH_3 (1 mmol) in THF (3 mL) was added 2-methylbut-2-ene (0.14 g, 2 mmol) dropwise at –15 °C under argon, and the mixture was stirred for 2 h at 0 °C to form a solution of disiamylborane in THF. To this solution was added oct-1-yne (0.11 g, 1 mmol) dropwise at –15 °C, and the mixture was stirred for 2 h at 0 °C. A solution of (*E*)-oct-1-enyldisiamylborane (**1a**, 1 mmol) in THF, thus prepared, was cooled to –15 °C, and $Cu(acac)_2$ (0.013 g, 0.05 mmol) was added to the solution under a flow of argon, followed by dropwise addition of (trimethylsilyl)ethynyl bromide (0.119 g, 0.67 mmol) and NaOMe (1 M, 0.75 mL, 0.75 mmol). The resulting mixture was allowed to warm gradually to r.t. and stirred overnight. Methanol resulting from 1 M NaOMe was removed under reduced pressure, accompanied by the solvent. After addition of THF (3 mL) to the residue under argon, the resulting mixture including (*E*)-dec-3-en-1-yne (**2a**) was cooled to 0 °C, and $Pd(OAc)_2$ (0.002 g, 0.01 mmol) and Ph_3P (0.005 g, 0.02 mmol) were added successively under a flow of argon, followed by dropwise addition of benzoyl chloride (0.141 g, 1 mmol) and Et_3N (0.101 g, 1 mmol). The resultant mixture was stirred for 2 h at r.t. and then oxidized by the successive addition of 3 M NaOH (1 mL) and 30% H_2O_2 (0.5 mL) at 0 °C. After being stirred for 1 h at this temperature, the mixture was extracted three times with Et_2O. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography on silica gel, with hexane–CH_2Cl_2 (1:1) as eluent, to give (*E*)-1-phenylundec-4-en-2-yn-1-one (**3aa**, 0.103 g, 86%).
Compound **3aa**: ^1H NMR (500 MHz, $CDCl_3$): δ = 0.89 (t, J = 7.1 Hz, 3 H), 1.25–1.35 (m, 6 H), 1.42–1.49 (m, 2 H), 2.21–2.26 (m, 2 H), 5.74 (dt, J = 16.1, 1.5 Hz, 1 H), 6.63 (dt, J = 16.1, 7.1 Hz, 1 H), 7.46–7.50 (m, 2 H), 7.58–7.62 (m, 1 H), 8.13–8.16 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.06 (CH_3), 22.56 (CH_2), 28.22 (CH_2), 28.78 (CH_2), 31.59 (CH_2), 33.64 (CH_2), 86.05 (≡C), 92.85 (≡C), 107.65 (=CH), 128.50 (2 × =CH), 129.50 (2 × =CH), 133.90 (=CH), 136.92 (=C), 153.10 (=CH), 178.11 (C=O). IR (neat): 2954, 2927, 2856, 2183, 1641, 1620, 1596, 1579, 1448, 1313, 1265, 1174, 956, 937, 700 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{17}H_{20}O$: 240.1514; found: 240.1508.

(26) Compounds **2b**–**d** were formed in 72–74% GC yields based on $Me_3SiC{\equiv}CBr$ employed; unpublished results.