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An Alkynyliodide Cycloaddition Strategy for the Construction of Iodoisoxazoles

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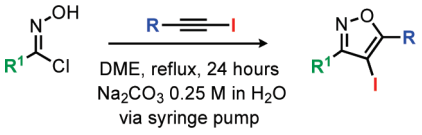
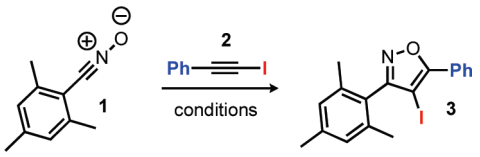


The thermally promoted cycloaddition between alkynyliodides and nitrile oxides is reported. The process offers excellent regioselectivity and a broad scope with respect to both the iodoalkynes and chloro-oximes. Further functionalization of the highly decorated iodoisoxazole motifs can be achieved via Suzuki cross-coupling.

Aromatic and heteroaromatic halides constitute an extremely useful set of molecules in modern day organic synthesis. The ability to transform a C−X bond into a C−C or C−Y bond (where Y is a heteroatom) has been studied and described extensively.[1] Given the importance of such scaffolds, we were intrigued by the prospect of an alternative route to their synthesis. Currently, most C−X bonds are installed once the aromatic system is already in place via an electrophilic or nucleophilic substitution reaction. Often such processes require the employment of strong reagents such as PCl_5, ICl, or X_2 in strong acid. Our proposed route to circumvent this extra halogenation step features the concomitant synthesis and iodination of the targeted ring system through the cycloaddition of an alkynyliodide. We were surprised to find that there are relatively few reports on the cycloaddition of alkynyliodides, particularly toward functionalized heterocycles.[2] Indeed, perhaps the most notable example is that reported by Hein et al. in 2009, where alkynyliodides were found to react with azides under copper-catalyzed conditions to furnish a broad range of iodotriazoles in good yields and as single regioisomers.[2d] Given our recent interest in nitrile oxide cycloadditions,[3] we opted to assess their potential to undergo simple thermal cycloadditions with alkynyliodides toward the synthesis of iodoisoxazoles; our results are reported herein.

TABLE 1. Initial Results



entry	solvent	**1**:**2**	time	temp (°C)[a]	yield (%)
1	THF	1:2	20 min	100 (MW)	78
2	THF	1:1.1	20 min	100 (MW)	65
3	***DME***	***1:2***	***20 min***	***120 (MW)***	***83***
4	THF	1:1.1	18 h	reflux (SHP)	51[b]

[a]MW = microwave, SHP = stirrer hot plate. [b]Recovered starting material also observed.

Isoxazoles are important biologically active motifs featured in a variety of pharmaceutical and agrochemical products.[4] A plethora of methods exist for their synthesis, including condensation between hydroxylamine and 1,3-dicarbonyl compounds or α,β-unsaturated carbonyls, and [3 + 2] cycloadditions between nitrile oxides and alkynes.[5] However, the latter approach is often hampered with issues relating to poor cycloaddition regioselectivity or nitrile oxide dimerization.[6] With these issues in mind, we commenced our studies by using mesityl *N*-oxide (a stable, isolable nitrile oxide).[7] During the course of our initial studies, we sought a practical procedure for the synthesis of alkynyliodides. While several methods for their synthesis are reported in the literature, we found that those reported by Hein et al.[2d] were most practical in terms of operational simplicity and applicability. With mesityl *N*-oxide and a range of alkynyliodides in hand, we commenced our analysis of the thermally induced cycloaddition. Initially treating *N*-oxide **1** with 2 equiv of alkynyliodide **2** in a solution of THF at 100 °C in the microwave for 20 min pleasingly delivered the desired iodoisoxazole **3** in 78% yield (entry 1, Table 1). Attempts to lower the ratio of *N*-oxide to alkynyliodide to 1:1.1, respectively, resulted in a diminished yield (65%, entry 2, Table 1). However, switching solvents to dimethoxyethane (DME) and conducting the reaction with 2 equiv of alkyne at

(1) *Metal-Catalyzed Cross-Coupling Reactions II*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004.

(2) For examples of metal-mediated cycloadditions of alkynyliodides, see: (a) Yoo, W.-J.; Allen, A.; Villeneuve, K.; Tam, W. *Org. Lett.* **2005**, *7*, 5853. (b) Yamamoto, Y.; Hattori, K. *Tetrahedron* **2008**, *64*, 847. (c) Miura, T.; Murata, H.; Kiyota, K.; Kusama, H.; Iwasawa, N. *J. Mol. Catal. A* **2004**, *213*, 59. (d) Hein, J. E.; Tripp, J. C.; Krasnova, L. B.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2009**, *48*, 8018. For a thermally promoted cycloaddition, see: (e) Iwasawa, T.; Kamei, T.; Hama, K.; Nishimoto, Y.; Nishiuchi, M.; Kawamura, Y. *Tetrahedron Lett.* **2008**, *49*, 5244 (footnote 12).

(3) Crossley, J. A.; Browne, D. L. *Tetrahedron Lett.* **2010**, *51*, 2271.

(4) Giomi, D.; Cordero, F. M.; Machetti, F. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Oxford, 2008; Vol. 4, p 365.

(5) For a variety of recent methods for the preparation of isoxazoles, see: (a) Sheng, S.-R.; Liu, X.-L.; Xu, Q.; Song, C.-U. *Synthesis* **2003**, 2763. (b) Hansen, T. V.; Wu, P.; Fokin, V. V. *J. Org. Chem.* **2005**, *70*, 7761. (c) Ahmed, M. S. M.; Kobayashi, K.; Mori, A. *Org. Lett.* **2005**, *7*, 4487. (d) Waldo, J. P.; Larock, R. C. *Org. Lett.* **2005**, *7*, 5203. (e) Moore, J. E.; Davies, M. W.; Goodenough, K. M.; Wybrow, R. A. J.; York, M.; Johnson, C. N.; Harrity, J. P. A. *Tetrahedron* **2005**, *61*, 6707. (f) Itoh, K.-I.; Sakamaki, H.; Nakazato, N.; Horiuchi, A.; Horn, E.; Horiuchi, A. *Synthesis* **2005**, 3541. (g) Denmark, S. E.; Kalleymeyn, J. M. *J. Org. Chem.* **2005**, *70*, 2839. (h) Béha, S.; Giguère, D.; Patnam, R.; Roy, R. *Synlett* **2006**, 1739. (i) Cecchi, L.; De Sarlo, F.; Machetti, F. *Eur. J. Org. Chem.* **2006**, 4852. (j) Bourbeau, M. P.; Rider, J. T. *Org. Lett.* **2006**, *8*, 3679. (k) Dadiboyena, S.; Xu, J.; Hamme, A. T., II. *Tetrahedron Lett.* **2007**, *48*, 1295. (l) Waldo, J. P.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 9643. (m) Willy, B.; Rominger, F.; Müller, T. J. J. *Synthesis* **2008**, 293. (n) Xu, J.; Hamme, A. T., II. *Synlett* **2008**, 919. (o) Grecian, S.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2008**, *47*, 8285.

(6) Grundmann, C. *Synthesis* **1970**, 344.

(7) Grundmann, C.; Frommeld, H.-D.; Flory, K.; Datta, S. K. *J. Org. Chem.* **1968**, *33*, 1464.

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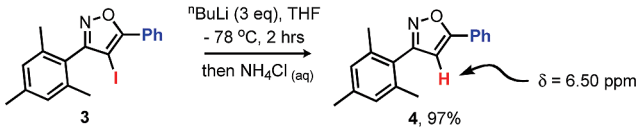
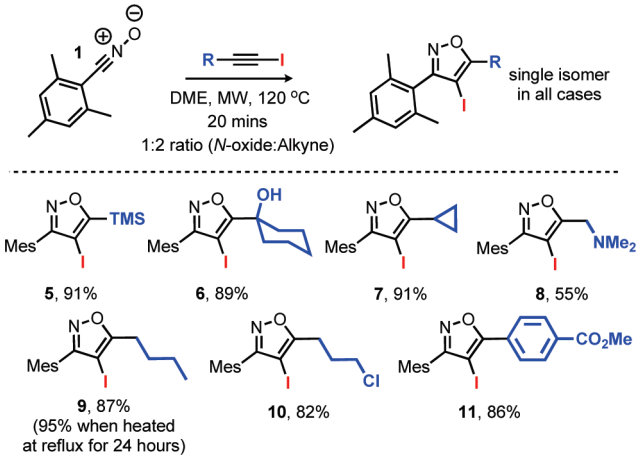
SCHEME 1. Confirming the Regioselecivity



SCHEME 2. Scope with Respect to Alkynylidodide



120 °C afforded the product in an improved 83% yield. Carrying out the reaction on a stirrer hot plate under traditional heating modes also proved feasible. Heating a 1:1.1 mixture of **1** and **2**, respectively, in THF at reflux for 18 h furnished the product in a 51% yield, with the remaining mass balance appearing to be recovered starting material (entry 4, Table 1).

With regards to the regioselectivity of this cycloaddition, we were able to confirm by a lithium−halogen exchange experiment that one isomer was produced (Scheme 1).[8] The diagnostic proton shift of the obtained product unequivocally confirms the formation of the 4-iodoisoxazole (the chemical shift of the 5*H*-isoxazole congener is expected between 8 and 9 ppm).[9]

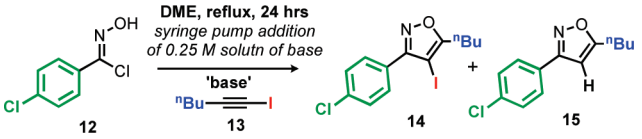
With the optimal conditions in hand (DME, 1:2 ratio of nitrile oxide/alkynyliodide, 120 °C, 20 min, microwave), we assessed the scope of the reaction with respect to various alkynyliodides (Scheme 2). We were pleased to find that a wide variety of iodoalkynes readily participate in the cycloaddition to furnish the desired functionalized isoxazoles in moderate to excellent yields.

Moreover, in every case studied, it was apparent from the ^{1}H NMR spectrum that the cycloaddition reaction was completely regioselective. Primary, secondary, and tertiary substituted alkynes all underwent smooth cycloaddition. Functional groups such as halides, esters, amines, free alcohols, and silyl groups were all tolerated. The electron-rich, propargylamine-derived iodoalkyne participated less well in the cycloaddition reaction to give the desired dimethylamino-substituted product **8** in a reduced 55% yield. We were mindful that the scope with respect to the nitrile oxide component would be dependent on the relative reactivities of homodimerization of the nitrile oxide and the desired product-forming process. Given the propensity of nitrile oxides to dimerize

(8) NOE analysis of the product provided no evidence for the interaction of the hydrogens of the phenyl ring with those of the mesityl group; see the Supporting Information.

(9) We were aware that lithiation of a 5-iodoisoxazole isomer may well result in ring decomposition. Sakamoto, T.; Kondo, Y.; Uchiyama, D.; Yamanaka, H. *Tetrahedron* **1991**, *47*, 5111. However, given the yield and purity of crude products **4** and **22**, we believe that this implies excellent regioselectivity in the preceeding cycloaddition.

TABLE 2. Finding a Suitable Base for the In Situ Generation of Nitrile Oxide



entry	solvent for base	base	yield (%)	**14**:**15**
1	DME	Et_3N	75	2.2:1
2	DME	$^iPr_2NEt$	63	1:1.3
3	DME	2,6-lutidine	50	1:3.5
4	DME	TBAF	68	6.4:1
5	DME	TBAOAc	42	2.5:1
6	***H_2O***	***Na_2CO_3***	***64***	***> 19:1***

with themselves preferentially in the presence of alkynes (under thermal, noncatalyzed conditions), we suspected that recourse to addition of a base via syringe pump would be required. We therefore used mesityl *N*-oxide to identify optimal conditions for performing this reaction on a stirrer hot plate (i.e., conditions where the employment of a syringe pump would be viable). As shown by the formation of **9** in Scheme 2, this consisted of stirring and heating under reflux for 24 h before isolating the product in 95% yield. Identifying a useful base for the unveiling of the nitrile oxide at low concentrations became the next objective (Table 2).

Subjecting a mixture of *p*-chlorobenzaldehyde-derived chloro-oxime **12** and alkynyliodide **13** to Et_3N (delivered via a syringe pump over the duration of the reaction, entry 1, Table 2) at reflux in DME resulted in formation of the desired product **14** in good yield. However, deiodinated product **15** was also observed in significant quantities, and it proved difficult to separate the two products. Moving to alternative amine bases resulted in a poorer ratio of the iodo/deiodo products (entries 2 and 3, Table 2). In line with our previous findings on the formation of nitrile oxides,[3] TBAF served as a useful base for this reaction, offering good yield and selectivity for the desired product (entry 4, Table 2). Employment of tetrabutylammonium acetate (TBAOAc) led to reduced yield and selectivity (perhaps owing to its poor solubility in DME). Given that the integrity of the C−I bond in the products was fundamental to our original goal, we further sought improvement over the selectivity obtained with TBAF. Delightfully, syringe pump addition of an aqueous solution of sodium carbonate rendered the desired cycloadduct with minimal deiodination and in good yield (entry 6, Table 2). Notably, this result also serves as a testament to the stability of alkynyliodides in the presence of water.

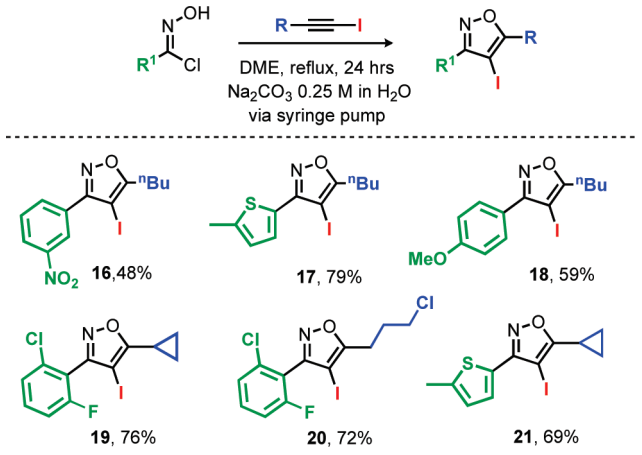
Applying these newly discovered conditions to a variety of hydroximinoyl chlorides and iodinated terminal alkynes provided a range of interesting iodoisoxazole scaffolds (Scheme 3).

Although product yields were variable, a variety of functionality was compatible with this process. Both electron-withdrawing and electron-donating nitrile oxide partners participated in the cycloaddition, as did the 5-methylthiophen-2-carboxaldehyde-derived nitrile oxide. Furthermore, in every combination studied, it was apparent that the reaction was highly regioselective.[10] Lithium−halogen exchange of iodide **17** served to demonstrate that the cycloaddition favored formation of the 4-iodo isomer in these cases also (Scheme 4).[9]

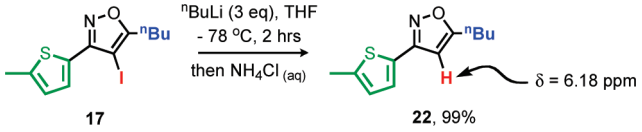
With the halogenated isoxazoles in hand, we looked to demonstrate their functionalization via Suzuki cross-coupling.

(10) The ^{1}H NMR spectra of some of the products contain a < 5% impurity, which could not be separated and characterized but may be a minor regioisomer.

SCHEME 3. Application to a Variety of Substrates



SCHEME 4. Confirming the Regioselectivity



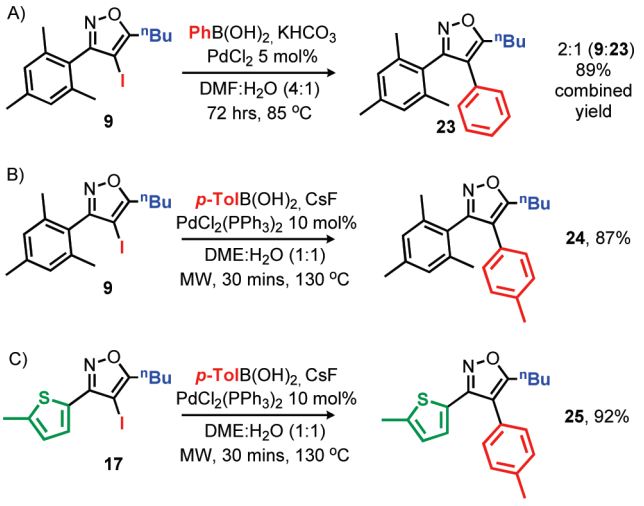
Several methods have been reported for the cross-coupling of 4-haloisoxazoles.[5l,11] We initially attempted to couple the sterically encumbered system **9** by employing the conditions reported by Larock et al. However, in the event, and after a significantly prolonged reaction time, a 2:1 ratio of starting material/product was observed (Scheme 5A). Moving to more forcing conditions,[12] we were able to secure the coupled product **24** in 87% yield (Scheme 5B). Lastly, the biheteroaryl substrate **17** was also demonstrated to competently participate in Suzuki cross-coupling, leading to the highly substituted isoxazole **25** in an excellent 92% yield (Scheme 5C).

In conclusion, we have established a thermally promoted cycloaddition reaction of alkynyliodides with nitrile oxides which proceeds in a highly regioselective manner.[13] The process offers excellent scope with respect to both the dipole and dipolarophile components, allowing for the incorporation of a variety of interesting pendant motifs. The exploration of other diene/dipole substrates for cycloaddition with alkynyliodides is currently under investigation.

Experimental Section

General Procedure for the Cycloaddition of Stable Nitrile Oxides. Synthesis of 4-Iodo-5-phenyl-3-(2,4,6-trimethylphenyl)-isoxazole (3). Mesityl *N*-oxide (72 mg, 0.45 mmol, 1 equiv) (**1**) and iodoethynylbenzene (205 mg, 0.9 mmol, 2 equiv) were added to a microwave vessel followed by dissolution in dimethoxyethane (DME) (2 mL), addition of a stirrer bar, and capping of the vial. The reaction vessel was then heated at 120 °C for 20 min in a microwave reactor with constant stirring. After completion, the reaction mixture was dry loaded and purified by flash column chromatography using a gradient starting with petroleum ether and ending with 4% ethyl acetate in petroleum ether. Product **3** was isolated as a pale yellow solid (144 mg, 0.37 mmol, 83% yield): mp 127−129 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.24−8.2 (2H, m), 7.58−7.55 (3H, m), 7.03 (2H, s), 2.40 (3H, s), 2.17 (6H, s); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 167.9, 166.8, 139.5, 137.5, 130.7, 128.8, 128.4, 128.3, 126.7, 125.4, 58.9, 21.3, 19.9; FTIR (CH_2Cl_2) 2920 (m), 1613 (s), 1562 (s), 1488 (s), 1446 (s), 1364 (s), 1180 (w), 1094 (m), 1030 (s) cm^{-1}; HRMS (ES) *m*/*z* [MH]$^+$ calcd for $C_{18}H_{17}NOI$ 390.0355, found 390.0355.

SCHEME 5. Suzuki Cross-Coupling of Iodoisoxazoles



General Procedure for the Cycloaddition of In Ditu Generated Nitrile Oxides. Synthesis of 5-Butyl-3-(4-chlorophenyl)-4-iodoisoxazole (14). The chloro-oxime (95 mg, 0.5 mmol, 1 equiv) (**12**), 1-iodohex-1-yne (208 mg, 1.0 mmol, 2 equiv), and dimethoxyethane (DME) (3 mL) were added to a two-necked round-bottom flask, which was then equipped with a suba seal and a condenser. The mixture was heated to 100 °C for 24 h with syringe pump addition of a Na_2CO_3 solution (2.1 mL of a 0.25 M aqueous solution). After 24 h, the reaction was cooled, extracted with DCM, dried with $MgSO_4$, filtered, concentrated onto silica gel, and purified by flash column chromatography using a gradient starting with petroleum ether and ending with 4% ethyl acetate in petroleum ether. Product **14** was isolated as a pale yellow oil (115 mg, 0.32 mmol, 64% yield): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.76 (2H, d, J = 9.0 Hz), 7.48 (2H, d, J = 9.0 Hz), 2.89 (2H, t, J = 7.5 Hz), 1.69−1.83 (2H, m), 1.36−1.52 (2H, m), 0.99 (3H, t, J = 7.0 Hz); ^{13}C NMR (62.82 MHz, $CDCl_3$) δ 175.1, 161.7, 136.2, 129.8, 128.9, 127.3, 57.0, 29.3, 26.9, 22.2, 13.7; FTIR (CH_2Cl_2) 2958 (s), 2931 (s), 2872 (m), 1601 (s), 1565 (s), 1507 (m), 1412 (s), 1378 (s), 1093 (s), 1032 (s) cm^{-1}; HRMS (ES) *m*/*z* [MH]$^+$ calcd for $C_{13}H_{14}NO^{35}ClI$ 361.9809, found 361.9793.

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Supporting Information Available: Full experimental details and characterization data, copies of ^{1}H and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

(11) For some examples of palladium-catalyzed cross-coupling of 4-haloisoxazoles, see: (a) Sahoo, A. K.; Oda, T.; Nakao, Y.; Hiyama, T. *Adv. Synth. Catal.* **2004**, *346*, 1715. (b) Kwok, T. J.; Virgilio, J. A. *Org. Process Res. Dev.* **2005**, *9*, 694. (c) Frølund, B.; Jensen, L. S.; Storustovu, S. I.; Stensbøl, T. B.; Ebert, B.; Kehler, J.; Krogsgaard-Larsen, P.; Liljefors, T. *J. Med. Chem.* **2005**, *50*, 1988. (d) Waldo, J. P.; Mehta, S.; Neuenswander, B.; Lushington, G. H.; Larock, R. C. *J. Comb. Chem.* **2008**, *10*, 658. (e) Organ, M. G.; Çalimsiz, E.; Sayah, M.; Hoi, K. H.; Lough, A. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2383. (f) Sore, H. F.; Boehner, C. M.; MacDonald, S. J. F.; Norton, D.; Fox, D. J.; Spring, D. R. *Org, Biomol. Chem.* **2009**, *7*, 1068. (g) Piller, F. M.; Metzger, A.; Schade, M. A.; Haag, B. A.; Gavryushin, A.; Knochel, P. *Chem.—Eur. J.* **2009**, *15*, 7192.

(12) Browne, D. L.; Taylor, J. B.; Plant, A.; Harrity, J. P. A. *J. Org. Chem.* **2009**, *74*, 396.

(13) We believe that the regioselectivity is determined by steric effects. For a list of appropriate "A-Values", see: *Stereochemistry of Organic Compounds*; Eliel, E. L., Wilen, S. H., Mander, L. N., Eds.; Wiley-Interscience: New York, 1994; pp 696−697.