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A Convenient Method for the Preparation of Furans by the Phosphine-Initiated Reactions of Enynes Bearing a Carbonyl Group

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Abstract

Furans having a double bond at the α-position were obtained by phosphine-initiated cyclization of enynes bearing a carbonyl group at the ene-side in the presence of aldehyde in high yield. The reaction may involve the 1,6-addition of phosphine toward the enynes, ring closure, and Wittig reaction of the ylid resulted from the cyclization with aldehyde.

Keywords: furans, enynes, cyclization, and phosphine

The development of cyclization reactions is essentially important in organic chemistry to construct the cyclic systems that can be seen in naturally occurring products. A number of cyclic systems containing one oxygen atom are present in nature (*e.g.*, hydrofuran, furan ring). As long-standing, useful synthetic procedures of the furan ring, the Paal-Knorr method[1a], the Feist-Benary method[1b], the synthetic method[1c] from acetylenes, the method[1d] from ylids, and others have employed. A recent tendency in the system construction has been the predominant use of organometallic catalysts[2]. For example, Trost *et al.* have reported synthesis of furans by palladium catalyzed cross-coupling reaction of two acetylenes[2a]. However, in the procedures mentioned above, the variation of substituents and the position of substituents on the ring may be much more limited. Herein, we wish to propose a novel,

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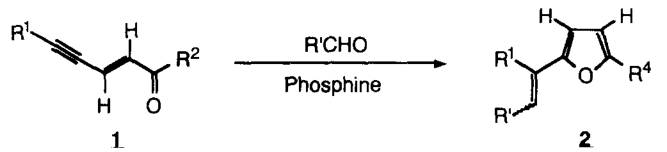
convenient procedure of furan ring construction from enynes (**1**) bearing a carbonyl group at the ene-side (Scheme 1). The development of this reaction is expected to overcome the limitations of the foregoing long-standing methods.

Scheme 1



1, **2**	R^1	R^2
a	Bu	Ph
b	Bu	Me
c	Ph	Ph
d	Ph	Me

The reaction of **1a**-**d** with benzaldehyde (1 equiv.) was carried out in CH$_2$Cl$_2$ for 12 h at room temperature in the presence of tributylphosphine (1 equiv.) to yield the corresponding furans (**2a**-**d**)^2. In the case of R^1: alkyl groups (*i.e.*, **1a** and **1b**), **2a** and **2b** were obtained in 83 and 56 % yields, respectively. On the other hand, in the case of R^1: aromatics (*i.e.*, **1c** and **1d**), the reaction gave a complex mixture only containing slightly the corresponding furan. From the results, it was found that the yields were markedly influenced by R^1 rather than R^2.

The reaction of **1a** with benzaldehyde was carried out in various solvents. As shown in Table 1, CH$_2$Cl$_2$ was the most favorable as solvent. Although the yields decreased slightly, benzene and THF also gave good results as well as CH$_2$Cl$_2$. On the other hand, nitromethane, DMF, and methanol were less appropriate due to occurrence of some side-reactions.

Table 1. The reaction of **1a** with benzaldehyde in the various solvents$^{a)}$

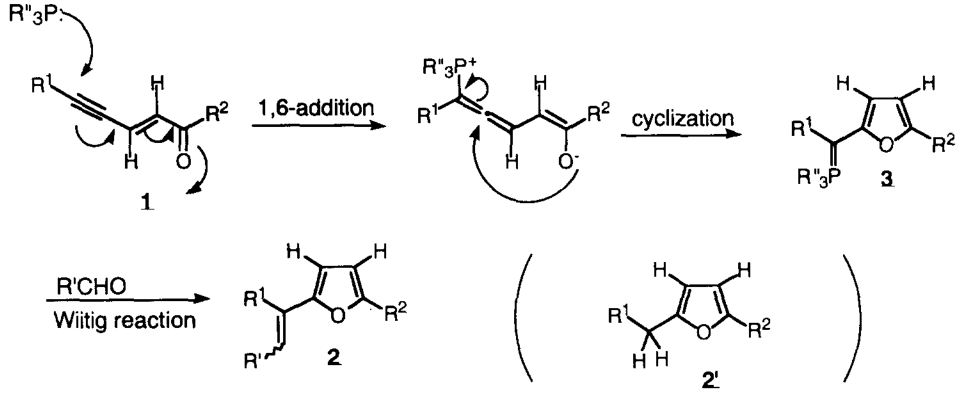
Runs	Solvent	Yield / %	Runs	Solvent	Yield / %
1	CH$_2$Cl$_2$	83	5	DMF	34
2	THF	78	6	MeOH	6
3	Benzene	75	7	MeCN	52
4	Hexane	56	8	MeNO$_2$	0$^{b)}$

a) The reaction of **2a** with benzaldehyde (1 equiv.) was carried out in various solvents at room temperature for 12 h in the presence of tributylphosphine (1 equiv.).

b) 1,4-Adduct of **2a** with nitrometane was obtained in 50 % yield.

The reaction of **1a** with benzaldehyde was carried out in CH$_2$Cl$_2$ in the presence of a stoichiometric amount of triphenylphosphine or triethylamine instead of tributylphosphine, respectively. Although the corresponding furan (**2a**) was obtained in 73% yield in the presence of triphenylphosphine, the starting material (**1a**) was mostly recovered in the case of triethylamine. Moreover, when 0.5 equiv. of tributylphosphine was used, the yield reduced approximately by half. These results may suggest the plausible mechanism shown in Scheme 2.

Scheme 2



The reaction may be initiated by 1,6-addition of phosphine toward **1**, followed by cyclization to yield ylid (**3**) as an intermediate, and then Wittig reaction of **3** with aldehyde may take place to give furan (**2**) having a double bond at the α-position. Therefore, in the presence of triethylamine, the reaction might not proceed, thus, precluding generation of **3**. To reveal the formation of ylid (**3**), **1a** was treated in CH_2Cl_2 with tributylphosphine (1equiv.) in the presence of water (5 equiv.) without aldehyde. As the result, furan (**2'**) containing no double bonds at the α-position was obtained by the hydrolysis[3] of the ylid in 58% yield. **2'** was not obtained when **1a** was treated with tributylphosphine without water and aldehyde. These results may suggest formation of ylid (**3**) in the reaction process. In the cases of **1c** and **1d**, **3** stabilized by double aromatic rings might generate as the intermediate based on the mechanism. Generally, such a ylid is too inert to react with aldehyde[4]. Therefore, the corresponding furans might not be obtained in the case of **1c** and **1d**.

Although this reaction was severely limited by substituents R^1, the effects of other substituents on the enyne compounds and aldehydes relating to the yield may be mostly disregarded in the plausible mechanism. Therefore, if various types of **1** can be prepared conveniently, this reaction might be an important method for synthesis of various multi-substituted furans which are currently being investigated in detail.

A typical procedure for preparation of **2a**: To a solution of **1a** (200 mg, 0.943 mmol) and benzaldehyde (100 mg, 0.943 mmol) in CH_2Cl_2 (1.9 mL) was added tributylphosphine (190 mg, 0.943 mmol) at room temperature. After stirring 12 h, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate=200/1) to give 236 mg (82.9%) of **2a**; R_f= 0.63 on TLC (hexane/ethyl acetate=4/1); IR (neat) 3057, 2957, 2930, 1701, 1653, 1599, 1456 cm^{-1}; ^{1}H NMR (400 MHz, δ, ppm) 0.95 (t, *J*=7.32 Hz, 3H, $C\underline{H}_3$-), 1.44 (m, 2H, $CH_3C\underline{H}_2$-), 1.66 (m, 2H, -$CH_2C\underline{H}_2CH_2$-), 2.61 (t, *J*=8.28 Hz, 2H, -$CH_2CH_2C\underline{H}_2$-), 6.45 (d, *J*=3.40 Hz, 1H, furan-H), 6.68 (d, *J*=3.40 Hz, 1H, furan-H) 7.19 (s, 1H, -C$\underline{H}$=), 7.20-7.75 (m, 10H, Ph), ; ^{13}C NMR(100 MHz, δ, ppm) 13.9, 23.0, 28.2, 32.0, 107.0, 108.6, 123.7, 124.2, 126.6, 127.3, 128.3, 128.7, 128.8, 130.8, 131.6, 137.5, 137.5, 153.0, 155.2. The obtained furan (**2a** and **2b**) was a single isomer as revealed by instrument analysis (*e.g.*, ^{1}H NMR). Although the stereo of the double bond containing the structure has not been determined, we consider the obtained furans (**2a** and **2b**) *E*-isomer from the general reactive character of the ylids stabilized by Ar as **3**[5].

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