ORGANIC LETTERS

2012
Vol. 14, No. 9
2418–2421

Synthesis of 3,5-Disubstituted Isoxazoles via Cope-Type Hydroamination of 1,3-Dialkynes

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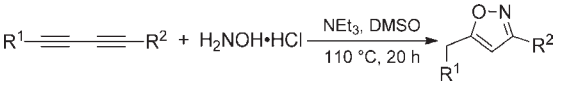
Received April 5, 2012

ABSTRACT



An efficient method for the synthesis of 3,5-disubstituted isoxazoles is described. The reactions of 1,3-dialkynes with hydroxylamine proceeded smoothly in DMSO under mild reaction conditions to produce 3,5-disubstituted isoxazoles in satisfactory to excellent yields.

The development of convenient and efficient methods for the synthesis of isoxazoles has attracted considerable attention. Isoxazoles represent an interesting structural motif found frequently in various bioactive molecules and natural products.[1] Over the past four decades, many methods have been developed for the construction of the isoxazole nucleus, including the [3 + 2] cycloaddition of alkenes/alkynes with nitrile oxides (1,3-dipoles derivated from hydroximinoyl chlorides, nitro compounds, and aldoximes);[2] the reaction of hydroxylamine with a three-carbon atom component (such as 1,3-dicarbonyl compound, α,β-unsaturated carbonyl compound, and α,β-unsaturated nitrile);[3] the cyclization of alkynyl oxime ethers;[4] and others.[5] Although mono- and polysubstituted-isoxazoles can be obtained using these methods, the synthesis frequently suffers from drawbacks, such as multistep reactions, harsh reaction conditions (strong bases or strong mineral acids are often required, or prolonged heating to high temperature is necessary), and the use of transition-metal catalysts or special starting materials.

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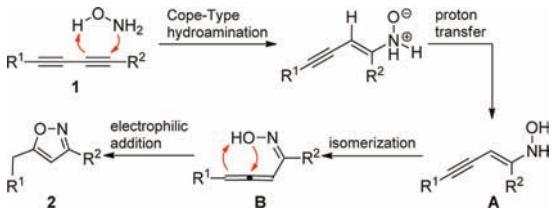
10.1021/ol300872e
Published on Web 04/26/2012

Scheme 1. Synthesis of 3,5-Disubstituted Isoxazoles via Cope-Type Hydroamination of 1,3-Dialkynes



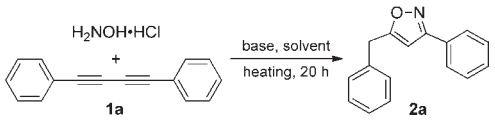
In the course of our continuous research on alkyne chemistry,[6] we found that 3,5-disubstituted isoxazoles can be readily obtained from the reaction of 1,3-dialkynes with hydroxylamine (H_2NOH) (Scheme 1). The intermolecular Cope-type hydroamination reaction of 1,3-dialkynes **1** with hydroxylamine occurred during heating to produce intermediate **A** upon a proton-transfer process.[7,8] The isomerization of **A** subsequently took place to produce an allenyl oxime intermediate **B**, which then transformed into a 3,5-disubstituted isoxazole **2** via intramolecular electrophilic addition. In the present paper, a method of preparing 3,5-disubstituted isoxazoles was reported using simple and readily available starting materials under mild conditions.

In our initial studies, the reaction of 1,4-diphenylbuta-1,3-diyne (**1a**) with hydroxylamine hydrochloride ($H_2NOH\cdot HCl$) was chosen as a model to optimize the reaction conditions. The optimization included the selection of the most suitable solvents, bases, and reaction temperature. The results are shown in Table 1. Nonpolar (toluene) and polar [dioxiane, ethanol, isopropyl alcohol (IPA), tetrahydrofurane (THF), *N*,*N*-dimethylformamide (DMF), and dimethyl sulfoxide (DMSO)] solvents were examined (entries 1−7). DMSO proved to be the best solvent (entry 7). The yield of the desired product, 5-benzyl-3-phenylisoxazole (**2a**), dramatically increased to 86% when DMSO was used as a solvent (entry 7 vs entries 1−6). However, the reason behind this behavior remains unclear. The bases were then screened using DMSO as solvent, which included NEt_3, $^iPr_2NEt$, N^nBu_3, $NHEt_2$, K_2CO_3, K_3PO_4, and NaOAc (entries 7−13). Among the tested bases, the use of NEt_3 led to the formation of **2a** in relatively high yield (entry 7, 86% yield). The effect of reaction temperature on the yield of **2a** was evaluated (entries 7, 14, and 15). The obtained results indicated that the yield of **2a** increased with the enhanced reaction temperature. A reaction temperature of 110 °C was essential in achieving good yield of **2a**. Therefore, the subsequent reactions of the symmetric (**1a**−**1h**) and unsymmetric (**3a**−**3h**) 1,3-dialkynes with hydroxylamine hydrochloride were performed in the presence of NEt_3 as the base in DMSO solvent at 110 °C for 20 h.

(7) For the Cope-type hydroamination reaction of alkynes, see: (a) Moran, J.; Gorelsky, S. I.; Dimitrijevic, E.; Lebrun, M.-E.; Bedard, A.-C.; Seguin, C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 17893. (b) Beauchemin, A. M.; Moran, J.; Lebrun, M.-E.; Bedard, A. C.; Seguin, C.; Seguin, C.; Dimitrijevic, E.; Zhang, L.; Gorelsky, S .I. *Angew. Chem., Int. Ed.* **2008**, *47*, 1410.

(8) For the proton-transfer process, see:Cooper, N. J.; Knight, D. W. *Tetrahedron* **2004**, *60*, 243.

Table 1. Reaction Conditions Screening[a]



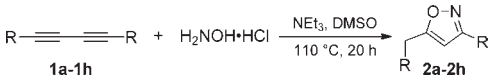
entry	solvent	base	temp (°C)	yield (%)[b]
1	toluene	NEt_3	110	NR[c]
2	dioxiane	NEt_3	110	10
3	ethanol	NEt_3	110	10
4	IPA	NEt_3	110	15
5	THF	NEt_3	110	NR[c]
6	DMF	NEt_3	110	10
7	DMSO	NEt_3	110	86
8	DMSO	$^iPr_2NEt$	110	80
9	DMSO	N^nBu_3	110	82
10	DMSO	$NHEt_2$	110	80
11	DMSO	K_2CO_3	110	60
12	DMSO	K_3PO_4	110	68
13	DMSO	NaOAc	110	70
14	DMSO	NEt_3	90	55
15	DMSO	NEt_3	100	70

[a] Reaction conditions: 1,4-diphenylbuta-1,3-diyne (**1a**, 0.4 mmol, 81.0 mg), hydroxylamine hydrochloride (2.5 equiv, 69.5 mg), base (4.0 equiv), and solvent (3.0 mL) in sealed flask. [b] Isolated yield. [c] No reaction.

The reactions of symmetric 1,3-dialkynes **1a**−**1h** with hydroxylamine hydrochloride were performed under optimized conditions, and the results are summarized in Table 2. 3,5-Disubstituted isoxazole **2a**−**2f** were obtained from the reactions of aromatic 1,3-dialkynes **1a**−**1f** in good to excellent yields (entries 1−6, 81%−98%). The formation of 3,5-disubstituted isoxazole in relatively higher yield from a 1,3-dialkyne bearing an electron-withdrawing group on benzene ring than those from a 1,3-dialkyne bearing an electron-donating group on benzene ring was observed (entries 5 and 6 vs entries 1−4). This result indicated that 1,3-dialkyne can be activated by decreasing its electron density. The aliphatic 1,3-dialkynes **1g** and **1h** were also employed successfully in the synthesis of 3,5-disubstituted isoxazoles. The corresponding products **2g** and **2h** were obtained in 66% and 89% yields, respectively (entries 7 and 8). These results indicated that the reactivity of cyclic alkyl-substituted 1,3-dialkynes was higher than that of the normal alkyl-substituted analogues. It was considered that the formation of *Z*-oxime isomer (intermediate **B**, Scheme 1) was accelerated by the bulky substituent group, such as aryl and *c*-hexyl groups.

The successful acquisition of 3,5-disubstituted isoxazoles from the reaction of symmetric 1,3-dialkynes with hydroxylamine hydrochloride encouraged the current authors to examine the reaction of unsymmetric 1,3-dialkynes with hydroxylamine hydrochloride. The results are summarized in Table 3. The reactions of unsymmetric 1,3-dialkynes **3a**−**3c** having the same *p*-methoxyphenyl group with hydroxylamine hydrochloride proceeded smoothly to produce a mixture of two products, which can be separated with chromatography. Products **4a**−**4c** and **5a**−**5c** were obtained in

Table 2. Synthesis of 3,5-Disubstituted Isoxazoles from Symmetric 1,3-Dialkynes[a]



1a-1h 2a-2h

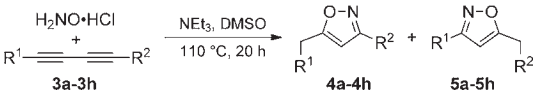
entry	R	product 2		yield (%)[b]
1	Ph	**1a**	**2a**	86
2	*p*-MeOC$_6$H$_4$	**1b**	**2b**	81
3	*p*-MeC$_6$H$_4$	**1c**	**2c**	84
4	*m*-MeC$_6$H$_4$	**1d**	**2d**	81
5	*p*-BrC$_6$H$_4$	**1e**	**2e**	91
6	*p*-NO$_2$C$_6$H$_4$	**1f**	**2f**	98
7	*n*-Hexyl	**1g**	**2g**	66
8	*c*-Hexyl	**1h**	**2h**	89

[a] Reaction conditions: symmetric 1,3-dialkyne (**1a**−**1h**, 0.4 mmol), hydroxylamine hydrochloride (2.5 equiv, 69.5 mg), and NEt$_3$ (4.0 equiv, 162.0 mg) in DMSO (3.0 mL) at 110 °C for 20 h. [b] Isolated yield.

47%−58% and 30%−35% yields, respectively (entries 1−3). The ratios of the two isolated products increased in the order **4a** to **5a**, **4b** to **5b**, and **4c** to **5c**. Interestingly, this order was consistent with those of Hammett substituent constants (σ_p: H, 0; F, +0.15; NO$_2$, +0.81).[9] The reactions of unsymmetric 1,3-dialkynes **3d**−**3f** having the same phenyl group with hydroxylamine hydrochloride also provided two products. Products **4d**−**4f** and **5d**−**45** were isolated in 54%−72% and 11%−27% yields, respectively (entries 4−6). Surprisingly, the use of unsymmetric 1,3-dialkynes **3g** and **3h** having a *p*-nitrophenyl group and an

(9) March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 4th ed.; John Wiley & Sons:, New York, 1992; p 280.

Table 3. Synthesis of 3,5-Disubstituted Isoxazoles from Unsymmetric 1,3-Dialkynes[a]



3a-3h 4a-4h 5a-5h

entry	alkyne **3**	yield of **4** (%)[b]	yield of **5** (%)[b]
1	**3a**, R^1 = Ph R^2 = *p*-MeOC$_6$H$_4$	**4a**, 47	**5a**, 35
2	**3b**, R^1 = *p*-FC$_6$H$_4$ R^2 = *p*-MeOC$_6$H$_4$	**4b**, 52	**5b**, 31
3	**3c**, R^1 = *p*-NO$_2$C$_6$H$_4$ R^2 = *p*-MeOC$_6$H$_4$	**4c**, 58	**5c**, 30
4	**3d**, R^1 = *p*-NO$_2$C$_6$H$_4$ R^2 = Ph	**4d**, 54	**5d**, 27
5	**3e**, R^1 = Ph R^2 = *n*-Hexyl	**4e**, 72	**5e**, 11
6	**3f**, R^1 = Ph R^2 = *c*-Hexyl	**4f**, 70	**5f**, 18
7	**3g**, R^1 = *p*-NO$_2$C$_6$H$_4$ R^2 = *n*-Hexyl	**4g**, 88	**5g**, 0
8	**3h**, R^1 = *p*-NO$_2$C$_6$H$_4$ R^2 = *c*-Hexyl	**4h**, 90	**5h**, 0

[a] Reaction conditions: unsymmetric 1,3-dialkyne (**3a**−**3h**, 0.4 mmol), hydroxylamine hydrochloride (2.5 equiv, 69.5 mg), and NEt$_3$ (4.0 equiv, 162.0 mg) in DMSO (3.0 mL) at 110 °C for 20 h. [b] Isolated yield.

alkyl group led to the formation of 3,5-disubstituted isoxazole **4g** or **4h** as a sole product (entry 7, **4g**: 88% yield; entry 8, **4h**: 90% yield).

Finally, the one-pot synthesis of 3,5-disubstituted isoxazoles from alkynes was examined, and the results are summarized in Table 4. After the Cu-catalyzed homocoupling reaction of alkyne was completed,[10] hydroxylamine hydrochloride and triethylamine were added to the resultant mixture. The reaction mixture was then treated at 110 °C for 20 h. The same good yield of **2a** was observed in the reaction of phenylacetylene (**6a**) (entry 1, 86%). The reactions of arylacetylenes **6b**−**6d** bearing an electron-donating group (MeO, Me) on the *para* or *meta* position of benzene ring produced the desired products **2b**−**2d** in good yields (entries 2−4, 78%−81%). However, the reaction of *o*-methyl phenylacetylene (**6i**) produced 3,5-disubstituted isoxazole **2i** in low yield (entry 9, 65%). The poor reactivity of **6i** was considered due to the steric effect of the *o*-methyl group in alkyne substrate. The relatively high yields were also observed in the reactions of arylacetylenes **6e**, **6f**, **6j**, and **6k** bearing an electron-withdrawing group on benzene ring. The desired products, 3,5-disubstituted isoxazoles **2e**, **2f**, **2j**, and **2k**, were isolated in 88%−95% yields (entries 5, 6, 10, and 11). The aliphatic alkynes **6g** and **6h** were also utilized successfully for the synthesis of 3,5-disubstituted isoxazoles. Products **2g** and **2h** were obtained in 60% and 86% yields, respectively (entries 7 and 8). Finally, the reactions of

(10) For the Cu-catalyzed homo-coupling reaction of alkynes, see: Yin, K.; Li, C.; Li, J.; Jia, X. *Green Chem.* **2011**, *13*, 591.

(11) The structural assignment was based on the analysis of the ^{1}H and ^{13}C NMR spectra. The product **5a** was further identified by determining its X-ray structure.

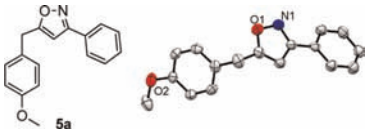
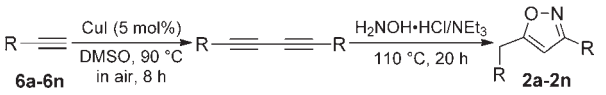


Table 4. One-Pot Synthesis of 3,5-Disubstituted Isoxazoles from Alkynes[a,b]



entry	alkyne **6**	product **2**	yield (%)[c]
1	**6a**	**2a**	86
2	**6b**	**2b**	78
3	**6c**	**2c**	81
4	**6d**	**2d**	80
5	**6e**	**6e**	88
6	**6f**	**2f**	95
7	**6g**	**2g**	60[d]
8	**6h**	**2h**	86
9	**6i**	**2i**	65
10	**6j**	**2j**	94
11	**6k**	**2k**	88
12	**6l**	**2l**	60
13	**6m**	**2m**	88
14	**6n**	**2n**	92

[a] Reaction conditions for first step: alkyne (**6a**–**6n**, 0.6 mmol) and CuI (5 mol %, 3.0 mg) in DMSO (3.0 mL) at 90 °C in air for 8 h. [b] Reaction conditions for second step: hydroxylamine hydrochloride (1.5 equiv, 62.5 mg) and NEt_3 (2.5 equiv, 152.0 mg) at 110 °C for 20 h. [c] Isolated yield. [d] 3.0 equiv and 4.0 equiv of hydroxylamine hydrochloride and NEt_3, respectively, were used.

1-naphthylacetylene (**6l**), 3-pyridinylacetylene (**6m**), and 3-thienylacetylene (**6n**) were investigated under the same conditions. The corresponding products **2l**–**2m** were obtained in moderate to excellent yields (entries 12–14, 60%, 88%, and 92%, respectively). All the new products **2a**–**2n**, **4a**–**4 h**, and **5a**–**5f** were identified through their NMR and HRMS data as well as IR spectra.[11]

In summary, a novel and general method for the synthesis of 3,5-disubstituted isoxazoles was developed using simple and readily available starting materials, namely, 1,3-dialkynes/alkynes and hydroxylamine hydrochloride. The intermolecular Cope-type hydroamination reaction of 1,3-dialkynes with hydroxylamine and the subsequent electrophilic addition proceeded smoothly under very mild conditions to produce 3,5-disubstituted isoxazoles in satisfactory to excellent yields. The wide availability of the starting materials, mild reaction conditions, and experimental simplicity must make the present methodology more useful in organic synthesis. Further study focusing on the extension of the reaction scope using hydrazines is underway.

Acknowledgment. We are grateful to the National Natural Science Foundation of China (nos. 20972021 and 21173032) for their financial support. This work was also supported by the Specialized Research Fund for the Doctoral Program of Higher Education (no. 200900411-10012).

Supporting Information Available. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.