

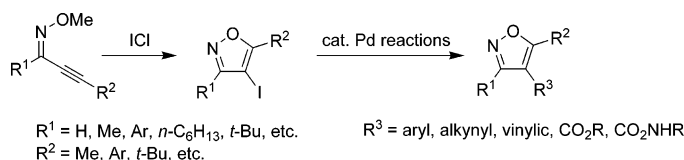
The Synthesis of Highly Substituted Isoxazoles by Electrophilic Cyclization: An Efficient Synthesis of Valdecobix

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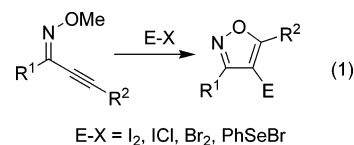
A large number of functionally substituted 2-alkyn-1-one *O*-methyl oximes have been cyclized under mild reaction conditions in the presence of ICl to give the corresponding 4-iodoisoxazoles in moderate to excellent yields. The resulting 4-iodoisoxazoles undergo various palladium-catalyzed reactions to yield 3,4,5-trisubstituted isoxazoles, including valdecobix.

Introduction

The isoxazole skeleton has been the focus of many biological studies in recent years.¹ Our group and others have reported that the electrophilic cyclization of functionally substituted acetylenes is a powerful synthetic tool for constructing a diverse assortment of ring systems, including benzo[*b*]thiophenes,² isoquinolines and naphthyridines,³ isocoumarins and α -pyrones,⁴ benzofurans,⁵ furans,⁶ indoles,⁷ furopyridines,⁸ cyclic carbonates,⁹ 2,3-dihydropyrroles and pyrroles,¹⁰ pyrilium salts and isochromenes,¹¹ bicyclic β -lactams,¹² 2*H*-benzopyrans,¹³ naph-

thalenes and 2-naphthols,¹⁴ chromones,¹⁵ isoindolin-1-ones,¹⁶ and benzo[*b*]selenophenes.¹⁷

We recently reported the synthesis of numerous highly substituted isoxazoles through the cyclization of various 2-alkyn-1-one *O*-methyl oximes (eq 1)¹⁸ by a variety of electrophiles.



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. We now report the full details of our work on the ICl-induced cyclization of 2-alkyn-

(1) (a) For a brief review, see: Carlsen, L.; Döpp, D.; Döpp, H.; Duus, F.; Hartmann, H.; Lang-Fugmann, S.; Schulze, B.; Smalley, R. K.; Wakefield, B. J. In *Houben-Weyl, Methods in Organic Chemistry*; Schumann, E., Ed.; Georg Thieme Verlag: Stuttgart, Germany, 1992; Vol. E8a, pp 45–204. (b) Rowley, M.; Broughton, H. B.; Collins, I.; Baker, R.; Emms, F.; Marwood, R.; Patel, S.; Ragan, C. I. *J. Med. Chem.* **1996**, 39, 1943. (c) Frolund, B.; Jorgensen, A. T.; Tagmose, L.; Stensbol, T. B.; Vestergaard, H. T.; Engblom, C.; Kristiansen, U.; Sanchez, C.; Krogsgaard-Larsen, P.; Liljefors, T. *J. Med. Chem.* **2002**, 45, 2454. (d) Daidone, G.; Raffa, D.; Maggio, B.; Plescia, F.; Cutuli, V. M. C.; Mangano, N. G.; Caruso, A. *Arch. Pharm. Pharm. Med. Chem.* **1999**, 332, 50. (e) Tomita, K.; Takahi, Y.; Ishizuka, R.; Kamamura, S.; Nakagawa, M.; Ando, M.; Nakanishi, T.; Nakamura, T.; Udaire, H. *Ann. Sankyo Res. Lab.* **1973**, 1, 25; *Chem. Abstr.* **1974**, 80, 120808. (f) Talley, J. J. *Prog. Med. Chem.* **1999**, 13, 201. (g) Talley, J. J.; Brown, D. L.; Carter, J. S.; Graneto, M. J.; Koboldt, C. M.; Masferrer, J. L.; Perkins, W. E.; Rogers, R. S.; Shaffer, A. F.; Zhang, Y. Y.; Zweifel, B. S.; Seibert, K. *J. Med. Chem.* **2000**, 43, 775. (h) Giovannoni, M. P.; Vergelli, C.; Ghelardini, C.; Galeotti, N.; Bartolini, A.; Kal Piaz, V. *J. Med. Chem.* **2003**, 46, 1055. (i) Li, W.-T.; Hwang, D.-R.; Chen, C.-P.; Shen, C.-W.; Huang, C.-L.; Chen, T.-W.; Lin, C.-H.; Chang, Y.-L.; Chang, Y.-Y.; Lo, Y.-K.; Tseng, H.-Y.; Lin, C.-C.; Song, J.-S.; Chen, H.-C.; Chen, S.-Y.; Wu, S.-H.; Chen, C.-T. *J. Med. Chem.* **2003**, 46, 1706.

(2) (a) Larock, R. C.; Yue, D. *Tetrahedron Lett.* **2001**, 42, 6011. (b) Yue, D.; Larock, R. C. *J. Org. Chem.* **2002**, 67, 1905. (c) Flynn, B. L.; Verdier-Pinard, P.; Hamel, E. *Org. Lett.* **2001**, 3, 651.

(3) (a) Huang, Q.; Hunter, J. A.; Larock, R. C. *Org. Lett.* **2001**, 3, 2973. (b) Huang, Q.; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, 67, 3437.

(4) (a) Yao, T.; Larock, R. C. *Tetrahedron Lett.* **2002**, 43, 7401. (b) Yao, T.; Larock, R. C. *J. Org. Chem.* **2003**, 68, 5936. (c) Oliver, M. A.; Gandour, R. D. *J. Org. Chem.* **1984**, 49, 558. (d) Biagetti, M.; Bellina, F.; Carpita, A.; Stabile, P.; Rossi, R. *Tetrahedron* **2002**, 58, 5023. (e) Rossi, R.; Carpita, A.; Bellina, F.; Stabile, P.; Mannina, L. *Tetrahedron* **2003**, 59, 2067.

(5) (a) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L. *Synlett* **1999**, 1432. (b) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, 70, 10292.

(6) (a) Bew, S. P.; Knight, D. W. *J. Chem. Soc. Chem. Commun.* **1996**, 1007. (b) Djuardi, E.; McNelis, E. *Tetrahedron Lett.* **1999**, 40, 7193. (c) Sniady, A.; Wheeler, K. A.; Dembinski, R. *Org. Lett.* **2005**, 7, 1769. (d) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, 126, 11164. (e) Yao, T.; Zhang, X.; Larock, R. C. *J. Org. Chem.* **2005**, 70, 7679.

(7) (a) Barluenga, J.; Trincado, M.; Rublio, E.; Gonzalez, J. M. *Angew. Chem., Int. Ed.* **2003**, 42, 2406. (b) Muhammad, A.; Knight, D. W. *Tetrahedron Lett.* **2004**, 45, 539. (c) Yue, D.; Larock, R. C. *Org. Lett.* **2004**, 6, 1037. (d) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2006**, 71, 62.

(8) Arcadi, A.; Cacchi, S.; Di Giuseppe, S.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2002**, 4, 2409.

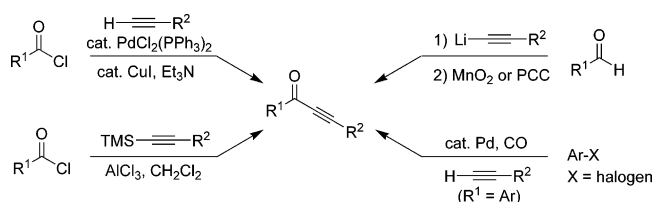
(9) Marshall, J. A.; Yanik, M. M. *J. Org. Chem.* **1999**, 64, 3798.

1-one *O*-methyl oximes, which provides a very efficient synthesis of 4-iodoisoxazoles. Numerous examples are reported. The resulting 4-iodoisoxazoles are readily elaborated by conventional palladium-catalyzed processes to afford highly substituted isoxazoles, including valdecocib.

Results and Discussion

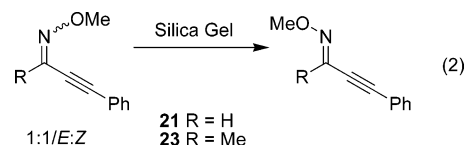
The requisite ynones can be easily prepared (Scheme 1) by the palladium/copper-catalyzed Sonogashira coupling of an acid chloride with a terminal acetylene¹⁹ or by Pd-catalyzed carbonylative coupling of terminal acetylenes with aryl iodides.²⁰ The ynones can also be prepared by allowing a lithium acetylide to react with an aldehyde, followed by oxidation of the resulting secondary alcohol.²¹ In addition, ynones can be conveniently prepared by the treatment of silyl acetylenes with an acid chloride in the presence of aluminum chloride.²²

SCHEME 1



The *O*-methyl oximes required in our isoxazole synthesis are readily prepared by stirring the ynone in the presence of methoxylamine hydrochloride, pyridine, and Na₂SO₄ or MgSO₄ at room temperature using methanol as the solvent.²³ Heating is sometimes required, especially when R¹ is an aromatic ring bearing electron-donating groups. When R¹ is a bulky group relative to the alkyne moiety, the desired *Z* isomer is the predominant product. However, if R¹ is significantly less bulky, a mixture of isomers often results and the desired isomer must be separated by column chromatography. Upon preparation of the 2-alkyn-1-one *O*-methyl oximes **21** and **23**, a 1:1 mixture of *E*-*Z* *O*-methyl oximes, observable by ¹H NMR spectroscopy, was obtained. Our attempts at separating these isomers on a silica gel column led to the unwanted *E* isomer exclusively (eq 2). The 1:1 mixture of *E*:*Z* *O*-methyl oximes **21** and **23** isomerized exclusively to their *E* isomers. This isomerization only occurred when R was either a proton or a methyl group

but was not observed in any other cases. Nevertheless, in the cases when R is equal to a proton (**21**) or methyl (**23**), the desired *Z*-*O*-methyl oxime could be isolated by utilizing a basic alumina column, although the yields were only modest. It was discovered that only the *Z* isomer cyclized when subjected to our usual ICl cyclization conditions. Our attempts at simultaneous isomerization and cyclization of the *E* isomer were unsuccessful. Consequently, it is essential that the *Z*-*O*-methyl oxime isomer be employed in the cyclization process.



With the desired *Z*-*O*-methyl oximes in hand, we studied the scope of the cyclization methodology (Table 1). In our earlier studies,¹⁸ we discovered that using ICl as the source of electrophilic iodine provided the best results for the formation of isoxazoles. I₂ may also be used to induce the cyclization of compound **1**. However, the reactions are slower and higher molar equivalents of I₂ are required to achieve yields comparable to those of ICl (Table 1, compare entries 1 and 2).

When the terminus of the alkynyl moiety was substituted with aliphatic substituents ranging from compact to bulky, the yields were excellent (Table 1, entries 3–5). Furthermore, the introduction of substituents on the aryl group has little effect on the yield of the reaction. The electron-withdrawing group CO₂Et (**9**) and the electron-donating group OMe (**11**), both in the para position of the phenyl ring, did not significantly change the reaction yields compared to the parent system (Table 1, entries 6 and 7). Furthermore, substituting the alkynyl unit with a thiophene heterocycle (**13**) lowered the yield only slightly (Table 1, entry 8).

The effect of changing the substituents in the 1 position of the 2-alkyn-1-one *O*-methyl oxime was also studied. The para electron-withdrawing groups in compounds **15** and **17** provided the corresponding isoxazoles **16** and **18** in excellent yields (Table 1, entries 9 and 10). The electron-donating group NMe₂ in the para position of compound **19** required a dramatic increase in reaction time and 2.2 mol equiv of ICl had to be used to achieve an excellent yield of **20**; 1.2 mol equivalent of ICl provided only a trace of **20**, and the reaction suffered from low conversion. No further iodinated products were observed in the reaction.

Other substituents in the 1 position of the 1-alkynone were generally quite successful. For example, compounds **21** and **23**, as the pure *Z*-isomers, afforded the expected product with only a slight decrease in yields (Table 1, entries 12 and 13) using our standard procedure, whereas compound **25** provided an excellent yield of **26** (Table 1, entry 14). Introducing a bulky *t*-Bu group (**27**) into the alkynone provided a quantitative yield of the desired isoxazole **28** (Table 1, entry 15). Compounds **29** and **31** introduce steric bulk at the ortho positions of the parent phenyl rings. This did not hinder the reaction, and high yields of the isoxazole products **30** and **32** were obtained using short reaction times (Table 1, entries 16 and 17). Thus, steric effects appear to be minimal in this process. Compound **31** cyclized exclusively to the desired 5-*endo dig* isoxazole product **32**, and the possible 6-*exo dig* chromone oxime product was not observed, even though we have successfully cyclized closely related ketones to the corresponding chromones¹⁵ (Scheme 2).

- (10) Knight, D. W.; Redfern, A. L.; Gilmore, J. J. *Chem. Soc. Chem. Commun.* **1998**, 2207.
 (11) (a) Barluenga, J.; Vazquez-Villa, H.; Ballesteros, A.; Gonzalez, J. M. *J. Am. Chem. Soc.* **2003**, 125, 9028. (b) Yue, D.; Della Cà, N.; Larock, R. C. *Org. Lett.* **2004**, 6, 1581. (c) Yue, D.; Della Cà, N.; Larock, R. C. *J. Org. Chem.* **2006**, 71, 3381.
 (12) Ren, X.-F.; Konaklieva, M. I.; Shi, H.; Dickey, S.; Lim, D. V.; Gonzalez, J.; Turos, E. *J. Org. Chem.* **1998**, 63, 8898.
 (13) Worlikar, S. A.; Kesharwani, T.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2007**, 72, 1347.
 (14) Zhang, X.; Sarkar, S.; Larock, R. C. *J. Org. Chem.* **2006**, 71, 236.
 (15) Zhou, C.; Dubrovsky, A. V.; Larock, R. C. *J. Org. Chem.* **2006**, 71, 1626.
 (16) Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, 70, 1432.
 (17) Kesharwani, T.; Worlikar, S. A.; Larock, R. C. *J. Org. Chem.* **2006**, 71, 2307.
 (18) Waldo, J. P.; Larock, R. C. *Org. Lett.* **2005**, 23, 5203.
 (19) Tohda, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1977**, 777.
 (20) (a) Kobayashi, T.; Tanaka, M. *J. Chem. Soc. Chem. Commun.* **1981**, 333. (b) Mohamed Ahmed, M. S.; Mori, A. *Org. Lett.* **2003**, 5, 3057.
 (21) Lin, C.-F.; Lu, W.-D.; Wang, I.-W.; Wu, M.-J. *Synlett* **2003**, 2057.
 (22) Birkofer, L.; Ritter, A.; Uhlenbrauck, H. *Chem. Ber.* **1963**, 96, 3280.
 (23) Beak, P.; Basha, A.; Kokko, B.; Loo, D. *J. Am. Chem. Soc.* **1986**, 108, 6016.

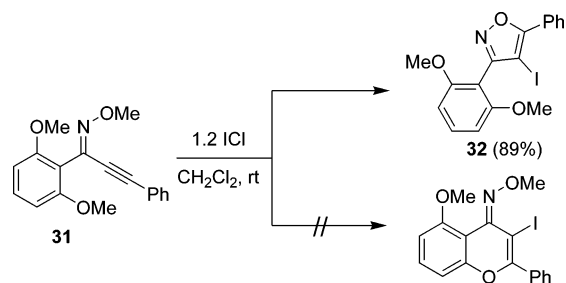
TABLE 1. Synthesis of 4-Iodoisoxazoles by Electrophilic Cyclization^a

entry	<i>O</i> -methyl oxime	electrophile	time (h)	product	yield (%) ^b
1	R = Ph (1)	3.0 I ₂ ^c	1.0	(2)	77
2		1.2 ICl	0.5		86
3	R = Me (3)	1.2 ICl	0.75	(4)	99
4	R = <i>n</i> -Bu (5)	1.2 ICl	0.75	(6)	91
5	R = <i>t</i> -Bu (7)	1.2 ICl	0.75	(8)	90
6	R =	1.2 ICl	0.5	(10)	87
7	R =	1.2 ICl	0.5	(12)	89
8	R =	1.2 ICl	0.5	(14)	82
9	R =	1.2 ICl	1.0	(16)	94
10	R =	1.2 ICl	1.0	(18)	93
11	R =	2.2 ICl	6.0	(20)	98
12	R = H (21)	1.2 ICl	0.5	(22)	83
13	R = Me (23)	1.2 ICl	0.75	(24)	79
14	R = <i>n</i> -C ₆ H ₁₃ (25)	1.2 ICl	0.75	(26)	94
15	R = <i>t</i> -Bu (27)	1.2 ICl	0.75	(28)	100
16	R =	1.2 ICl	0.5	(30)	93
17	R =	1.2 ICl	1.0	(32)	89
18	R =	1.2 ICl	1.0	(34)	82
19	R =	1.2 ICl	0.5	(36)	86
20	R =	1.2 ICl	0.5	(38)	55
21	R =	3.0 ICl	3.0	(40)	68
22		1.2 ICl	2.0		87
23		1.2 ICl	1.0		96

^a All reactions were carried out in CH₂Cl₂ (10 mL/mmol) at room temperature using 0.25 mmol of starting material unless otherwise specified.

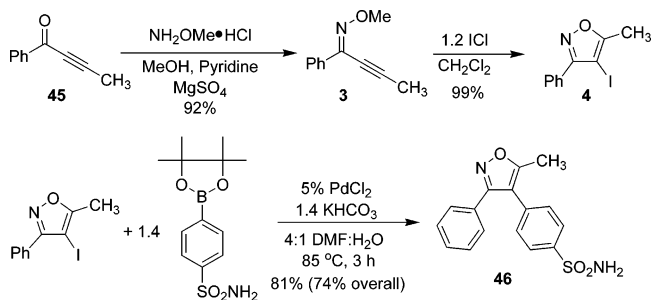
^b Isolated yields after column chromatography. ^c The reaction was carried out in CH₃CN.

Introduction of the oxygen-containing heterocycles **33** and **35** into the alkyne also provided isoxazoles in good yields (Table 1, entries 18 and 19). The nitrogen-containing heterocycles **37** and **39** also afforded the desired isoxazoles, although the yields were only modest (Table 1, entries 20 and 21). The

SCHEME 2

cyclization of compound **39** required the use of 3 equiv of ICl, as well as an increased reaction time. Compound **41** was synthesized to study the effect of having two sterically bulky *t*-Bu substituents present in the same substrate. The reaction required a slight increase in time. Nevertheless, isoxazole **42** was obtained in a very good yield (Table 1, entry 22). The highly substituted aryl group of *O*-methyl oxime **43** also provided an excellent yield of isoxazole **44** (Table 1, entry 23). Scaled up reactions, including multigram preparations of compounds **2**, **4**, and **44**, did not affect the yield or outcome of the methodology. This is important to note in cases where one wishes to produce a large quantity of product for use in total synthesis or library generation.

To demonstrate the value of the 4-iodoisoxazole products generated in this methodology, a number of reactions were carried out utilizing the iodine handle. We reasoned that we could approach the highly potent COX-2 inhibitor 4-(5-methyl-3-phenyl-4-isoxazolyl)benzenesulfonamide (valdecocixib) (**46**)^{24,1g} by a Suzuki–Miyaura cross-coupling of isoxazole **4** with the appropriate boronic acid ester.²⁵ Using our isoxazole methodology to prepare **4** and a Suzuki–Miyaura coupling with the commercially available benzenesulfonamide-4-boronic acid pinacol ester, we were able to develop a very efficient route to valdecocixib (Scheme 3). Starting with ynone **45**, *O*-methyl oxime **3** was obtained in a 92% yield. Compound **3** was subjected to our ICl cyclization conditions to afford isoxazole **4** in nearly a quantitative yield. After several protocols were screened, Suzuki cross-coupling was best accomplished using 5 mol % PdCl₂ catalyst, 1.4 equiv of KHCO₃ in 4:1 DMF:H₂O at 85 °C for 3 h to provide valdecocixib (**46**) in an 81% isolated yield, which constitutes a 74% overall yield from ynone **45**.

SCHEME 3

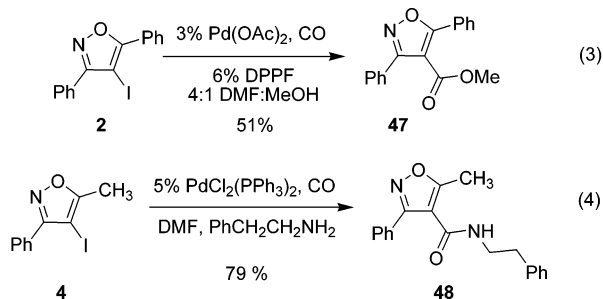
This synthetic route to valdecocixib provides a high overall yield and utilizes very mild reaction conditions compared to

(24) (a) Talley, J. J. (G. D. Searle & Company), U.S. Patent 5,859,257, 1999; *Chem. Abstr.* **1999**, 130, 110269. (b) Talley, J. J. *Prog. Med. Chem.* **1999**, 13, 201.

(25) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, 95, 2457. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, 576, 147 and references therein.

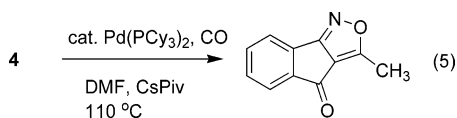
those previously reported. Earlier reports on the synthesis of valdecoxib required the use of strong bases, such as *n*-BuLi,^{1g,24,26} or the preparation of boronic acids *in situ* using air- and water-sensitive triisopropyl borate (*i*-PrO)₃B.²⁶ These previous processes also suffer from poor overall yields. In addition to the aforementioned advantages of this synthesis, one may construct many analogues of valdecoxib by choosing from the wide array of commercially available starting materials that are appropriate for this methodology.

Other palladium-catalyzed methodology has also proven useful for further elaboration of these iodoisoxazoles. For example, we were able to convert 4-iodo-3,5-diphenylisoxazole (**2**) to the corresponding methyl ester by allowing **2** to react in the presence of catalytic amounts of Pd(OAc)₂ plus a ferrocene ligand, carbon monoxide, and methanol to afford methyl ester **47** in a 51% yield (eq 3).²⁷ Reduction of compound **2** to 3,5-diphenylisoxazole was an observed minor side product. In addition, we were able to convert 4-iodo-5-methyl-3-phenylisoxazole (**4**) to the corresponding phenethylamide by a similar approach using a modified literature procedure.²⁸ By allowing compound **4** to react in the presence of catalytic amounts of PdCl₂(PPh₃)₂, carbon monoxide, and 2-phenethyl amine, we were able to obtain **48** cleanly in good yield (eq 4).



Additionally, we were able to affect Heck and Sonogashira cross-couplings on 4-iodo-5-methyl-3-phenylisoxazole (**4**) (Scheme 4). By allowing compound **4** to react under standard Sonogashira²⁹ conditions in the presence of 1.2 equiv of phenyl acetylene, alkyne **49** was obtained in a good yield. Also, allowing compound **4** to react under Heck³⁰ reaction conditions in the presence of *N*-acryloylmorpholine provided the desired α,β -unsaturated amide **50** in excellent yield.

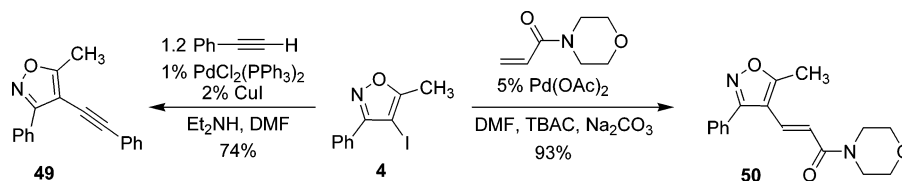
Unfortunately, the palladium-catalyzed carbonylative cyclization³¹ of isoxazole **4** failed, and reduction of the starting material was the only observed product (eq 5).



Conclusions

3,4,5-Trisubstituted isoxazoles have been generated in high yields under mild reaction conditions by the electrophilic

SCHEME 4



cyclization of Z-O-methyl oximes of 2-alkyn-1-ones. Our methodology tolerates a wide variety of functional groups, including heterocycles and sterically cumbersome substrates. This process can be scaled up to provide multigram quantities of the desired product without sacrificing the yield or outcome of the methodology. One can construct libraries of highly substituted isoxazoles by invoking the appropriate starting materials in an orderly fashion. Furthermore, the iodine handle of the products provides an opportunity for further functionalization, as demonstrated by the ester and amide products **47** and **48**, the Sonogashira product **49**, and the Heck product **50**.

Experimental Section

General Procedure for the Preparation of Alkynes from Acyl Chlorides. To a 25 mL flask were added CuI (0.05 mmol), PdCl₂(PPh₃)₂ (0.01 mmol), and triethylamine (5 mL). The flask was flushed with argon, and the terminal acetylene (2.5 mmol) was added to the stirred suspension, followed by immediate dropwise addition of the acyl chloride (3.25 mmol, 1.3 equiv). When the acyl chloride was a solid, it was added as a solution in THF. The resulting mixture was allowed to stir at room temperature overnight, water (5 mL) was added, and the aqueous layer was extracted with ethyl acetate. The organic layers were combined, dried, and concentrated under reduced pressure. The residue was then purified by column chromatography on silica gel to afford the desired alkyne.

1,3-Diphenylprop-2-yn-1-one. Purification by flash chromatography (hexanes/EtOAc) afforded 433 mg (84%) of the product as a yellow liquid with spectral properties identical to those previously reported.¹⁹

General Procedure for Preparation of the O-Methyl Oximes. The alkyne (3.5 mmol), methoxylamine hydrochloride (7.0 mmol, 579 mg), Na₂SO₄ (7.0 mmol, 994 mg), and pyridine (1 mL) in methanol (10 mL) were stirred at room temperature. The reaction was monitored by TLC until the reaction was complete. The mixture was diluted with water (25 mL) and extracted with EtOAc (3 × 5 mL). The organic layer was washed with brine, dried, and evaporated. The residue was then purified by column chromatography on silica gel to afford the desired O-methyl oxime.

(Z)-1,3-Diphenylprop-2-yn-1-one O-Methyl Oxime (1). Purification by flash chromatography (40:1 hexanes/EtOAc) afforded 617 mg (75%) of the product as an off-white solid: mp 40–42 °C; ¹H NMR (CDCl₃) δ 4.14 (s, 3H), 7.37–7.40 (m, 6H), 7.60–7.63 (m, 2H), 7.90–7.93 (m, 2H); ¹³C NMR (CDCl₃) δ 63.4, 79.7, 101.4, 122.0, 126.8, 128.6, 128.7, 129.8, 129.9, 132.4, 133.8, 140.2; IR (neat, cm⁻¹) 3052, 2935, 1598; HRMS Calcd for C₁₆H₁₃NO: 235.0997. Found: 235.1000.

General Procedure for Iodocyclization using ICl. To a stirred solution of the appropriate O-methyl oxime (0.25 mmol) in CH₂Cl₂ (2.5 mL) was added ICl (1 M in CH₂Cl₂, 1.2 equiv) dropwise, and the solution was allowed to stir at room temperature. The reaction was monitored by TLC to establish completion. The excess ICl was removed by washing with a saturated aqueous solution of Na₂S₂O₃. The aqueous solution was then extracted with CH₂Cl₂ (3 × 5 mL). The combined organic layers were dried over anhydrous MgSO₄ and concentrated under a vacuum to yield the crude product, which was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent.

Procedure for Iodocyclization using I₂. To a stirred solution of the *O*-methyl oxime (0.25 mmol) in CH₃CN (2.5 mL) was added I₂ (0.75 mmol, 191 mg), and the solution was allowed to stir at room temperature for 1 h. The excess I₂ was removed by washing with a saturated aqueous solution of Na₂S₂O₃. The aqueous solution was extracted with CH₂Cl₂ (3 × 5 mL). The combined organic layers were dried over anhydrous MgSO₄ and concentrated under reduced pressure to yield the crude product. Purification by flash chromatography afforded the product.

3,5-Diphenyl-4-iodoisoxazole (2). The product was obtained as a colorless solid: mp 176–178 °C (lit.³² mp 176.5–177.5 °C). The spectral properties were identical to those previously reported.³²

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Supporting Information Available: General experimental procedures and spectral data for all previously unreported starting materials and products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO701942E

(26) Kumar, J. S.; Ho, M. M.; Leung, J. M.; Toyokuni, T. *Adv. Synth. Catal.* **2002**, *344*, 1146.

(27) Friesen, R. W.; Ducharme, Y.; Ball, R. G.; Blouin, M.; Boulet, L.; Cote, B.; Frenette, R.; Girard, M.; Guay, D.; Huang, Z.; Jones, T. R.; Laliberte, F.; Lynch, J. J.; Mancini, J.; Martins, E.; Masson, P.; Muise, E.; Pon, D. J.; Siegl, P. K. S.; Styhler, A.; Tsou, N. N.; Turner, M. J.; Young, R. N.; Girard, Y. *J. Med. Chem.* **2003**, *46*, 2413.

(28) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327.

(29) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Chapter 5, pp 203–229. (b) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.

(30) (a) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2005**, *61*, 11771. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442. (c) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., de Meijere, A., Eds.; Wiley-Interscience: New York, 2002; Vol. 1, p 1223 and references therein. (d) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley & Sons: Chichester, England, 2004; p 135.

(31) (a) Campo, M. A.; Larock, R. C. *Org. Lett.* **2000**, *2*, 3675. (b) Campo, M. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 5616.

(32) Day, R. A.; Blake, J. A.; Stephens, C. E. *Synthesis* **2003**, 1586.