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Regioselective Formation of 2,4,5-Trisubstituted Oxazoles through Transition-Metal Free Heterocyclization of 1,3-Diynes with *N,O*-Bis(trimethylsiyl)acetamide

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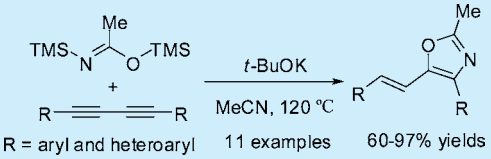
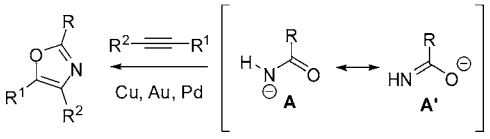
Supporting Information

ABSTRACT: Transition-metal free heterocyclization reaction of 1,3-diynes with *N,O*-bis(trimethylsiyl)acetamide was accomplished in the presence of *t*-BuOK and acetonitrile at 120 °C. This method regioselectively gave 2,4,5-trisubstituted oxazoles in yields up to 97%.



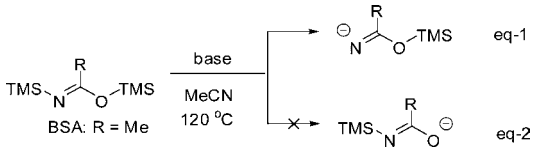
Oxazoles represent an important class of heterocycles with biological activities[1] and are of great importance to synthetic intermediates.[2] Several natural and bioactive molecules such as Diazonamide A,[3] Oxaprozin,[4] and Siphonazole[5] contain 2,4,5-trisubstituted oxazole fragments.[6] Therefore, synthetic methods for 2,4,5-trisubstituted oxazole attract great attention during the latest decade. A number of strategies for 2,4,5-trisubstituted oxazoles have emerged: (i) heterocyclization of alkynes with amides;[7] (ii) heterocyclization of alkynes with nitrides;[8] (iii) intramolecular annulations of *β*-alkoxy-*β*-ketoenamides;[9] and (iv) the annulation reaction between isonitriles and carboxylic acids mediated by Lewis acid.[10] In some methods, a key step is that an anion of amide is usually formed as a soft *N*-nucleophile **A**. In this regard, **A** is a resonance form of **A′**; however, **A′** is not allowed in such a reaction since it is a hard *O*-nucleophile (Scheme 1). We speculated that *N,O*-bis(trimethylsiyl)acetamide (BSA) may serve as a structural equivalent of **A′** to undergo a heterocyclization of 1,3-diynes (eq-1 of Scheme 2).

Scheme 1. Anion of Amides and Imines



To the best of our knowledge, BSA and its derivatives have not yet been employed as intermediates for the synthesis of 2,4,5-trisubstituted oxazoles. In fact, BSA is widely applicable as a silylating agent[11] in organic synthesis. More significantly, the analogue (R = Et, Ph, and other groups) of BSA can be readily synthesized according to the known procedure.[12] In connection with our effort on the synthesis of heterocyclic compounds derived from 1,3-diynes,[13] we herein report a transition-metal free heterocyclization reaction of 1,3-diynes with BSA, which specifically allows for the synthesis of (*E*)-2,4,5-trisubstituted oxazoles.

Scheme 2. Possible Desilylation Process of BSA with Base



Our studies commenced with a heterocyclization reaction between 1,4-diphenylbuta-1,3-diyne (**1a**) and BSA **2** in the absence of transition-metal catalyst. This reaction was performed in acetonitrile (MeCN) at 120 °C and the corresponding oxazoles were not observed (entry 1). To our delight, the formation of (*E*)-2-methyl-4-phenyl-5-styryloxazole **3a**[13c] was obtained in a 45% yield when tetrabutylammonium fluoride trihydrate (TBAF·3H_2O) was utilized (entry 2). It is of interest to note that (*E*)-2-methyl-4-styryl-5-phenyloxazole **4a** was not observed (entry 2). Note that the treatment of BSA **2** with 2 equiv of base such as TBAF·3H_2O could competitively form either an anion on nitrogen (eq-1 in Scheme 1) or on oxygen (eq-2 in Scheme 1) since O−Si and N−Si bond energy is ∼410 and ∼510 kJ/mol, respectively.[14] The results indicated that only the anion on nitrogen was formed since the N−Si bond is more reactive than O−Si toward the desilylation in the presence of TBAF in this case (entry 2).

Then a diversity of solvents including MeCN, toluene, dioxane, and 1,2-dichloroethane (DCE) was screened. The results revealed that MeCN gave a better yield than both toluene and dioxane (entries 3−4); DCE is ineffective for this reaction (entry 5). The nature of bases has a great influence on the results of this reaction. A range of bases such as K_2CO_3, K_3PO_4, sodium methylate (MeONa), Cs_2CO_3, and potassium *tert*-butoxide (*t*-BuOK) was examined. We found that *t*-BuOK was the optimum

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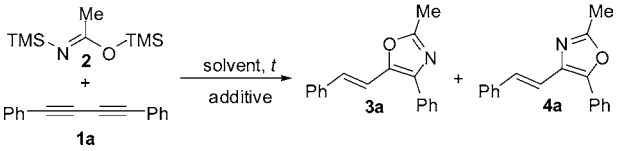
one, producing **3a** in 95% yield (entry 10). K_3PO_4, MeONa, and Cs_2CO_3 resulted in good to high yields (entries 6–9). Interestingly, this reaction is temperature sensitive in the 100–130 °C range. The reaction at 120 °C gave rise to the highest yield (entry 10). The reaction at 100 and 130 °C led to fair to excellent yields, respectively (entries 11 and 12). The reaction was carried out at 80 °C and it gave a poor yield (entry 13). Note that when 1 equiv of *t*-BuOK instead of 2 equiv of *t*-BuOK was utilized it only provided **3a** in 15% yield (entry 14). (*E*)-2-Methyl-4-styryl-5-phenyloxazole **4a** was not detected in all cases (entries 2–14).

With the optimized reaction conditions presented in entry 10 of Table 1 in hand, the scope of a range of symmetrical 1,3-diynes

Table 1. Optimizing Reaction Conditions for Heterocyclization of 1,4-Diphenylbuta-1,3-diyne 1a with BSA 2[a]



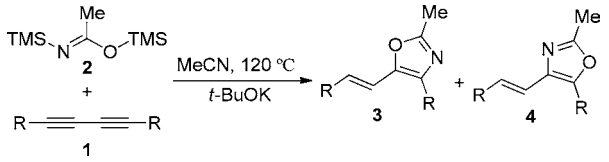
entry	solvent	additive	temp (°C)	yield of **3a**[b] (%)
1	MeCN		120	0
2	MeCN	TBAF·3H_2O	120	45
3	dioxane	TBAF·3H_2O	120	20
4	toluene	TBAF·3H_2O	120	10
5	DCE	TBAF·3H_2O	120	0
6	MeCN	K_2CO_3	120	20
7	MeCN	K_3PO_4	120	61
8	MeCN	MeONa	120	73
9	MeCN	Cs_2CO_3	120	84
10	MeCN	*t*-BuOK	120	95
11	MeCN	*t*-BuOK	130	93
12	MeCN	*t*-BuOK	100	54
13	MeCN	*t*-BuOK	80	13
14[c]	MeCN	*t*-BuOK	120	15

[a]Reaction conditions: **1a** (0.2 mmol), BSA **2** (0.24 mmol), and additive (0.4 mmol) in solvent (2 mL) in a sealed tube at 120 °C. The crude products (**3a** and **4a**) were analyzed by ^{1}H NMR and HPLC. [b]Isolated yields. [c]*t*-BuOK (0.2 mmol) was employed.

1 was investigated (Table 2). The results revealed the following factors: one, the reaction favored **1a** and 1,3-diynes substrates **1b–1d** and **1h** bearing the electron-donating groups (e.g., 4-Me, 4-MeO, 4-pent, and 3-Me) on the phenyl ring, which afforded (*E*)-2,4,5-trisubstituted oxazoles[13c] (**3b–d** and **3h**) in excellent yields (entries 1–4 and 8); two, 1,3-diynes substrates **1e–g** with electron-withdrawing groups (e.g., 4-F, 4-Cl, and 4-Br) on the phenyl ring led to (*E*)-2,4,5-trisubstituted oxazoles[13c] (**3e–g**) in moderate yields (entries 5–7); three, 2-thienyl-substituted 1,3-diyne **1i** worked well at somewhat elevated reaction temperature 140 °C (entry 9); four, tetradeca-6,8-diyne **1j** (entry 10) and hexa-2,4-diyne-1,6-diyl diacetate **1k** failed to undergo this reaction. Furthermore, the trisubstituted oxazoles **4** were not observed in all cases (entries 1–10). In addition, (*E*)-trimethylsilyl 2,2,2-trifluoro-*N*-(trimethylsilyl)acetimidate was examined and the corresponding product was not obtained.

We further extended this method to unsymmetrical 1,3-diynes **1′** under the optimal conditions (Table 3). The results indicated that 1,3-diynes **1′** with either electron-donating (e.g., 4-$MeOC_6H_4$ and 4-pent-C_6H_4) groups or electron-withdrawing

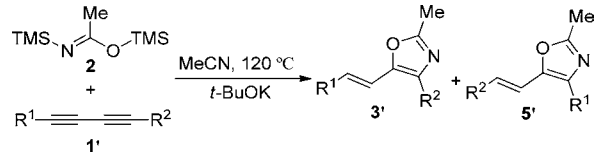
Table 2. Scope of Symmetrical 1,3-Diyne 1[a]



entry	R	product	yield[b] of **3** (%)
1	C_6H_5	**3a**	95
2	*p*-MeC_6H_4	**3b**	94
3	*p*-$MeOC_6H_4$	**3c**	97
4	*p*-pent-C_6H_4	**3d**	93
5	*p*-FC_6H_4	**3e**	67
6	*p*-ClC_6H_4	**3f**	65
7	*p*-BrC_6H_4	**3g**	60
8	*m*-MeC_6H_4	**3h**	91
9[c]	2-thienyl	**3i**	71
10	*n*-Bu	**3j**	

[a]Reaction conditions: 1,3-diynes **1** (0.2 mmol), BSA **2** (0.24 mmol), and *t*-BuOK (0.4 mmol) in MeCN (2 mL) in a sealed tube at 120 °C; the crude products (**3** and **4**) were analyzed by ^{1}H NMR and HPLC. [b]Isolated yields. [c]At 140 °C.

Table 3. Scope of Unsymmetrical 1,3-Diynes 1′[a]



entry	R^1	R^2	yield[b] of **3′**	yield[b] of **5′**
1	4-$MeOC_6H_4$	4-pent-C_6H_4	**3a′**, 61	**5a′**, 28
2	4-$MeOC_6H_4$	4-FC_6H_4	**3b′**, 57	**5b′**, 27

[a]Reaction conditions: **1′** (0.2 mmol), BSA **2** (0.24 mmol), and *t*-BuOK (0.4 mmol) in MeCN (2 mL) in a sealed tube at 120 °C. [b]Isolated yields.

group (e.g., 4-FC_6H_4) on the phenyl ring resulted in the corresponding oxazoles **3a′–b′** and **5a′–b′** in total 84–89% yields with acceptable regioselectivities (entries 1 and 2).

The controlled experiments were conducted under the optimized conditions: (i) diphenylacetylene and hex-1-ynylbenzene other than 1,4-diphenylbuta-1,3-diyne (**1a**) were employed, and no heterocyclization reaction occurred. These outcomes illustrated that two triple bonds are required for the heterocyclization between 1,3-diynes **1** and BSA **2**; (ii) the component solvent (2 mL of CD_3CN and 50 μL of H_2O) was used in entry 1 of Table 2, a dideuterated vinyl unit was observed; (iii) the component solvent (2 mL of CH_3CN and 50 μL of D_2O) was employed, and no deuterated products were obtained (see ^{1}H NMR spectra in SI).

A plausible mechanism was proposed and shown in Scheme 3. The treatment of BSA with *t*-BuOK in MeCN at 120 °C predominantly forms an anion **A′**,[15] an addition of which to 1,3-dyine produces **B**. A protonation of **B** with CH_3CN, followed by a desilylation[15] in the presence of *t*-BuOK gives **C**. A heterocyclization reaction of **C** occurs, followed by quenching with CH_3CN, to produce (*E*)-2,4,5-trisubstituted-(prop-1-enyl)-oxazole.

In conclusion, we have developed the heterocyclization reaction of 1,3-diynes **1** with BSA **2** in the presence of *t*-BuOK, which specifically provided (*E*)-2,4,5-trisubstituted-(prop-1-

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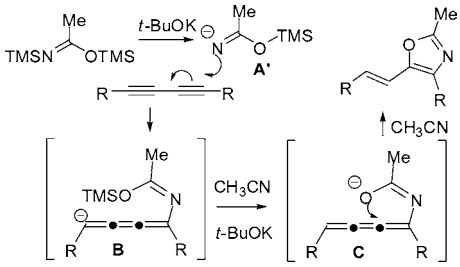
Scheme 3. Plausible Mechanism of the Present Reaction



enyl)-oxazoles in moderate to excellent yields. These are the first examples in which BSA is used as a building block for the synthesis of (*E*)-2,4,5-trisubstitutedoxazoles.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data for all new compounds, descriptions of stereochemical assignments, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds reported in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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