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Reaction of Allenyl Esters with Sodium Azide: An Efficient Synthesis of *E*-Vinyl Azides and Polysubstituted Pyrroles

Xian Huang,*[,†,‡] Ruwei Shen,[†] and Tiexin Zhang[†]

Department of Chemistry, Zhejiang University (Xixi Campus), Hangzhou 310028, P. R. China, and State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, P. R. China

huangx@mail.hz.zj.cn

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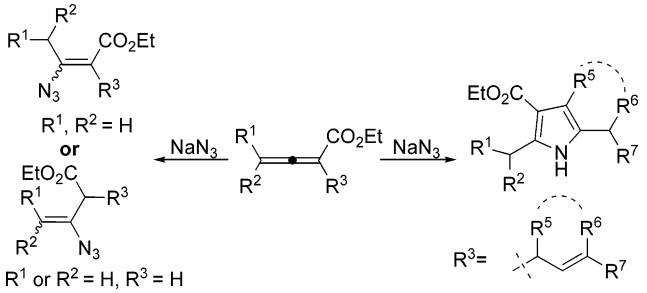

The nucleophilic addition of sodium azide to 1,2-allenyl esters can generate vinyl azides in excellent yields with excellent regio- and stereoselectivities. Moreover, pyrroles are synthesized using 1-allyllic 1,2-allenyl esters as substrates in *t*-BuOH at 65 °C. The sequential reaction for pyrroles is developed on the basis of a novel domino process involving nucleophilic addition, cycloaddition, denitrogenation, and aromatization.

Allenes show unique reactivity in organic synthesis due to the presence of the cumulated C═C double bonds.[1] In past decades, much attention has been paid to the study of their reactivity, especially the control of the related selectivity and their potential synthetic utilities.[2−4] Recently, researchers have found that regioselective and in some cases stereoselective addition of allenes can be conducted by introducing various nucleophilic functionalities at the α-carbon atom, leading to stereodefined functionalized vinylic products efficiently.[3] Moreover, with diverse and appropriate substitutes connected, allenes can be utilized as versatile starting materials to develop sequential reactions either employing metal catalysts or not, affording an efficient method for preparation of many compounds with synthetic and biological importance.[4,5]

Meanwhile, vinyl azides have drawn much attention for their growing applications in synthesis of various heterocycles,[6,7] as well as polysubstituted pyrroles, because of their wide occurrence in nature,[8] profound pharmaceutical activities,[9] and considerable application in material science.[10] Hence, continuous interest has been directed to development of new and efficient synthesis of vinyl azides and polysubstituted pyrroles.[11] Based upon the above considerations and in the context of our effort on developing new strategies toward heterocycles and related libraries,[12] herein we wish to present our findings in the reaction of allenyl esters with sodium azide affording functionalized vinyl azides and describe a facile synthesis of polysubstituted pyrroles from 1-allylic 1,2-allenyl esters. To the best of our knowledge, the reaction of allenyl esters with sodium azide has not yet been

† Zhejiang University.

‡ Shanghai Institute of Organic Chemistry.

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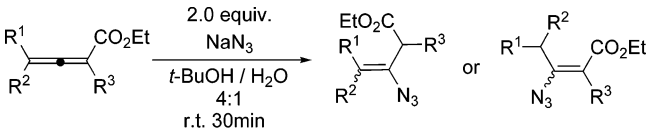
TABLE 1. Preparation of Functionalized Vinyl Azides from 1,2-Allenyl Esters

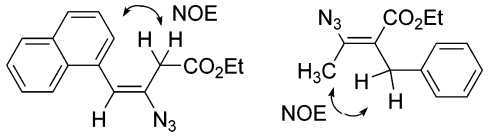


1 2 3

entry	R^1	R^2	R^3	**2** or **3**	yield[a] (%)	*E*/*Z*
1	Ph	H	H	**2a**	95	91:9[b]
2	Me	H	H	**2b**	89	89:11[b]
3	Et	H	H	**2c**	93	93:7[b]
4	α-$C_{10}H_7$	H	H	**2d**	88	100:0[b]
5	*n*-Bu	H	H	**2e**	96	94:6[b]
6	*n*-C_7H_{15}	H	H	**2f**	93	94:6[b]
7	H	H	H	**3a**	91	94:6
8	H	H	Me	**3b**	90	94:6
9	H	H	allyl	**3c**	93	93:7
10	H	H	Bn	**3d**	91	93:7
11	H	H	2-methylallyl	**3e**	95	92:8
12	*n*-Bu	Me	H		mixture	

[a] Isolated yields. [b] Deduced by ^{1}H NMR.

SCHEME 1. Configuration of *E*-2d and *Z*-3d

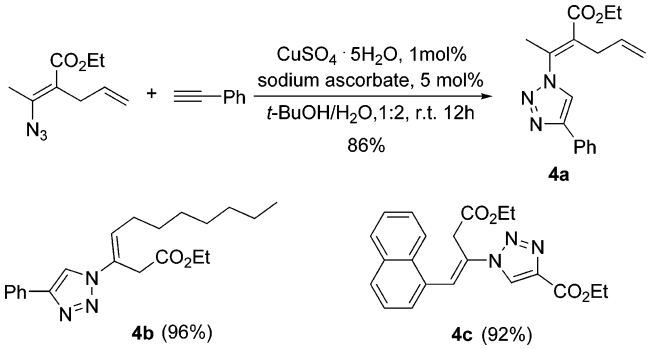


***E*-2d** ***Z*-3d**

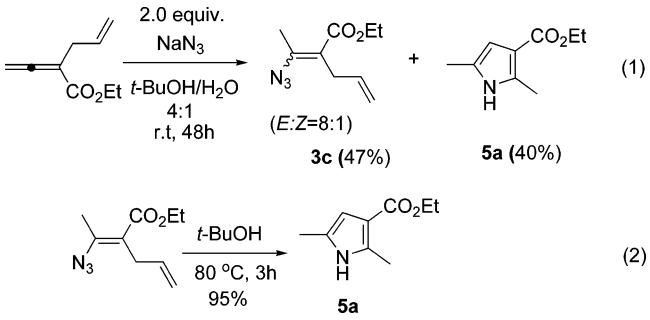
fully studied[13] and the synthesis of substituted pyrroles by this type of reactions is novel and of interest.

The reaction of allenyl esters with sodium azide was initially carried out by mixing 2.0 equiv of sodium azide with ethyl 4-phenylbuta-2, 3-dienoate in *t*-BuOH/H_2O (4:1) at room temperature. After the mixture was stirred for 30 min, an excellent yield of (*E*)-ethyl 3-azido-4-phenylbut-3-enoate was obtained along with a small amount of (*Z*)-ethyl 3-azido-4-phenylbut-3-enoate (entry 1, Table 1). Then a series of allenyl esters were tested. The results in Table 1 show that the reactions proceeded smoothly to give the corresponding vinyl azides **2** for 3-monosubstituted allenyl esters; only the C═C bond migrated products **3** were obtained when 3-unsubstituted allenyl esters were used as substrates; the two types of vinyl azides **2** and **3** were both obtained in high yields with good *E*-selectivities; however, for disubstituted allenyl esters it gave an inseparable mixture (entry 12, Table 1). Configurations of the products ***E*-2d** and ***Z*-3d** were established by the NOESY spectrum studies (Scheme 1). Our further experimental results demonstrate that these stereodefined vinyl azides are ready

SCHEME 2



SCHEME 3



precursors to generate novel 1-vinylic substituted 1,2,3-triazoles via Cu(I)-catalyzed cycloaddition with alkyne (Scheme 2).

Furthermore, it was interesting to observe that the reaction of ethyl 2-vinylidenepent-4-enoate with sodium azide afforded **5a** in 40% yield and **3c** (*E*/*Z* = 8:1) in 47% yield with prolonged reaction time at room temperature (eq 1, Scheme 3). Thus, the formation of **5a** may come from a series of consecutive transformations of ***E*-3c**. This hypothesis is further supported by the fact that **5a** was obtained in 95% yield after ***E*-3c** being heated for 3 h at 80 °C (eq 2, Scheme 3). Because of the instablility and potentially explosive nature of organic azides, we then attempted a one-pot synthesis of pyrroles. After a variety of reaction conditions (typically shown in Table 2) were examined, we fortunately found **5a** could be obtained in good yield when the reaction was carried out in *t*-BuOH at 65 °C, and no ***Z*-3c** was observed. It is important to note here that (1) a trace amount of ***Z*-3c** was obtained using water as proton source mainly due to the fast addition of azide anion to allenyl esters and its instability in such conditions (entries 1−4, Table 2); (2) relative low yield of **5a** was observed when DMSO and water were used as solvents (entry 3, Table 2); (3) 3.0 equiv of sodium azide was enough for the reaction in *t*-BuOH (entries 5−7, Table 2) and the yield dropped when the reaction was performed at higher temperature (entry 8, Table 2); (4) solvents such as MeOH, EtOH, and *i*-PrOH were proven to be ineffective (entries 10−12, Table 2).

Main results for synthesis of tri- and tetrasubstituted pyrroles are summarized in Table 3. The reaction generated corresponding products in moderate to good yields in most cases; one more C═C bond at the side chain in **1′** was tolerated (entries 8, 14, and 15, Table 3); and pyrroles annulated with a 6- or 8-membered ring could also be obtained in satisfactory yields using the present protocol (entries 7 and 8, Table 3). However,

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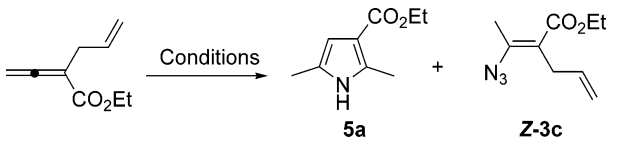
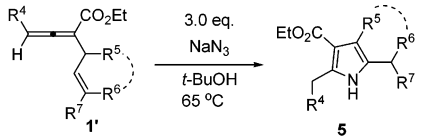
TABLE 2. Optimization of Conditions for the Synthesis of Pyrrole 5a[a]



entry	NaN_3 (equiv)	solvent	*T* (°C)	time (h)	yield[b] (%) (**5a**)	yield[b] (%) (***Z*-3c**)
1	2.0	*t*-BuOH/H_2O (4:1)	65	8	78	trace
2	3.0	*t*-BuOH/H_2O (8:1)	65	8	79	trace
3	3.0	DMSO/H_2O (8:1)	65	12	55	trace
4	3.0	acetone/H_2O (8:1)	55	16	78	trace
5	2.0	*t*-BuOH	65	20	85	
6	3.0	*t*-BuOH	65	20	91	
7	5.0	*t*-BuOH	65	20	92	
8	3.0	*t*-BuOH	80	16	81	
9[c]	3.0	*t*-BuOH	rt	60	11	
10	3.0	MeOH	reflux	24	complex	
11[d]	3.0	EtOH	65	24		
12	3.0	*i*-PrOH	65	24	complex	

[a] All of the reactions were carried out on a 1.0 mmol scale. [b] Isolated yields. [c] 68% of starting material was recovered; 9% of ***E*-3c** was isolated. [d] Ethyl 2-(1-ethoxyethylidene)pent-4-enoate was isolated as the major product.

TABLE 3. Synthesis of Tri- and Tetrasubstituted Pyrroles from 1-Allylic 1,2-Allenyl Esters

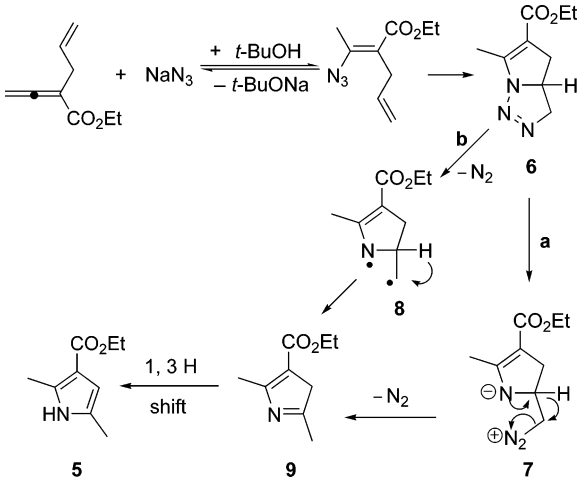


	1'						
entry	R^4	R^5	R^6	R^7	pyrroles **5**	time (h)	yield (%)
1	H	H	H	H	**5a**	20	91
2	Me	H	H	H	**5b**	24	77
3	H	H	H	Me	**5c**	36	85
4	Et	H	H	H	**5d**	24	65
5	n-C_7H_{15}	H	H	H	**5e**	24	61
6	H	H	Me	Me	**5f**	60	76
7	H	-$(CH_2)_3$-		H	**5g**	46	89 (68[b])
8	H	-$(CH_2CH{=}CHCH_2CH_2)$-		H	**5h**	60	76
9	Ph	H	H	H	**5i**	36	-
10	H	H	H	Ph	**5j**	36	-
11	H	H	*n*-Pr	H	**5k**	60	84
12	H	H	H	*n*-Pr	**5k**	60	79
13	H	H	H	n-C_5H_{11}	**5l**	60	75
14	H	H		Me	**5m**	60	38[c]
15	H	H		Me	**5m**	72	51[d]

[a] Isolated yields. [b] *t*-BuOH/H_2O (8:1) were used as solvents. [c] 17% of starting material was recovered. [d] Reaction conditions: the mixture of 1, 2-allenyl ester and 5.0 equiv of NaN_3 was heated with stirring in *t*-BuOH at 80 °C.

the reaction failed to afford the expected pyrrole when R^4 or R^7 was a phenyl group (entries 9 and 10, Table 3).

SCHEME 4



A plausible mechanism for the reaction is outlined in Scheme 4. Conjugate addition of azide anion to allenyl ester occurs first to give vinyl azide in which the double bond has "migrated" on the given conditions, followed by a thermally intramolecular 1,3-dipolar cycloaddition to form the unstable triazoline intermediate **6**. Then, **6** may decompose to produce zwitterionic species **7**, which undergoes 1,2 H-shift with loss of nitrogen and 1,3 H-shift to give the stable pyrrole **5** (path a).[14] Another possiblility is that the formed triazoline **6** may expel N_2 to produce biradical intermediate **8** which would provide the expected pyrroles **5** after 1,2 H-radical shift and the following 1,3 H-shift (path b).[15]

In conclusion, we found that hydroazidation of allenyl esters can give vinyl azides in excellent yields with high regio- and stereoselectivities. A new method for the synthesis of pyrroles from 1-allylic allenyl esters through a series of consecutive transformations has been developed. Further studies of this type of reaction are currently underway in our laboratory.

Experimental Section

General Procedure for Access to Vinyl Azides. To a solution of NaN_3 (1 mmol) in *t*-BuOH/H_2O (v/v = 4:1, 2 mL) was added 1,2-allenyl ester **1** (0.5 mmol) at room temperature with stirring. After the reaction was complete (30 min), the reaction was quenched with saturated NH_4Cl and extracted with EtOAc (3 × 10 mL). The organic phase was washed with saturated brine and dried over $MgSO_4$. After filtration and removal of the solvent in vacuo, the residue was purified with flash chromatography (silica/petroleum ether−ethyl acetate 20:1 v/v) to afford **2** or **3**.

General Procedure for Access to Polysubstituted Pyrroles. A solution of NaN_3 (3 mmol) and 1-allyllic 1,2-allenyl esters **1′** (1 mmol) in *t*-BuOH (3 mL) was heated to 65 °C with stirring. After the reaction was complete (monitored by TLC), the reaction was quenched with saturated NH_4Cl and extracted with EtOAc (3 × 15 mL). The organic phase was washed with saturated brine and dried over $MgSO_4$. After filtration and removal of the solvent in

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vacuo, the residues were purified with flash chromatography (silica/petroleum ether−ethyl acetate 6:1 v/v) to afford **5**.

Acknowledgment. We are grateful to the National Natural Science Foundation of China (Project Nos. 20472072 and 20332060) for financial support.

Supporting Information Available: General experimental details and ^{1}H and ^{13}C NMR spectra for compounds **2a**−**f**, **3a**−**e**, **4a**−**c**, **5a**−**h**,**k**−**m** are given in this section. This material is available free of charge via the Internet at http://pubs.acs.org.

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