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RESEARCH ARTICLE

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A stereo-controlled route to conjugated *E*-enediynes

Abstract 3-Ene-1, 5-diynes are important components of many enediyne antitumor agents and luminescent materials. A stereo-controlled approach to the synthesis of *E*-enediynes was developed, and it consists of the following two steps: (1) a mild and economical synthesis of dihalo vinyl derivatives *via* addition of $CuBr_2$ to alkynes; (2) the Sonogashira coupling reaction of the dihalo vinyl derivatives with terminal alkynes to form conjugated enediynes.

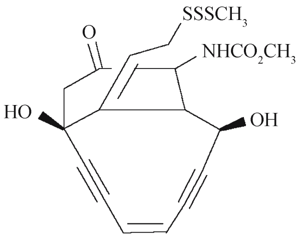
Keywords enediynes, Sonogashira reaction, dihalo alkenes, $CuBr_2$

1 Introduction

3-Ene-1,5-diynes are important components of many enediyne antitumor agents and luminescent materials [1]. There are many *cis*- or *trans*-fused examples of the enediynes derivatives, such as the recently discovered ten-member antibiotics calicheamicinone **1** [2], the cross-coupling annulus dodecadehydro[18] annulenes **2** [3], and the poly-alkynes nano-tube material **3** [4].

Various methods have been developed for the synthesis of *cis*- or *trans*-fused enediynes [5]; however, these multi step approaches are hardly handled and thus applied in a limited scope. Furthermore, in some methods, toxic and photosensitive zirconium complexes have been used as the reaction intermediate [6]. Therefore, it is still of great significance to develop new methods for the synthesis of enediyne compounds bearing structural units **6** and **7** from the alkynes **4** by a simple and easy handling way (Scheme 1).

Dihalo vinyl derivatives are highly valuable compounds with wide applications in the synthesis of medicine, pesticide, flavoring, and polymer. The traditional method to prepare these compounds involves direct addition reaction of halogen



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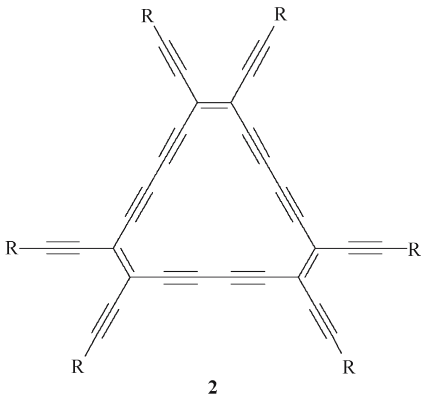

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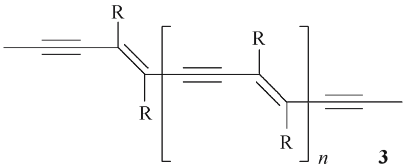

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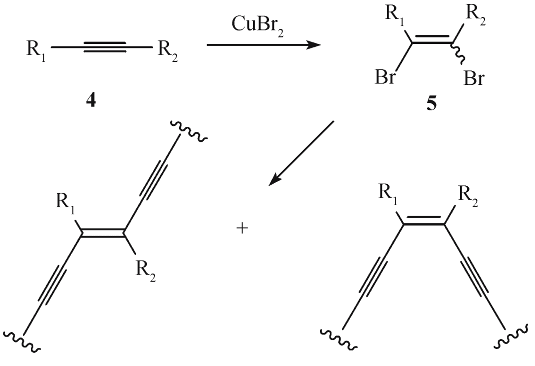

Scheme 1

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with alkynes. However, this addition often results in poor regio- and stereo-selectivity, and separation of the resulting isomeric products is often non-trivial. Other halides, such as BX_3 [7], $TBAX_3$ [8], SOX_2 [9], are also employed in the halogen addition, but they are very irritant and baleful to health. These facts promote us to explore new and practical halogenating reagents for the synthesis of dihalo vinyl derivatives.

Herein reported is a stereo-controlled approach to the synthesis of *E*-enediynes *via* addition of $CuBr_2$ to alkynes followed by Sonogashira coupling reaction of the obtained dihalo vinyl derivatives with terminal alkynes.

2 Results and discussion

2.1 Synthesis of dihalo vinyl derivatives

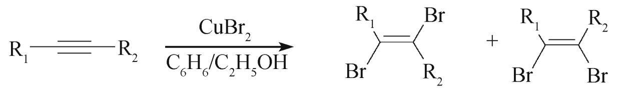
Initially a variety of solvents were screened to evaluate their effects on yield and *E/Z* selectivity. In our research, but-2-ynedioic acid diethyl ester was used as the alkyne reagent. Among the solvents being tried (C_2H_5OH, CH_3CN, DMSO, THF and benzene), C_2H_5OH, CH_3CN and DMSO resulted in satisfactory yield, but poor *E/Z* selectivity (entry 1−3). On the contrary, THF or benzene was found to afford the corresponding product in lower yields but with high *E/Z* selectivity (entries 5, 6). This observation suggested that the *E/Z* selectivity was strictly controlled by the polarity of the solvents. Taking to account, both the selectivity and yield, benzene was mixed with ethanol, and it was found that the ratio of benzene/ethanol (10:0.6) was suitable for the desired yield and *E/Z* selectivity (Table 1).

Table 1 Effect of solvent on the yields and *E/Z* ratios of the addition

Entry	Copper halide	Solvent	Isolated yield /%	E/Z[a)]
1	$CuBr_2$	EtOH	87	64:36
2	$CuBr_2$	CH_3CN	94	58:42
3	$CuBr_2$	DMSO	90	62:38
4	$CuBr_2$	THF	52	74:26
5	$CuBr_2$	C_6H_6	36	99:1
6	$CuBr_2$	C_6H_6/EtOH(10:0.6)	89	96:4
7	$CuCl_2$	C_6H_6/EtOH(10:0.6)	92	96:4

[a)] Ratio was determined by GC.

Under the optimized reaction conditions, a variety of alkynes were employed to probe the scope of this halogenation reaction (Scheme 2).



4a-4f

5a-f

a: $R_1 = R_2 = CO_2C_2H_5$; b: $R_1 = R_2 = CH_2Cl$; c: $R_1 = Ph$, $R_2 = CH_3$;
d: $R_1 = R_2 = C_3H_7$; e: $R_1 = C_2H5$, $R_2 = CH_2OH$; f: $R_1 = R_2 = CH_2OH$

Scheme 2

As shown in Table 2, using various alkynes as the reagents, the addition reaction was carried out smoothly giving the corresponding dihalo vinyl derivatives, with excellent yields and high stereo- and chemo-selectivity with an exception of **5b**. The modest yield of **5b** was due to the halogen exchange between **4b** and $CuBr_2$.

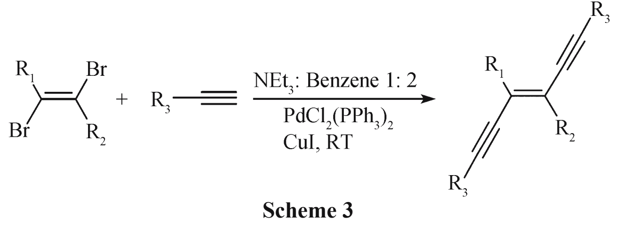
Table 2 Results of various alkynes reaction with $CuBr_2$

Entry	Reagents[a)]	Time/h	Isolated yield	E/Z[b)]
1	**4b**	8	58	99:1
2	**4c**	6	87	99:1
3	**4d**	2	96	99:1
4	**4e**	12	91	95:5
5	**4f**	12	95	99:1

[a)] Reaction condition: alkynes (0.01 mol/L) and 2.2 equiv of CuX_2 in benzene/ethanol (10:0.6), 70°C, 2−12 h; [b)] determined by ^1H and/or ^{13}C-NMR

2.2 Synthesis of enediynes via Sonogashira coupling reaction

The Sonogashira coupling, Pd/CuI-catalyzed C—C formation of terminal alkynes with halides in the presence of excess amounts of organic amine, has widely been used as a practical tool of synthetic strategies [10]. The above dihalo vinyl derivatives were then used in the Sonogashira coupling with terminal alkynes to construct conjugated enediynes (Scheme 3). Reactions were performed with dihalo olefins **5** under the optimized conditions including $PdCl_2(PPh_3)_2$-CuI catalysis. We found that the coupling reaction was relatively sensitive to the electronic nature of the substituents on the carbon-carbon double bonds. The reaction was carried out smoothly with good yield when there were electron-withdrawing groups on the double bonds (entry 1−2). When the groups on the double bonds were electron-donating, the yields decreased sharply (entry 3, 5). In addition, the reaction must be carried out under N_2 atmosphere, otherwise, the Glaser coupling products were obtained predominantly [11]. The use of less reactive vinyl chlorides as coupling reagent (**5a'**, obtained by replacing Br of **5a** with Cl) afforded the desired product **8** only in 24% yield (entry 6), indicating that the coupling reaction was also influenced by the leaving groups on the double bonds.



Scheme 3

In conclusion, we have described a highly stereo-selective synthesis of *E*-enediynes *via* the Sonogashira coupling reaction of terminal alkyne with dihalo ethylene. We also developed a stereo-controlled route for the synthesis of dihaloe vinyl derivatives using copper salts in mixed solvents (benzene/ethanol 10:0.6) at moderate temperature. This method was more efficient and convenient than those previously reported methods.

Table 3 Results of Sonogashira coupling reaction

Entry	Reagents	R_3	Products	Yield[a)]/%
1	**5a**	Ph	**8**	91
2	**5a**	p-toylene	**9**	83
3	**5c**	Ph	**10**	15
4	**5d**	Ph	**11**	47
5	**5f**	Ph	**12**	0
6	**5a’**	Ph	**8**	24

[a)] Isolated yield

3 Experimental

3.1 General procedure for the dihalo vinyl compounds 5

To a stirred mixture of $CuBr_2$ (4.95 g, 0.022 mol) in benzene and ethanol (53 mL, volume ratio = 10:0.6) was added alkynes **4** [12] (0.01 mmol), and the resulting mixture was stirred at 70°C for 12 h. After the completion of the reaction, the mixture was poured into saturated aqueous sodium chloride (50 mL) and extracted with ether. The organic layer was separated, washed twice with saturated aqueous sodium chloride, dried over magnesium sulfate, and concentrated by rotary evaporation under diminished pressure to yield the product **5**.

5a: yellow oil, yield 92%; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 4.34 (q, J = 7.2 Hz, 2H), 1.35 (t, J = 6.8 Hz, 3H); IR (KBr) ν: 3460, 2987, 1740, 1603, 1465, 1371, 1242, 1028, 853, 756 cm^{-1}. MS (70 eV) *m*/*z*: 330 (M$^+$, 46), 285 (100), 256 (67), 205 (82), 177 (73), 131 (36), 29 (81).

5b: yellow oil, yield 58%; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 4.09 (s, 2H); IR (KBr) ν: 3024, 2974, 1735, 1604, 1427, 1376, 1266, 1214, 1106, 925, 723, 624 cm^{-1}. MS (70 eV) *m*/*z*: 282 (M$^+$, 80), 246 (77), 203 (72), 167 (77), 122 (70), 87 (100), 51 (98).

5c: yellow oil, yield 87%; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.34−7.35 (m, 5H), 2.59 (s, 3H); ν: 3042, 2975, 1723, 1604, 1501, 1459, 1380, 1112, 764, 706, 620 cm^{-1}. MS (70 eV) *m*/*z*: 276 (M$^+$, 17), 195 (23), 115 (100), 87 (14).

5d: yellow oil, yield 96%; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 2.64 (t, J = 7.2 Hz, 2H), 1.58(m, 2H), 0.93 (t, J = 8.0 Hz, 3H); IR (KBr) ν: 2963, 2931, 2872, 1721, 1459, 1380, 1113, 887, 746, 620 cm^{-1}. MS (70 eV) *m*/*z*: 270 (M$^+$, 100), 189 (6), 109 (85), 79 (28), 67 (32).

5e: yellow oil, yield 91%; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 4.49 (s, 2H), 2.70 (q, J = 7.2 Hz, 2H), 1.12 (t, J = 7.6 Hz, 3H); IR (KBr) ν: 3268, 2970, 1715, 1436, 1378, 910, 742, 622 cm^{-1}. MS (70 eV) *m*/*z*: 244 (M$^+$, 22), 163 (17), 145 (20), 83 (100), 55 (78), 39 (46).

5f: yellow solid, yield 95%; m.p. 112−114°C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 4.47 (d, J = 6.0 Hz, 2H), IR (KBr) ν: 3262, 2939, 1630, 1442, 1369, 1251, 1078, 1016, 740 cm^{-1}. MS (70 eV) *m*/*z*: 246 (M$^+$, 14), 165 (9), 85 (35), 31 (76), 29 (100).

3.2 General procedure for the enediynes

A nitrogen-flushed round bottom flask was charged with $PdCl_2$ (10 mg), PPh_3 (30 mg) and CuI (19 mg), then the mixture of **5a** (110 mg, 0.5 mmol) and phenylacetylene (222 mg, 2.2 mmol) dissolved in NEt_3 and benzene (6 mL, volume ratio = 1:2) was added. The reaction was carried out at room temperature for 48 h. Most of the solvents was removed by distillation and the crude product was purified by silica gel chromatography (petroleum ether:ethyl acetate = 15:1 *V*:*V*) to give the product.

8: yellow solid, yield 91%; m.p. 87−90°C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.53−7.55 (m, 2H), 7.45−7.48 (m, 3H), 4.39 (q, J = 7.2 Hz, 2H), 1.37 (t, J = 7.2 Hz, 3H). IR (KBr) ν: 3037, 2960, 1742, 1648, 1564, 1490, 935, 813, 752 cm^{-1}. MS (70 eV) *m*/*z*: 372 (M$^+$, 41), 327 (100), 272 (68), 271 (31), 131 (39), 29 (74). Anal. calcd for $C_{24}H_{20}O_4$: C 77.42, H 5.38; found C 77.56, H 5.31.

9: yellow solid, yield 83%; m.p. 105−106°C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.50−7.52 (m, 2H), 7.30−7.33 (m, 2H), 4.35 (q, J = 7.2 Hz, 2H), 2.34 (s, 3H), 1.37 (t, J = 7.2 Hz, 3H). IR (KBr) ν: 3057, 1742, 1637, 1251, 1056, 943, 854 cm^{-1}. MS (70 eV) *m*/*z*: 400 (M$^+$, 27), 355 (100), 310 (81), 284 (15), 131 (39), 97 (8), 53 (20), 29 (74). Anal. calcd for $C_{26}H_{24}O_4$: C 78.00, H 6.00; found C 78.27, H 6.11.

10: yellow oil, yield 15%; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.51−7.53 (m, 4H), 7.24−7.36 (m, 9H), 2.65 (s, 3H). IR (KBr) ν: 3038, 2962, 1643, 1560, 1495, 923, 854, 813, 758, 690 cm^{-1}. MS (70 eV) *m*/*z*: 318 (M$^+$, 83), 303 (100), 202 (66), 77 (51), 63 (18), 39 (32). Anal. calcd for $C_{25}H_{18}$: C 94.34, H 5.67; found C 94.29, H 5.77.

11: yellow oil, yield 47%; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.47−7.52 (m, 4H), 7.24−7.32 (m, 6H), 2.39(t, J = 7.56 Hz, 4H), 1.58−1.66 (m, 4H), 1.36−1.48 (m, 4H), 0.96 (t, J = 7.30 Hz, 6H), IR (KBr) ν: 2932, 1599, 1450, 760, 696 cm^{-1}. MS (70 eV) *m*/*z*: 312 (100), 211 (16), 109 (81), 79 (28), 67 (32).

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