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Base-Mediated Reaction of Vinyl Bromides with Aryl Azides: One-Pot Synthesis of 1,5-Disubstituted 1,2,3-Triazoles

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KO'Bu One-pot Reaction ABSTRACT

A one-pot base-mediated reaction of azides and β - or α -vinyl bromides has been reported. The effects of bases and solvents have been investigated in the process. A variety of 1,5-disubstituted triazoles were prepared in low to good yields. Further studies reveal that the corresponding alkynes were produced as the intermediates *via* elimination reaction. Under the same reaction conditions, the reactions of alkyl alkynes with phenyl azide would give 1,5-disubstituted 1,2,3-triazoles.

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1. Introduction

The 1,2,3-triazole is an important structural motif found in many biologically active compounds and material industries.¹ Its extensive applications stimulated more and more interests to develop synthetic methodologies of the 1,2,3-triazole formation over the past decades.² Among numerous synthetic approaches, one of the most important and efficient methods to form the triazole ring system is the Huisgen cycloaddition reaction between azides and unsaturated compounds with multi carboncarbon bonds (e.g. alkynes, alkenes).³ In many reports concerning Huisgen cycloaddition reaction, two isomers were formed when unsymmetric alkynes or alkenes without activated functional groups were used. This unbearable disadvantage limited the application of the Huisgen cycloaddition reaction. About ten years ago, the Cu-catalyzed cycloaddition from organic azides and terminal alkynes to form 1,4-regioisomers (as sole product) of 1,2,3-triazoles was disclosed by Tornøe and Sharpless et al.⁴ Stimulated by the reports, other regioselective and reliable 1,2,3-triazole-forming processes have been explored from azides and alkynes, especially terminal alkynes.⁵

To some extent, terminal alkynes are more expensive and less easily available intermediates. Therefore, the *in situ* generations of terminal alkynes from desilylation of TMS-alkynes, decarboxylation of alkynoic acids or Seyferth-Gilbert Homologation of aldehydes have been applied in the synthesis of 1,2,3-triazoles.⁶

Vinyl halides are important intermediates in organic synthetic chemistry⁷ and can be acquired handily from dihalogenoalkanes, alkenes or other structures.^{7a,8} Elimination reaction of vinyl halides, one of most classical reactions to synthesize alkynes (including terminal alkynes), has received intensively attentions.⁵ Up to now, a few papers have studied the reactions of vinyl bromides with sodium azide or trimethylsilyl azide to generate 1H-1,2,3-triazoles under transition metal catalytic conditions.¹⁰ It is indicated that these reactions underwent cycloadditionelimination processes. However, to the best of our knowledge, one-pot synthesis of 1,2,3-triazoles without transition metal catalysis from vinyl bromides and aryl- or alkyl- azides has rarely been reported. In addition, the nucleophilic attack at organic azides by alkynyl anions which are *in situ* generated through further deprotonation of the intermediates that are formed from the dehydrohalogenation of vinyl halides would enable us to develop a new approach to synthesize 1,5-disubstituted 1,2,3triazoles.¹¹ (Scheme 1).

$$R^{1} \xrightarrow{Br} + R^{2}N_{3} \xrightarrow{\text{base}} R^{2}N^{N}N$$
Scheme 1

2. Results and discussions

To confirm the viability of the envisioned one-pot protocol, our initial study chose the reaction of (E)- β -phenyl vinyl bromide (1a) with phenyl azide (2a) as the model reaction, and the results

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were summarized in Table 1. Considering that the strong bases were necessary in the elimination of vinyl halides and the formation of alkynyl anions, we firstly carried out the cascade reaction with 2.0 equivalent KO'Bu as the base in DMSO. As expected, the desired product 3a was isolated and identified by ¹H NMR and ¹³C NMR spectra, however, only a moderate yield was obtained (Table 1, entry 1). In the process, the reaction mixture turned black and the temperature increased sharply when KO'Bu was added. On the other hand, several unknown byproducts were observed by TLC. The dissatisfactory results were probably related to the strong alkalinity and the high solubility of KO'Bu in DMSO. Employment of KOH powder as the base with or without the presence of the phase-transfer catalyst was less effective (Table 1, entry 2-4). When the base was switched to KH or sodium bis(trimethylsilyl)amide in DMSO, 3a was furnished in low yields (Table 1, entries 5 and 6). Subsequently, we screened other solvents for the reactions of 1a with 2a, and found that the best results were obtained when the reactions were performed in DMF or THF as the solvent in the presence of KO'Bu (Table 1, entries 10 and 13). Theoretically, 1.0 equivalent of KO'Bu is necessary to promote the elimination reaction of arylvinyl bromide, and the catalytical amount of KO'Bu is sufficient to promote the nucleophilic attack at phenyl azide by the intermediate (phenylacetylene).^{11c} However, in our experiments, the decreasing yields were observed when the amount of KO'Bu was reduced to 1.5 equivalent (Table 1, entries 17 and 18). When toluene, tert-butanol and ethyl nitrile as solvents were used, no product was monitored. Then, NaO'Bu was attempted and very low yield was obtained (Table 1, entry 16). Foregoing results confirmed that KO'Bu-mediated one-pot reaction of (E)- β -phenyl vinyl bromide with phenyl azide could be efficiently applied in the synthesis of 1,5-diphenyl 1,2,3triazole.

Table 1. Conditions screening of reaction of (E)- β -phenyl vinyl bromide with phenyl azide^a

Ph	_Br _	PhN ₃ base, solvent	base, solvent		
1a		2a Ph	3a		
Entry	Solvent	Base	Yield(%) ^b		
1	DMSO	KO'Bu	62		
2	DMSO	KOH (4.0 equiv.)	47		
3	DMSO	KOH/ $Bu_4N^{\dagger} \cdot Br^{-}$	50°		
4	DMSO	KOH (4.0 equiv.) / $Bu_4N^{+} \cdot Br^{-}$	58°		
5	DMSO	КН	11		
6	DMSO	(Me ₃ Si) ₂ NNa	22		
7	DMF	КОН	23		
8	DMF	KOH/ $Bu_4N^+ \cdot Br^-$	41 ^c		
9	DMF	KOH (4.0 equiv.)/ $Bu_4N^{\dagger} \cdot Br^{-}$	51 ^c		
10	DMF	KO'Bu	89		
11	DMF	KH	78		
12	DMF	(Me ₃ Si) ₂ NNa	79		
13	THF	KO'Bu	88		
14	THF	KH	trace		
15	THF	(Me ₃ Si) ₂ NNa	81		
16	DMF	NaO'Bu	14		
17	DMF	KO'Bu (1.5 equiv.)	71		
18	THF	KO'Bu (1.5 equiv.)	68		

^a Unless otherwise indicated, all reactions were performed with **1a** (0.5 mmol), **2a** (0.5 mmol) and 2.0 equivalent base (1 mmol) in solvent (1 mL) under an argon atmosphere at ambient temperature.

^b Isolated yield.

 $^{\rm c}\,10$ mol% phase-transfer catalyst was used.

After optimizing the elimination-cyclization reaction of (E)- β -phenyl vinyl bromide with phenyl azide, we attempted to employ similar reaction conditions to synthesize 1,5-diphenyl 1,2,3-triazole from α -phenyl vinyl bromide and phenyl azide; and the results were summarized in Table 2. In general, compared to (E)- β -phenyl vinyl bromide, α -phenyl vinyl bromide exhibited different reaction activity in this cascade approach. When the reactions were performed in the presence of KO'Bu, the temperature of reaction mixtures rose sharply, and the product was afforded in 40-69% yield along with some unidentified byproducts (Table 2, entries 1, 7 and 13). Addition of KO'Bu to

Table 2. Conditions screening of reaction of α -phenyl vinyl bromide with phenyl azide^a



^a Unless otherwise indicated, all reactions were performed with **1b** (0.5 mmol), **2a** (0.5 mmol) and base (1 mmol) in solvents (1 mL) under an argon

atmosphere at ambient temperature.

^bIsolated yield. ^c10 mol% phase-transfer catalyst was used.

 $^{\rm d}$ The reaction was performed at 0 $^\circ\!{\rm C}$.

a solution of **1b** and **2a** in DMF under ice-cold condition gave **3a** in a similar yield (Table 2, entry 3). When KOH powder was employed in DMSO, slightly high yields were given (Table 2, entries 6 and 8). When saturated aqueous solution of KOH was used, no product was monitored on TLC (Table 2, entry 11). The employment of sodium bis(trimethylsilyl)amide as the base in THF or DMF improved the yields up to 84-90% (Table 2, entries 5 and 15). KH was tested in the reaction and the product was isolated in poor to good yield (Table 2, entries 4, 9 and 14).

When the mixture of phenyl azide and (E)- β -phenyl vinyl bromide or α -phenyl vinyl bromide was heated at 80°C for 24h in the presence of K₂CO₃ in DMSO, only a trace amount of triazole was observed as a mixture of geometrical isomers accompanied by starting materials. The results would indicate that the thermal cycloaddition of vinyl bromide with phenyl azide takes place

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very slowly, and this base-mediated reaction is different from Huigen cycloaddion reaction.

Although sodium bis(trimethylsilyl)amide and KH could promote the reaction of vinyl bromide with phenyl azide in good yields, considering their high prices, our further studies were performed with KO'Bu as the base. To demonstrate the efficiency of KO'Bu-mediated one-pot reaction of phenyl vinyl halide with phenyl azide, we examined the transformations from phenyl azide and (E)- β -phenyl vinyl chloride or (Z)- β -phenyl vinyl bromide under the optimized condition, and the corresponding product was given in high yields (Scheme 2).



The efficient one-pot protocol was further extended to the reactions of other (E)-\beta-aryl vinyl bromides with aryl azides to synthesize 1,5-disubstituted 1,2,3-triazoles. The obtained results were summarized in Table 3. Firstly, various substituted phenyl azides 2a-2l were treated with 1a under the optimized conditions. In general, electron-withdrawing or electron-donating substituted groups have less influence on the reactions and good to excellent yields were given (Table 3, entries 1-10 and 12) with the exception of 2k in which some unknown yellowish byproduct was isolated (Table 3, entry 11). Interestingly, ortho substituents of azides showed little steric hindrance in the reaction (Table 3, entries 6 and 9). Meanwhile, 3-azidopyridine and 1azidonaphthaline were also effective to provide the desired products in good yields (Table 3, entries 13 and 14). Other (E)- β aryl vinyl bromides were also employed in the reaction, and gave corresponding adducts with considerable yields (Table 3, entries 15-20). When the substituted group was a electron-donating group, the yield decreased to 54% (Table 3, entry 19).

		BrBr	+ R ² N ₃	$\xrightarrow{\text{KO}^{t}\text{Bu}} \xrightarrow{\text{R}^{2}\text{N}^{-N}} \xrightarrow{N}$			
		1	2	DMF or	THF R ¹		
Е	ntry 1		R ¹	2	R ²	Product	Yield(%) ^b
1	1a		C ₆ H ₅	2a	C ₆ H ₅	3a	87
2	1a		C ₆ H ₅	2b	<i>p</i> -BrC ₆ H ₄	3b	88
3	1a		C ₆ H ₅	2c	p-CH ₃ C ₆ H ₄	3c	82
4	1a		C_6H_5	2d	<i>p</i> -ClC ₆ H ₄	3d	88 ^c
5	1a		C ₆ H ₅	2e	m-CH ₃ C ₆ H ₄	3e	82
6	1a		C ₆ H ₅	2f	o-CH ₃ C ₆ H ₄	3f	77
7	1a		C ₆ H ₅	2g	p-CH ₃ OC ₆ H ₄	3g	85
8	1a		C ₆ H ₅	2h	m-CF ₃ C ₆ H ₄	3h	96
9	1a		C ₆ H ₅	2i	o-ClC ₆ H ₄	3i	94
10	10 1a	0	C_6H_5	2ј	m-ClC ₆ H ₄	3ј	92 ^c
11 12 13	1a		C ₆ H ₅	2k	p-O ₂ NC ₆ H ₄	3k	37
	. 1a		C_6H_5	21	p-Et ₂ NCOC ₆ H ₄	31	80 ^c
	1a		C ₆ H ₅	2m	1-naphthyl	3m	82
14	- 1a		C ₆ H ₅	2n	3-pyridyl	3n	77
15	1c	p-	CH ₃ C ₆ H ₄	2a	C_6H_5	30	86
16	1d	0-	CH ₃ C ₆ H ₄	2a	C_6H_5	3p	79
17	1e	p	-ClC ₆ H ₄	2a	C_6H_5	3q	79 ^c
18	1e	p	-ClC ₆ H ₄	2c	p-CH ₃ C ₆ H ₄	3r	77
19) 1f	р-0	CH ₃ OC ₆ H ₄	2a	C_6H_5	3 s	54
20) 1d	0-	CH ₃ C ₆ H ₄	2d	<i>p</i> -ClC ₆ H ₄	3t	86

Table 3. One-pot synthesis of 1,5-diaryl 1,2,3-triazoles from (E)- β -aryl vinyl bromides and aryl azides

^a Unless otherwise indicated, all reactions were performed with 1 (1.0 mmol), 2 (1.0 mmol) and KO^tBu (2 mmol) in DMF (2 mL) under an argon atmosphere. ^b Isolated yield.

^c THF was used as the solvent.

Subsequently, we turned our attention to the reaction of alkyl azides with (E)- β -phenyl vinyl bromide. Different from the results of the methodologies concerning the nucleophilic attack at azides by magnesium acetylides,^{11a,12} n-octyl azide, cyclohexyl azide and benzyl azide failed to provide the expected products when reacting with phenyl azide in the presence of KO⁷Bu in DMF. After quenching the reactions, phenyl acetylene was

monitored by GC/MS, which indicated that the initial dehydrohalogenation of (E)- β -phenyl vinyl bromide was successful. However, the existence of n-octyl azide or cyclohexyl azide manifested that the nucleophilic attack of phenylacetylene was almost unsuccessful. When benzylic azide was used, phenylacetylene and phenylaldehyde were observed in GC/MS after quenching the reaction. Further experiment indicated

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phenylaldehyde was generated from benzylic azide via strong base-mediated denitrogenation. Considering the acidity of benzylic H-atom, we proposed the hypothetical mechanism as shown in Scheme 3.



Scheme 3

Furthermore, the reactions of phenyl azide with methyl vinyl bromides (2-bromo prop-1-ene and 1-bromo prop-1-ene) were tested and the desired triazole 3u was isolated in the low yield (30% and 35%, respectively) (Scheme 4a). The mixture of 1-bromo oct-1-ene and 2-bromo oct-1-ene (1:1) was also transformed into the triazole 3v in the yield of 36% by reacting with phenyl azide under the optimized condition (Scheme 4b). The results indicated alkyl acetylenes could be suitable substrates to react with phenyl azide under the current condition. Then, the reaction of phenyl azide with 1-octyne or 2,2-dimethyl-1-butyne was carried out and gave moderate yields (Scheme 4c).



On the basis of the above results and literature precedents, a plausible pathway for the base-mediated one-pot reaction of vinyl

Scheme 5. Plausible Pathway of base-mediated reaction of vinyl halide with aryl azide



halide with aryl azide was outlined in Scheme 5. Dehydrohalogenation of vinyl halide generates an terminal alkyne which further transforms to an alkynyl anion through the base-mediated deprotonation. Subsequently, nucleophilic attack of alkynyl anion to aryl azide affords a triazenide intermediate. Based on intramolecular cyclization, 1,5-disubstituted-1,2,3-triazolyl anion is formed. Finally, the product is afforded after the triazolyl anion is protonated.

3. Conclusion

In summary, a base-mediated reaction of vinyl bromides with azides was investigated and a methodology for the synthesis of 1,5-disubstituted 1,2,3-triazoles was presented. These studies point out the importance of bases and solvents in the one-pot multistep reaction. Meanwhile, the reactions of aryl vinyl bromides and aryl azides tend to give better results.

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Scheme 1. Base-Promoted Reaction of Vinyl Bromides with Azides

Scheme 2. Reaction of Phenyl Azied with (E)-β-Phenyl Vinyl Chloride or (Z)- β -Phenyl Vinyl Bromide

Scheme 3. Plausible Mechanism Base-mediated of Denitrogenation in Benzylic Azide

Scheme 4. Reactions of phenyl azide with alkyl vinyl bromides or alkyl acetylenes

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