



A general approach to arylated furans, pyrroles, and thiophenes



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ABSTRACT

A general and practical synthetic method for aryl-substituted five-membered heterocycles has been developed. In the presence of KOH (30%), 1,4-diaryl-1,3-butadiynes undergo the cyclocondensation reaction with water, primary amines, and $\text{Na}_2\text{S}\cdot 9\text{H}_2\text{O}$ in DMSO at 80 °C to afford 2,5-diarylfurans, 1,2,5-trisubstituted pyrroles, and 2,5-diarylthiophenes in good to high yields. Further studies have disclosed that aryl-substituted five-membered heterocycles can be also synthesized by a one-pot, two-step strategy from the terminal alkynes in DMSO firstly catalyzed by CuCl, and then via addition of KOH to promote the cyclocondensation of 1,3-butadiynes generated in situ.

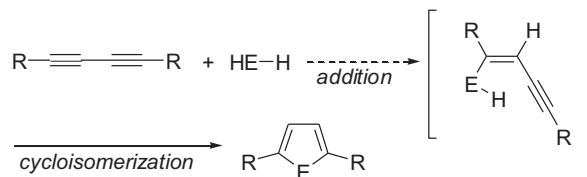
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1. Introduction

Cyclocondensation of alkynes represent one of the most powerful methods for the synthesis of cyclic compounds with the significant advantages of high-atom efficiency and easy availability of starting materials, which has been well applied in the synthesis of highly functionalized cyclic compounds.¹ Development of efficient and practical synthetic methods to synthesize functionalized five-membered heterocycles of furans, pyrroles, and thiophenes is one of important research topics in synthetic chemistry, since they have interesting biological and physiological activities, and versatile applications in the synthesis of other heterocycles. On the other hand, 1,3-butadiyne derivatives have been applied as important building blocks for the synthesis of various carbo- and heterocyclic compounds, and recently, a number of reports on the transition metal-catalyzed synthesis of naphthalenes,² furans,³ thiophenes,^{3d,4} pyrroles,^{3b,5} and other cyclic compounds⁶ using 1,3-butadiyne derivatives as starting materials have appeared in the literature. Encouraged by our previous success in the preparation of pyrroles,^{5c} furans,^{3e} and benzo[*f*]quinazolines⁷ via the cycloaddition of 1,3-butadiynes with primary amines, water, and nitriles, respectively, we investigated the possibility in this paper to establish a general procedure for the synthesis of five-membered heterocycles using 1,4-disubstituted 1,3-butadiynes as one of the reactants and without use of transition metal complex as catalyst.

2. Results and discussion

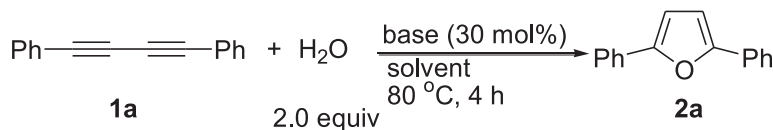
As depicted in [Scheme 1](#), the five-membered heterocycles are expected to form via the cycloaddition of 1,3-butadiynes with E–H bond (E=O, S, and N). The challenging work is to optimize a general catalytic system, which can promote both intermolecular addition and intramolecular cycloaddition of E–H bond across C–C triple bonds. On the basis of the previous reports, it seems that the presence of basic additives is one of the crucial factors to promote the transformation of 1,3-butadiynes to furan derivatives in the presence of Cu^{3d} and Pd.^{3e} Therefore we examined the reaction of 1,4-diphenyl-1,3-butadiyne (**1a**) with water in presence of a variety of basic compounds without the use of transition metal catalyst to investigate the possibility to synthesize 2,5-diarylfuran (**2a**).



Scheme 1. Formation of five-membered heterocycles via the cyclocondensation of 1,3-butadiyne.

As concluded in [Table 1](#), it proved possible to obtain the desirable **2a** in high isolated yield when 30% of KOH was used as catalyst in DMSO at 80 °C for 4 h (entry 7), although other inorganic bases, such as NaHCO_3 , Na_2CO_3 , K_2CO_3 , K_3PO_4 , Cs_2CO_3 (entries 1–5), and organic bases such as DBU (1,8-diazabicyclo[5.4.0]undec-7-ene),

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Table 1Formation of 2,5-diphenylfuran from the cyclocondensation of 1,4-diphenyl-1,3-butadiyne with water under different conditions^a

Entry	Base	Solvent	Yield ^b (%)
1	NaHCO ₃	DMSO	0
2	Na ₂ CO ₃	DMSO	0
3	K ₂ CO ₃	DMSO	0
4	K ₃ PO ₄	DMSO	0
5	CS ₂ CO ₃	DMSO	<5
6	NaOH	DMSO	67
7	KOH	DMSO	96 (92)
8	KOH	DMF	37
9	KOH	THF	13
10	KOH	CH ₃ CN	<5
11	KOH	1,4-Dioxane	0
12	KOH	1,2-DCE	0
13	DBU	DMSO	<5
14	NEt ₃	DMSO	0
15	DABCO	DMSO	0
16 ^c	KOH	DMSO	88
17 ^d	KOH	DMSO	72
18	—	DMSO	0

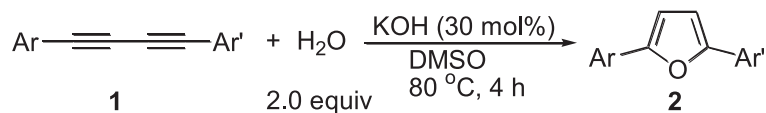
^a Reaction conditions: **1a** (1.0 mmol), H₂O (2.0 mmol), and base (0.3 mmol) in solvent (2.0 mL) at 80 °C for 4 h.^b GC yield of **2a**, and isolated yield in parenthesis.^c KOH of 20 mol % was used.^d KOH of 10 mol % was used.

Et₃N, and DABCO (1,4-diazabicyclo[2.2.2]octane) (entries 13–15) showed no catalytic activity at all. It was also found that NaOH in DMSO showed moderate catalytic activity (entry 6), and the catalytic activity of KOH greatly depended on the nature of solvents. When DMF, THF, and CH₃CN were used as solvents, KOH showed fair and low catalytic activity (entries 8–10), and in 1,4-dioxane and 1,2-DCE, no catalytic activity was observed (entries 11 and 12). Decrease of the amount of KOH resulted in the considerable

decrease of yields (entries 16 and 17). In addition, it was confirmed that no **2a** was formed in the absence of KOH (entry 18).

In fact, KOH/DMSO as the superbasic medium showing versatile diverse catalytic activity has been well applied in a variety of organic transformation reported by Trofimov,⁸ Bolm,⁹ and other groups.¹⁰

The results shown in Table 2 verify the scope and generality for the formation of 2,5-diarylfurans using KOH/DMSO catalyst system.

Table 2Synthesis of 2,5-diarylfurans from the reaction of 1,4-diaryl-1,3-butadiyne with water^a

Entry	Ar, Ar'	Yield of 2 ^b (%)
1	Ar=Ar'=p-tolyl	1b 2b 92
2	Ar=Ar'=o-tolyl	1c 2c 83
3	Ar=Ar'=m-tolyl	1d 2d 90
4	Ar=Ar'=p-EtC ₆ H ₄	1e 2e 90
5	Ar=Ar'=p- ⁿ PrC ₆ H ₄	1f 2f 87
6	Ar=Ar'=p- ⁿ BuC ₆ H ₄	1g 2g 89
7	Ar=Ar'=p- ⁿ C ₅ H ₁₁ C ₆ H ₄	1h 2h 86
8	Ar=Ar'=p-MeOC ₆ H ₄	1i 2i 91
9	Ar=Ar'=3,5-Me ₂ C ₆ H ₃	1j 2j 87
10	Ar=Ar'=2-naphthyl	1k 2k 87
11	Ar=Ar'=p-ClC ₆ H ₄	1l 2l 90
12	Ar=Ar'=p-FC ₆ H ₄	1m 2m 88
13	Ar=Ar'=p-CF ₃ C ₆ H ₄	1n 2n 85
14	Ar=Ar'=2-thienyl	1o 2o 90
15	Ar=Ph	1p 2p 91
16	Ar'=p-EtOC ₆ H ₄	
	Ar=Ph	1q 2q 86
	Ar'=2-Naphthyl	
17	Ar=p- ⁿ PrC ₆ H ₄	1r 2r 90
	Ar'=p-EtOC ₆ H ₄	

^a Unless otherwise noted, the reactions were carried out using **1** (1.0 mmol), H₂O (2.0 mmol), and KOH (0.3 mmol) in DMSO (2.0 mL) at 80 °C for 4 h.^b Isolated yield.

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