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Synthesis of alkynes under dry reaction conditions

Maddali L.N. Rao *, Sk Shamim Islam

Department of Chemistry, Indian Institute of Technology Kanpur, Kanpur 208016, India

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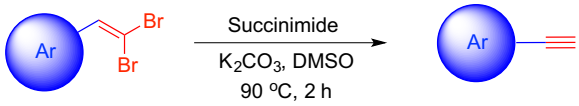
ABSTRACT

An easy synthetic method was developed under dry reaction conditions for the preparation of terminal alkynes from 1,1-dibromoalkenes and in the presence of succinimide which acts as a nucleophile and proton donor. It was demonstrated with the synthesis of a broad spectrum of terminal alkynes and extended to synthesize internal alkynes under tandem reaction conditions.

Alkynes are valuable synthons in organic chemistry for the synthesis of natural products, pharmaceuticals, and functional materials [1]. Terminal alkynes are also useful in several chemical transformations [2], including the preparation of conjugated diynes [3], heterocycles [4], in Sonogashira [5] and click reactions [6]. Importantly, 1,1-dibromoalkenes are easily accessible from aldehydes and serve as robust precursors in the preparation of terminal alkynes [7,8]. The preparation of terminal alkynes [8] from 1,1-dibromoalkenes occurs through the carbene pathway, β-elimination, or 1-bromoalkyne formation. Some of these reactions are known to involve strong and air-sensitive bases [7b-d,8] such as *n*-BuLi, LDA, Grignard reagents, and inorganic bases under aqueous conditions. In continuation of our interest in developing synthetic tools using 1,1-dibromoalkenes [9,10], it was interest to develop an efficient method for the synthesis of terminal alkynes under dry conditions. It led to the successful development of an effective protocol for the preparation of terminal alkynes from 1,1-dibromoalkenes and succinimide under dry conditions (Scheme 1).

The dual role of succinimide was envisaged as a good nucleophile in the DMSO solvent [11] and a proton donor in the reaction course. Our established protocol is more valuable and synthetically advantageous in comparison to various reported methods [8], which involve strong bases, pyrophoric reagents, and longer reaction times. Further, our dry protocol can be extended to one-pot tandem functionalizations.

To establish the reaction protocol, the reaction of 1,1-dibromoalkene (**1a**) was screened in the presence of succinimide under



Scheme 1. Preparation of terminal alkynes.

different conditions (Table 1). The initial screening was performed with K_3PO_4 in dry DMSO at 60 °C for 6 h (Table 1, entry 1). These conditions afforded the corresponding terminal alkyne (**2a**) in 65% yield and minor amount 1-bromoalkyne (**1.1**). It was further screened with $NaHCO_3$ and K_2CO_3 (Table 1, entries 2 and 3). Of these two bases, K_2CO_3 proved as more useful to furnish the alkyne **2a** in 74% yield. It was further screened to set the protocol conditions. For example, the reaction performed in 2 h conditions also gave alkyne **2a** in 76% yield (Table 1, entry 4). However, the reaction with 1 h conditions afforded only 53% yield (Table 1, entry 5). The reaction temperature with 70 °C proved to be low-yielding (Table 1, entry 6). The additional decrease in K_2CO_3 loading furnished a lowered yield (Table 1, entry 7). Also, the use of 1 equiv succinimide provided 36% yield (Table 1, entry 8). Another control reaction without succinimide did not furnish the alkyne **2a** and gave the corresponding 1-bromoalkyne in 72% yield (Table 1, entry 9). The formation of 1-bromoalkyne indicated the vital role of succinimide in the overall reaction course in furnishing the alkyne **2a**. This screening thus furnished the reaction conditions comprising 1,1-dibromoalkene (1 equiv), succinimide (2 equiv), K_2CO_3 (6 equiv) in DMSO at 90 °C for 2 h as the standardized protocol (Table 1, entry 4).

* Corresponding author.
E-mail address: maddali@iitk.ac.in (M.L.N. Rao).

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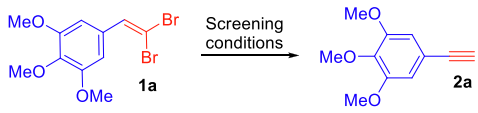
Table 1
Screening conditions.[a,b]



Entry	Base	Temp. (°C)	Time (h)	Yield (%)
1	K_3PO_4	60	6	65
2	$NaHCO_3$	90	6	58
3	K_2CO_3	90	6	74
4	K_2CO_3	90	2	76
5	K_2CO_3	90	1	53
6	K_2CO_3	70	2	61
7	K_2CO_3	90	2	49[c]
8	K_2CO_3	90	2	36[d]
9	K_2CO_3	90	2	–[e]

[a] Reaction conditions: **1a** (0.375 mmol, 1 equiv), succinimide (0.75 mmol, 2 equiv), base (2.25 mmol, 6 equiv), dry DMSO (3 mL), temp., time.
[b] Isolated yields.
[c] K_2CO_3 (4 equiv).
[d] Succinimide (1 equiv).
[e] Without succinimide.

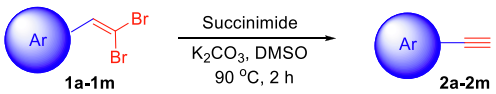
The synthetic efficacy of the above established protocol was further examined in the preparation of a variety of terminal alkynes involving different 1,1-dibromoalkenes (Table 2). The initial study using electronically rich 1,1-dibromoalkenes (**1a-1d**) furnished the corresponding terminal acetylenes **2a-2d** in 64–86% yields. Investigations using 1-naphthyl, 2-naphthyl, and 9-anthracenyl substituted 1,1-dibromoalkenes (**1e-1g**) delivered the corresponding terminal alkynes **2e-2g** in 75–96% yields. Also, 1,1-dibromoalkenes (**1h** and **1i**) with electron-withdrawing groups provided the corresponding terminal alkynes **2h** and **2i** in good yields. Halogenated 1,1-dibromoalkene such as 1-bromo-4-(2,2-dibromovinyl)benzene (**1j**) afforded the terminal alkyne **2j** in 75% yield. Our protocol was also applied to heteroaromatic 1,1-dibromoalkenes (**1k** and **1l**) and gave the corresponding terminal alkynes **2k** and **2l** in good yields. Similarly, 4-(2,2-dibromovinyl)-*N*,*N*-diphenylaniline (**1m**) also reacted well to give terminal alkyne **2m** in 69% yield. Notably, this study revealed the higher reactivity of electron-rich 1,1-dibromoalkenes over electron-deficient ones under the established optimized conditions (Table 2).

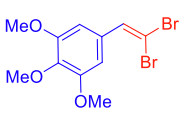
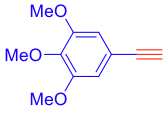
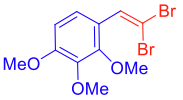
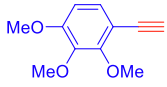
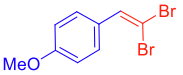
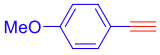
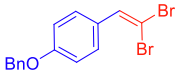
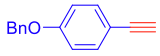
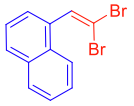
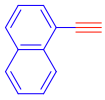
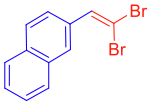
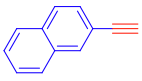
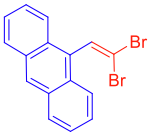
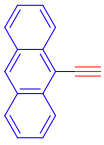
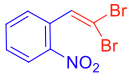
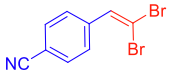
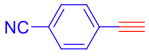
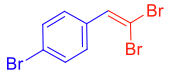
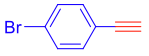
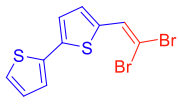
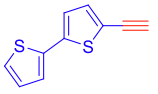
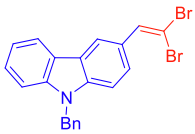
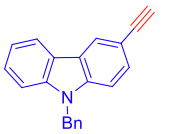
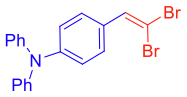
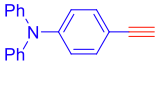
The reactivities of various functionalized 1,1-dibromoalkenes such as 1,3-dienyldibromide, 3-en-1-ynyldibromide, bis/tris-dibromoalkenes were further investigated under the optimized conditions (Table 3). The reaction of 1,3-dienyldibromide (**1n**) thus selectively provided (*E*)-but-1-en-3-ynylbenzene (**2n**) in high yield. Similarly, the reactivity of 3-en-1-ynyldibromide (**1o**) was proved to be selective to afford 1-(buta-1,3-diynyl)-4-methylbenzene (**2o**) in good yield. Next, the reactivity enumerated with bis- and tris-substituted systems. For example, the reaction of 1,4-bis(2,2-dibromovinyl)benzene (**1p**) gave the corresponding 1,4-diethynylbenzene (**2p**) in high yield. The study of tris(4-(2,2-dibromovinyl)phenyl)amine (**1q**) notably furnished the tris(4-ethynylphenyl)amine (**2q**) in 46% yield.

In comparison, our synthetic protocol was found to be more direct without involving protection/deprotection processes, as reported in the literature for the preparation of star-shaped tris (4-ethynylphenyl)amine (**2q**) [12].

The successful development of the dry protocol and its application in the synthesis of various terminal alkynes prompted us to adopt this method in the one-pot synthesis of internal alkynes involving the Sonogashira reaction. For that, a brief screening was done for step 2 involving the Sonogashira coupling, and it was to establish an overall one-pot two-step protocol (Table 4).

Table 2
Synthesis of terminal alkynes.[a,b]

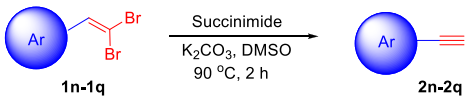


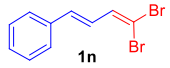
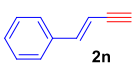
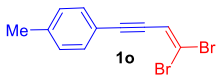
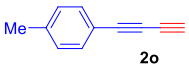
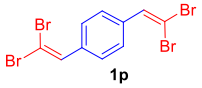
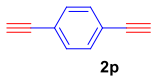
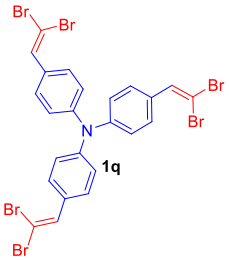
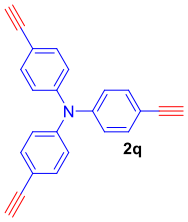
Entry	1,1-Dibromoalkene		Terminal alkyne		Yield (%)
1		**1a**		**2a**	76
2		**1b**		**2b**	86
3		**1c**		**2c**	69
4		**1d**		**2d**	64
5		**1e**		**2e**	88
6		**1f**		**2f**	75
7		**1g**		**2g**	96
8		**1h**		**2h**	58
9		**1i**		**2i**	57
10		**1j**		**2j**	75
11		**1k**		**2k**	63
12		**1l**		**2l**	70
13		**1m**		**2m**	69

[a] Reaction conditions: 1,1-dibromoalkene (0.375 mmol, 1 equiv), succinimide (0.75 mmol, 2 equiv), K_2CO_3 (2.25 mmol, 6 equiv), dry DMSO (3 mL), 90 °C, 2 h.
[b] Isolated yields.

It was carried out in a step-wise manner involving the standardized protocol in step 1 followed by the Sonogashira reaction using *p*-tolyliodide (**3a**) under palladium-catalyzed conditions in

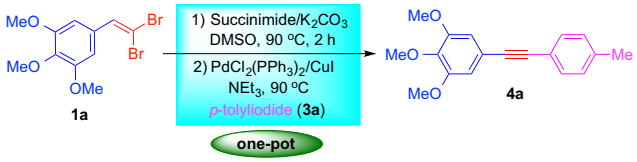
Table 3
Synthesis of functional alkynes.[a,b]



Entry	1,1-Dibromoalkene	Terminal alkyne	Yield (%)
1	 1n	 2n	73
2	 1o	 2o	65
3	 1p	 2p	84[c]
4	 1q	 2q	46[d]

[a] Reaction conditions: 1,1-dibromoalkene (0.375 mmol, 1 equiv), succinimide (0.75 mmol, 2 equiv), K_2CO_3 (2.25 mmol, 6 equiv), dry DMSO (3 mL), 90 °C, 2 h.
[b] Isolated yields.
[c] Succinimide (4 equiv), K_2CO_3 (12 equiv), DMSO (4 mL).
[d] Succinimide (6 equiv), K_2CO_3 (18 equiv), DMSO (4 mL).

Table 4
Screening conditions.[a,b]

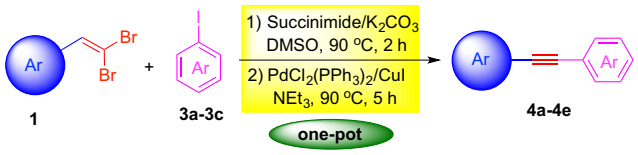


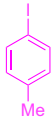
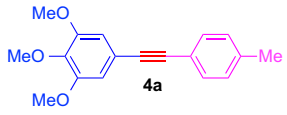
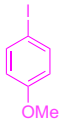
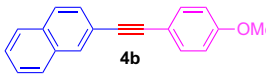
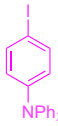
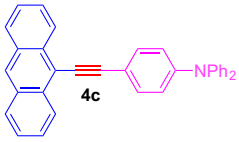
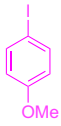
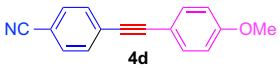
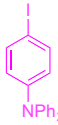
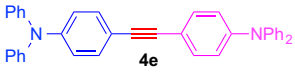
Entry	**3a** (equiv)	Time (h)	Yield (%)
1	1.5	4	61
2	1.0	4	56
3	1.5	5	68

[a] Reaction conditions: step 1: **1a** (0.375 mmol, 1 equiv), succinimide (0.75 mmol, 2 equiv), K_2CO_3 (2.25 mmol, 6 equiv), dry DMSO (3 mL), 90 °C, 2 h. Step 2: **3a**, NEt_3 (1.875 mmol, 5 equiv), CuI (0.018 mmol, 0.05 equiv), $PdCl_2(PPh_3)_2$ (0.006 mmol, 0.016 equiv), 90 °C, time.
[b] Isolated yields.

step 2 (Table 4, entry 1). This two-step one-pot operation afforded internal alkyne **4a** in 61% yield. Encouraged by this, further screening was done with *p*-tolyliodide (1 equiv), resulting in the internal alkyne in the 56% yield (Table 4, entry 2). However, some improvement was seen with increasing reaction time and internal alkyne was obtained in 68% yield (Table 4, entry 3). So, this protocol was taken as an optimized condition and successfully explored in the synthesis of internal alkynes involving a tandem two-step one-pot process (Table 5).

Table 5
Synthesis of internal alkynes.[a,b,c]



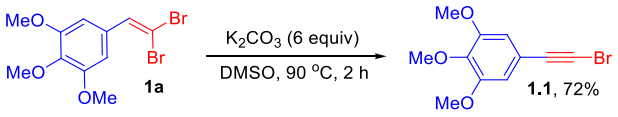
Entry	1,1-Dibromide	Ar-I	Internal alkyne	Yield (%)
1	**1a**	**3a** 	 **4a**	68
2	**1f**	**3b** 	 **4b**	62
3	**1g**	**3c** 	 **4c**	65
4	**1i**	**3b** 	 **4d**	57
5	**1m**	**3c** 	 **4e**	58

[a] Reaction conditions: step 1: 1,1-dibromoalkene (0.375 mmol, 1 equiv), succinimide (0.75 mmol, 2 equiv), K_2CO_3 (2.25 mmol, 6 equiv), dry DMSO (3 mL), 90 °C, 2 h. Step 2: Ar-I (0.562 mmol, 1.5 equiv), NEt_3 (1.875 mmol, 5 equiv), CuI (0.018 mmol, 0.05 equiv), $PdCl_2(PPh_3)_2$ (0.006 mmol, 0.016 equiv), 90 °C, 5 h.
[b] Homo-coupled 1,3-diynes from terminal alkynes formed in minor amounts.
[c] Isolated yields.

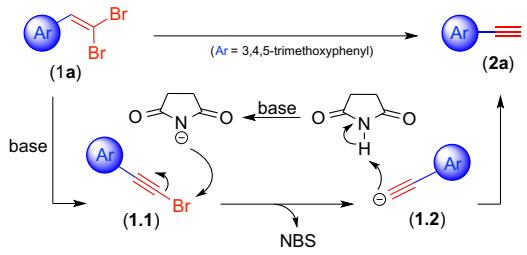
To test this one-pot protocol, few reactions have been attempted with different 1,1-dibromoalkenes and aryl iodides to synthesize internal alkynes (Table 5). Thus the reactions carried out with 1,1-dibromoalkenes (**1a**, **1f**, **1g**, **1i**, and **1m**) and in combination with different aryl iodides (**3a**-**3c**) furnished electronically various internal alkynes **4a**-**4e** in 57–68% yields. The symmetrical internal alkyne **4e** is a highly used substrate in optoelectronics devices [13]. Overall, this one-pot tandem synthesis of internal alkynes directly from 1,1-dibromoalkenes proved to as a versatile method under dry reaction conditions with minimized steps in a cost-effective manner [8].

A control reaction carried out earlier (Table 1, entry 9) is elaborated below in Scheme 2. This reaction in the absence of succinimide furnished 1-bromoalkyne exclusively (Scheme 2) [9a], indicating the important role of succinimide in terminal alkyne formation.

A representative mechanistic protocol is given in Scheme 3 involving the initial formation of 1-bromoalkyne (**1.1**) from 1,1-dibromoalkene (**1a**). This 1-bromoalkyne thus involves in X-philic reaction with *in situ* formed succinimide ion generates the acetylide anion [14] (**1.2**) and *N*-bromosuccinimide (NBS) [15]. Further, acetylide anion gets protonated [15] with succinimide and gives terminal alkyne (**2a**). All these elementary steps get completed in a facile manner under the established protocol conditions.



Scheme 2. Control experiment without succinimide.



Scheme 3. Proposed mechanism.

In conclusion, an easy synthetic method has been developed under dry reaction conditions for the synthesis of terminal alkynes from 1,1-dibromoalkenes. This protocol effectively utilizes succinimide as a nucleophile and proton donor under viable reaction conditions. A broad spectrum of terminal alkynes has been prepared [16] and applied to synthesize internal alkynes [17] under tandem reaction conditions involving Sonogashira coupling reaction.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153051.

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[16] General procedure for terminal alkynes preparation: To an oven-dried Schlenk tube, 1,1-dibromoalkene (1 equiv), succinimide (2 equiv), K_2CO_3 (6 equiv) were added along with dry DMSO (3 mL). This mixture was stirred at 90 °C for 2 h. After that, the mixture was cooled to room temperature and extracted with ethyl acetate (30 mL) and washed with water (10 mL) followed by brine solution (10 mL). The organic extract was dried over dry $MgSO_4$ and concentrated. The pure product was obtained by silica gel column chromatography using ethyl acetate/hexane as eluent.
[17] General procedure for internal alkynes preparation: To an oven-dried Schlenk tube, 1,1-dibromoalkene (1 equiv), succinimide (2 equiv), K_2CO_3 (6 equiv) were added along with dry DMSO (3 mL). This mixture was stirred at 90 °C for 2 h. After that, the contents in Schlenk tube were bought to room temperature and added aryl iodide (1.5 equiv), NEt_3 (5 equiv), CuI (0.05 equiv), $PdCl_2(PPh_3)_2$ (0.016 equiv) successively under nitrogen atmosphere. The reaction mixture was stirred at 90 °C for 5 h. The internal alkyne was isolated following the workup and purification protocol given for terminal alkyne preparation.