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Synthesis of Isoxazoles via Electrophilic Cyclization

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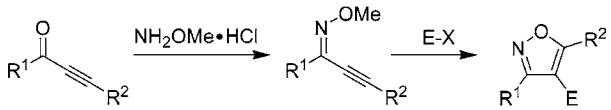
ABSTRACT



A variety of 3,5-disubstituted 4-halo(seleno)isoxazoles are readily prepared in good to excellent yields under mild reaction conditions by the reaction of 2-alkyn-1-one *O*-methyl oximes with ICl, I_2, Br_2, or PhSeBr.

The biological activity of substituted isoxazoles[1] has made them a focus of medicinal chemistry over the years. Isoxazoles are potent, selective agonists at human cloned dopamine D4 receptors[2] and exhibit $GABA_A$ antagonist,[3] analgesic,[4] antiinflammatory,[4] ulcerogenic,[4] antimicrobial,[5] antifungal,[5] COX-2 inhibitory,[6] antinociceptive,[7] and anticancer[8] activity.

Many synthetic methods have been employed in the synthesis of isoxazoles,[9] including reactions of hydroxylamine with 1,3-dicarbonyl compounds,[10] α,β-unsaturated carbonyl compounds,[11] and α,β-unsaturated nitriles.[12] The reaction of an oxime-derived dianion and an ester[13] or amide[14] also provides isoxazoles. [3 + 2] Cycloaddition reactions between alkynes and nitrile oxides have also been developed.[15] However, these methods often require strong bases, strong mineral acids, or high temperatures or provide poor regioselectivity.

It has been known for over a century that isoxazoles can be halogenated to give 4-haloisoxazoles.[16] However, even the mildest conditions for the halogenation of isoxazoles frequently require the use of harsh acids and high temperatures.[16c]

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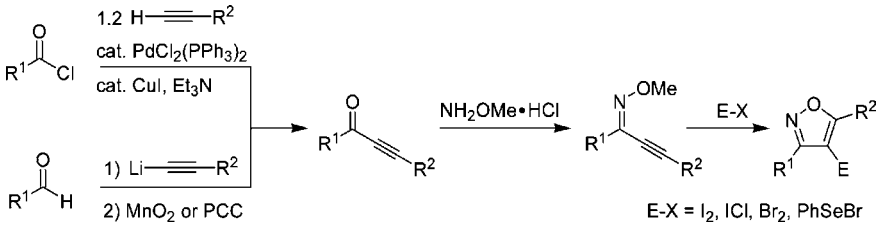
Scheme 1



Recent work by our group and others has shown the electrophilic cyclization of functionally substituted acetylenes to be an efficient way of generating benzo[*b*]thiophenes,[17] isoquinolines and naphthyridines,[18] isocoumarins and α-pyrones,[19] benzofurans,[20] furans,[21] indoles,[22] furopyridines,[23] cyclic carbonates,[24] 2,3-dihydropyrroles and pyrroles,[25] pyrilium salts and isochromenes,[26] and bicyclic *β*-lactams.[27] This work prompted us to examine the possible synthesis of isoxazoles by the electrophilic cyclization of 2-alkyn-1-one *O*-methyl oximes. We now report our success.

A three-step approach to isoxazoles has been examined involving (i) preparation of the ynone, (ii) formation of the *O*-methyl oxime, and (iii) electrophilic cyclization (Scheme 1).

The ynones required for this methodology are readily prepared by the palladium/copper-catalyzed Sonogashira coupling of an acid chloride with a terminal acetylene[28] or by allowing the lithium acetylide to react with an aldehyde, followed by oxidation of the secondary alcohol.[29] The requisite ynones can also be conveniently prepared by the Pd-catalyzed carbonylative coupling of terminal acetylenes with aryl iodides[30] or treatment of a silyl acetylene with an acid chloride in the presence of aluminum chloride.[31]

The *O*-methyl oximes are readily prepared by stirring the ynone in the presence of methoxylamine hydrochloride, pyridine, and Na_2SO_4 at room temperature using methanol as the solvent.[32] When R^1 is a bulky group relative to the alkyne moiety, the desired *Z* isomer is the predominant product. However, if R^1 is significantly less bulky, a mixture of isomers often results and the desired isomer must be separated by column chromatography. The yields of the desired *Z*-*O*-methyl oximes from the ynones are generally good, and these compounds are easily isolated by column chromatography on silica gel.

To study the scope of this electrophilic cyclization strategy, the reactions of *O*-methyl oximes **1** and **2** with different electrophiles (ICl, I_2, Br_2, and PhSeBr) at room temperature have been studied (Table 1, entries 1−6). *O*-Methyl oxime **1** reacts at room temperature in CH_2Cl_2 with ICl (Table 1, entry 1) to afford isoxazole **10** in a good yield. Treating *O*-methyl oxime **1** with I_2 in CH_3CN (entry 2) also affords the expected isoxazole **10** in good yield, although more of the electrophile was required to generate a high yield. The use of I_2 in CH_2Cl_2 resulted in lowered yields. Br_2 and PhSeBr can also be utilized in the cyclization process (entries 3−5). However, the reactions require more electrophile and longer reaction times.

Since ICl provided a higher yield and a shorter reaction time for the parent system, compared with I_2 (compare entries 1 and 2), this procedure was chosen to test the scope of the cyclization process. Alkynes bearing vinylic and alkyl groups provide good yields of the desired 4-iodoisoxazoles (entries 6 and 7). The reaction is not inhibited by the presence of bulky *tert*-butyl or TIPS groups (entries 8 and 9). However, 2.0 equiv of ICl is required in the latter reaction. When 1.2 equiv of ICl is used for the alkyne bearing a TIPS group, a comparable yield is achieved, but the reaction takes longer.

We have also examined the effect on the yield of varying the nature of the group R^1, while retaining R^2 as a phenyl group. The reaction works well when R^1 is a hydrogen, an alkyl chain, or a bulky alkyl group (entries 10−12). The *N*-methyl-3-indolyl heterocycle also gave a respectable yield of 55% (entry 13). The use of more ICl in the latter example did not provide a higher yield. In all cases, the desired isoxazoles have been obtained in good yields with no evidence of any products arising from simple addition of the electrophile to the alkyne.

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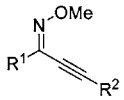
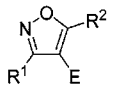
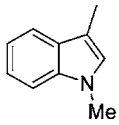
Table 1. Synthesis of Substituted Isoxazoles[a]

entry	substrate			E-X	time (h)	product		yield (%)[b]
								
	R^1	R^2				E		
1	Ph	Ph	**1**	1.2 ICl	0.5	I	**10**	(86)
2	Ph	Ph	**1**	3.0 I_2[c]	1.0	I	**10**	(77)
3	Ph	Ph	**1**	2.5 Br_2	24	Br	**11**	(75)
4	Ph	Ph	**1**	3.0 PhSeBr	24	PhSe	**12**	(91)
5	Ph		**2**	3.0 PhSeBr	24	PhSe	**13**	(88)
6	Ph		**2**	1.2 ICl	0.5	I	**14**	(78)
7	Ph	CH_3	**3**	1.2 ICl	0.75	I	**15**	(99)
8	Ph	*t*-Bu	**4**	1.2 ICl	0.75	I	**16**	(90)
9	Ph	TIPS	**5**	2.0 ICl	1.0	I	**17**	(82)
10	H	Ph	**6**	1.2 ICl	0.25	I	**18**	(83)
11	*n*-C_6H_{13}	Ph	**7**	1.2 ICl	0.75	I	**19**	(94)
12	*t*-Bu	Ph	**8**	1.2 ICl	0.75	I	**20**	(100)
13		Ph	**9**	1.2 ICl	0.5	I	**21**	(55)

[a] All reactions were carried out in CH_2Cl_2 (10 mL/mmol) at room temperature using 0.25 mmol of starting material unless otherwise specified. [b] Isolated yields after column chromatography. [c] The reaction was carried out in CH_3CN.

Our investigation has shown that highly substituted isoxazoles can be formed in good to excellent yields using mild reaction conditions. The preparation of starting materials is very general and can be applied to a wide variety of substrates. We believe that this approach to substituted isoxazoles should be quite useful in synthesis considering the many ways one can transform the resulting halogen and selenium functional groups. For example, the 3-haloisoxazoles should be useful in many palladium-catalyzed processes, such as Sonogashira,[33] Suzuki,[34] and Heck[35] reactions.

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

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