ORGANIC LETTERS

2001
Vol. 3, No. 26
4185−4187

# Use of Iodoacetylene as a Dipolarphile in the Synthesis of 5-Iodoisoxazole Derivatives†

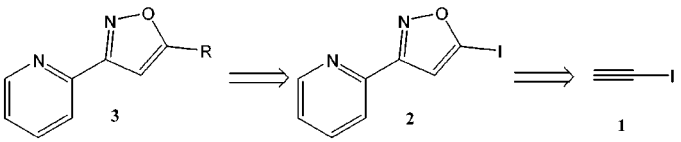
**Yi-Yin Ku,* Tim Grieme, Padam Sharma, Yu-Ming Pu, Prasad Raje, Howard Morton, and Steve King**

*D-45L, Chemical Process Research, Global Pharmaceutical Research and Development, Abbott Laboratories, North Chicago, Illinois 60064-4000*

*yiyin.ku@abbott.com*

**Received September 25, 2001**

## ABSTRACT




**Iodoacetylene 1 was prepared in situ from the reactions of ethynylmagnesium bromide or tributyl(ethynyl)tin with iodine. It was used as a dipolarphile in the [2 + 3] cyclization reaction with 1,3-dipolar nitrile oxide derivatives to produce 2-(5-iodoisoxazol-3-yl)pyridine 2 and 3-(4-fluorophenyl)-5-iodoisoxazole 8 in good yield (70–90%). Subsequently, several 5-substituted isoxazole derivatives 3 were obtained by Pd-catalyzed reactions.**

The haloacetylenes have the potential to be useful synthetic intermediates; however, they have not been utilized due to the fact that chloroacetylene and bromoacetylene are highly unstable and can be explosive.[1] As for iodoacetylene **1**, its physical chemistry has been extensively studied,[2] yet its synthetic utility has not been reported. Undoubtedly there is concern regarding its stability. On the other hand, preparation of iodoacetylene **1** has been a long-standing problem. The reported procedure of bubbling acetylene through a solution of iodine in liquid ammonia produced iodoacetylene in 1% yield.[3] In another procedure reacting acetylene with potassium hydroxide followed by $KI_3$ produced iodoacetylene in 3.9% yield.[4] Clearly iodoacetylene's synthetic utility would be enhanced if its synthesis were not as difficult. We would like to demonstrate here an efficient synthesis and an application of iodoacetylene **1** as a dipolarphile in the [2 + 3] cyclization reaction with nitrile oxides to produce 5-iodoisoxazoles.

The interesting biological properties[5] of isoxazoles[6] have promoted a great deal of research effort toward development of new synthetic methodologies for the preparation of

† This Letter is dedicated to Emeritus Professor Y. H. Ku of the University of Pennsylvania on the occasion of his 100th birthday.

(1) Tanaka, R.; Miller, S. I. *J. Org. Chem.* **1971**, *36*, 3856.

(2) (a) Ahonen, A.-M.; Ahonen, T.; Alanko, S. *J. Mol. Spectrosc.* **1998**, *191*, 117. (b) Kerstel, E. R. T.; Lehmann, K. K.; Mentel, T. F. l.; Scoles, G.; Timmermans, J. H. *J. Mol. Spectrosc.* **1993**, *162*, 342. (c) Abrash, S. A.; Pimentel, G. C. *J. Phys. Chem.* **1989**, *93*, 5828. (d) Andresen, U.; Heineking, N.; Dreizler, H. *J. Mol. Spectrosc.* **1989**, *137*, 296.

(3) Kloster-Jensen, E. *Tetrahedron Lett.* **1969**, *60*, 5323.

(4) Schafer, E.; Christiansen, J. *J. Mol. Struct.* **1983**, *97*, 101.

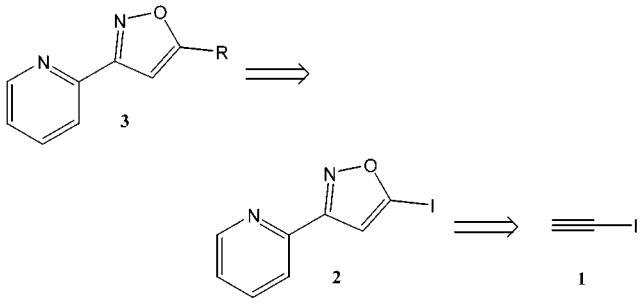
(5) (a) Ryng, S.; Glowiak, T. *J. Chem. Crystallogr.* **1998**, *28*, 373−8. (b) Nicolaides, D. N.; Fylaktakidou, K. C.; Litinas, K. E. *J. Heterocycl. Chem.* **1996**, *33*, 967−71. (c) Nkusi, G.; Neidlein, R. *J. Prakt. Chem.* **1992**, 278−80. (d) Bartlett, R. R. *Int. J. Immunopharmacol.* **1986**, *8*, 199−204. (e) *Textbook of Medicinal and Pharmaceutical Chemistry*; Pitman: London, 1966. (f) Khalil, M. A.; Mapaonya, M. F.; Ko, D.-H.; You, Z.; Oriaku, E. T.; Lee, H. *J. Med. Chem. Res.* **1996**, *6*, 52−60. (g) Basu, U. P.; Dhar, S. P. *J. Indian Chem. Soc.* **1946**, *23*, 189. (h) Takasaki, K.; Kaneko, M.; Fujii, T.; Kobayashi, H. *Nippon Yakurigaku Zasshi* **1973**, *69*, 977. (i) Honna, R.; Ogawa, K.; Tanaka, M.; Yamada, S.; Toratani, K.; Hashimoto, S. Jpn. Kokai Tokkyo Koho JP 79 14,968. (j) *Chem. Abstr.* **1980**, *92*, 41920. (k) Honna, R.; Ogawa, K.; Miyoshi, O.; Hashimoto, S.; Suzue, T. Jpn. Kokai Tokkyo Koho JP 79 09,278 (l) *Chem. Abstr.* **1979**, *91*, 20483. (m) Heubach, G.; Hoerlein, G.; Sachse, B. Ger. Offen. Patent 2,225,023. (n) *Chem. Abstr.* **1977**, *86*, 106569. (o) Kaemmerer, F. J.; Schleyerbach, R. Ger. Offen. Patents 2,854,438 and 2,854,439 (p) *Chem. Abstr.* **1980**, *93*, 239392 and 239393. (q) Diana, G. D.; Rudewicz, P.; Pevear, D. C.; Nitz, T. J.; Aldous, S. C.; Aldous, D. J.; Robinson, D. T.; Draper, T.; Dutko, F. J.; Aldi, C.; Gendron, G.; Oglesby, R. C.; Volkots, D. L.; Reuman, M.; Bailey, T. R.; Czerniak, R.; Block, T. *J. Med. Chem.* **1995**, *38*, 1355.

(6) Grünanger, P.; Vita-Finzi, P. *Isoxazoles. In The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Ed.; John Wiley & Sons: New York, 1991; Vol. 49.

10.1021/ol0168162 CCC: $20.00 © 2001 American Chemical Society
**Published on Web 12/01/2001**

isoxazoles and their derivatives.[7] In connection with our studies on the synthesis of pyridyl isoxazole derivatives **3**, it was envisioned that the 3-pyridyl 5-substituted isoxazole derivatives **3** would arise from the Pd-catalyzed coupling reactions of 2-(5-iodoisoxazol-3-yl)pyridine **2** with various organometallic substances to generate structurally diverse 5-substituted isoxazoles (Scheme 1).

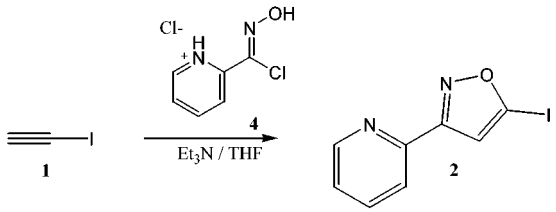
**Scheme 1**



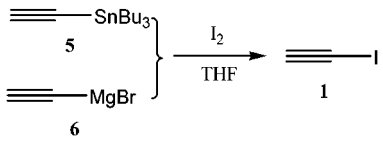

Generally, isoxazoles are constructed by [2 + 3] cycloaddition of a nitrile oxide to an alkyne,[8] with the 1,3-dipolar intermediate generated in situ from the corresponding hydroximoyl chloride[9] or primary nitro compound.[10] There are only a few reports for the preparation of 5-haloisoxazoles.[7,11] 5-Bromo- and 5-chloroisoxazole derivatives were synthesized by the reactions of halogenated cyclopropanes with nitrosyl cation.[7d] 5-Chloroisoxazoles were prepared by the cycloaddition of nitrile oxides to 1,1-dichloroethylene,[11a] and iodoisoxazole was prepared by iodination of the corresponding 5-(tributylstannyl)isoxazole.[11b]

We would like to report here a direct approach to 5-iodoisoxazole derivatives. The synthesis of **2** involves the [2 + 3] cycloaddition of 2-pyridyl nitrile oxide generated in situ from the corresponding 2-pyridyl oxime chloride **4** with iodoacetylene **1** as a dipolarphile (Scheme 2). The iodoacetylene **1** was prepared efficiently by reacting iodine with tributyl(ethynyl)tin **5** in THF (Scheme 3). Its formation was confirmed by GC-MS and NMR analysis.

**Scheme 2**




**Scheme 3**




Regarding the stability of iodoacetylene **1**, thermal stability studies were conducted using a differential scanning calorimeter (DSC) and an accelerating rate calorimeter (ARC). The studies indicated that a 0.5 M solution of iodoacetylene **1** in THF was stable up to 160 °C (DSC). An exotherm started at 160 °C and ended at 188 °C, evolving 57.4 J/g. The exothermic event was not sufficiently large to raise concern, and the THF solution of iodoacetylene **1** was stable under the normal conditions. The THF solution can be used directly in the [2 + 3] cycloaddition reaction with the 1,3-dipolar nitrile oxide to produce the desired 2-(5-iodoisoxazol-3-yl)pyridine **2**[12] in high yield (90%). Notably, the reaction is completely regioselective. The regioisomer, 4-iodoisoxazole, was not detected by HPLC.

Alternatively, iodoacetylene **1** can also be prepared in situ by reacting ethynylmagnesium bromide **6** with iodine in THF (Scheme 3). This procedure produced lower quality iodoacetylene **1**. Subsequently, the 2-(5-iodoisoxazol-3-yl)-pyridine **2** was prepared in lower yield (50%).[13]

By a different procedure, the iodoacetylene **1** generated from reacting iodine with tributyl(ethynyl)tin **5** in THF was further purified by co-distilling with THF at 70 °C under atmospheric pressure. The benefit of using this distilled THF

(7) (a) Lautens, M.; Roy, A. *Org. Lett.* **2000**, *2*, 555. (b) Martins, M. A. P.; Flores, A. F. C.; Bastos, G. P.; Sinhorin, A.; Bonacorso, H. G.; Zanatta, N. *Tetrahedron Lett.* **2000**, *41*, 293. (c) Sammelson, R. E.; Miller, R. B.; Kurth, M. J. *J. Org. Chem.* **2000**, *65*, 2225. (d) Falorni, M.; Giacomelli, G.; Spanu, E. *Tetrahedron Lett.* **1998**, *39*, 9241. (e) Lin, S. T.; Kuo, S. H.; Yang, F. M. *J. Org. Chem.* **1997**, *62*, 5229. (f) Kantorowski, E. J.; Kurth, M. J. *J. Org. Chem.* **1997**, *62*, 6797. (g) Lin, S. T.; Lin, L. H.; Yao, Y. F. *Tetrahedron Lett.* **1992**, 3155. (h) Lin, S. T.; Yang, Y. M. *J. Chem. Res. Synop.* **1996**, 276; *J. Chem. Res. Miniprint* **1996**, 1554.

(8) (a) Kozikowski, A. *P. Acc. Chem. Res.* **1984**, *17*, 410−416. (b) Caramella, P.; Grunanger, P. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984.

(9) Christl, M.; Huisgen, R. *Chem. Ber.* **1973**, *106*, 3345−3367.

(10) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339−5342.

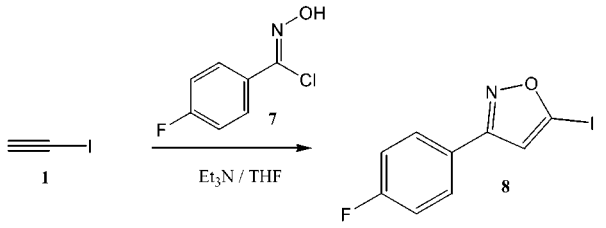
(11) (a) Stevens, R. V.; Albizati, K. F. *Tetrahedron Lett.* **1984**, *25*, 4587 (b) Sakamoto, T.; Kondo, Y.; Uchiyama, D.; Yamanaka, H. *Tetrahedron* **1991**, *47*, 5111.

(12) **Typical procedure:** To a cooled (0 °C) solution of tributyl(ethynyl)-tin **5** (11.6 mL, 40 mmol) in THF (20 mL) was added iodine (11.1 g, 43 mmol) portionwise keeping the temperature below 10 °C. The mixture was stirred at 0 °C until the iodine color persist (∼10 min). To the above solution was added the pyridyl oxime chloride **4** (prepared from the reaction of the corresponding oxime with chlorine gas, 962 mg, 5 mmol) followed by dropwise addition of a solution of $Et_3N$ (1.6 mL, 11 mmol) in THF (5 mL) over a period of 5 min. The reaction mixture was stirred at 0 °C for 15 min and then allowed to warm to room temperature and stirred until all the chloro-oxime was consumed (∼1 h, monitored by HPLC, HPLC assay yield is 90%). To the reaction mixture were added ethyl acetate and 10% sodium thiosulfate. The organic layer was separated, dried over $Na_2SO_4$, and concentrated to an oil. The product was purified by being passed through a pad of silica gel to obtain 2-(5′-iodoisoxazol-3-yl)pyridine **2** in high purity (99.5% peak area) in 75% isolated yield. The X-ray structure of **2** was obtained: mp 105 °C. Anal. Calcd for $C_8H_5IN_2O$: C, 35.32; H, 1.85; I, 46.65; N, 10.30. Found: C, 35.27; H, 1.92; I, 46.40; N, 10.19. $^1$H NMR ($CDCl_3$) $\delta$ 7.12 (1H, s), 7.37 (1H, m), 7.80 (1H, m), 8.04 (1H, m) and 8.69 (1H, m); $^{13}$CMR ($CDCl_3$) $\delta$ 110.6, 113.6, 121.6, 124.8, 136.9, 147.3, 149.8 and 164.5. DCIMS: *m/z* 273 ($M^+ + 1$), 290 ($M^+ + NH_4$). HRMS: requires 272.9525, found 272.9516.

(13) When ethynylmagnesium bromide **6** was used in the place of tributyl(ethynyl)tin for the preparation of **1**, longer stirring time (∼2 h) and higher temperatures were used after the addition of iodine. Water (∼1 mL) was added to the reaction mixture to destroy any unreacted Grignard reagent before the pyridinyl oxime chloride was added. $K_2CO_3$ was used instead of $Et_3N$.

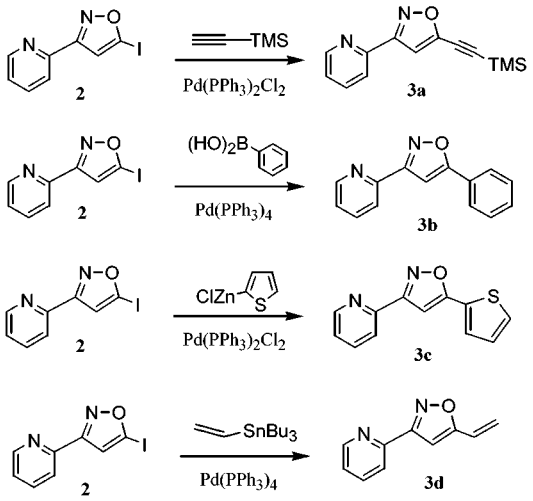
solution of iodoacetylene **1** in the [2 + 3] cyclization reaction was demonstrated for the preparation of 3-(4-fluorophenyl)-5-iodoisoxazole **8** (Scheme 4). Thus, the isolated yield was increased from 40% to 70%.

**Scheme 4**




With 2-(5-iodoisoxazol-3-yl)pyridine **2** in hand, Pd-catalyzed coupling reactions were carried out with a variety organometallic substances (Scheme 5). For example, the

**Scheme 5**




Sonogashira[14] reaction of **2** with TMS-acetylene was carried out in $Et_3N$ at 65 °C with $Pd(PPh_3)_2Cl_2$ as the catalyst to obtain **3a**[15] in 80% yield. Next, the Suzuki reaction[16] was carried out by reacting a toluene solution of **2** with phenylboronic acid in $EtOH/H_2O$ in the presence of $Pd(PPh_3)_4$ and $K_2CO_3$ at 80 °C to produce **3b**[17] in 90% yield. Previously, **3b** had been prepared as one of the two regioisomers from the reaction between 1-(2-pyridyl)-3-phenyl-1,3-propanedione and hydroxylamine hydrochloride.[17] The Negishi coupling reaction[18] of **2** with 2-thiophenylzinc chloride using $Pd(PPh_3)_2Cl_2$ in THF at reflux produced **3c**[17] in 94% yield. Also, the Stille coupling of **2** with tributyl(vinyl)tin was carried out using $Pd(PPh_3)_4$ in toluene at 80 °C to produce **3d**[19] in 93% yield. In principle, various 5-substituted isoxazoles could be prepared by the Pd-catalyzed reactions of 2-(5-iodoisoxazol-3-yl)pyridine **2** with a variety organometallic substances.

In summary, an application using iodoacetylene **1** has been demonstrated. Iodoacetylene **1** was used as a dipolarphile in the [2 + 3] cyclization for a direct approach to 2-(5-iodoisoxazol-3-yl)pyridine **2**. Previously, iodoacetylene **1** had not been utilized as an organic reagent and was prepared in low yield. We have studied the stability of iodoacetylene **1** and found that it is stable in a THF solution under normal conditions. A more efficient procedure for the preparation of iodoacetylene **1** was developed using either ethynylmagnesium bromide **6** or tributyl(ethynyl)tin **5** in a reaction with iodine. Subsequently, 2-(5-iodoisoxazol-3-yl)pyridine **2** was demonstrated to be a versatile intermediate for the preparation of a variety 5-substituted isoxazole derivatives **3**. The Pd-catalyzed coupling reactions provide an easy entry to a series of structurally diverse 5-substituted isoxazoles.

**Acknowledgment.** We would like to thank Rodger Henry for obtaining the X-ray structure for compound **2** and Zhenkun Ma and Ly Phan of the discovery team for their assistance. Finally, we would like to thank Herman Surjono and Zhenglong Xiao of the Hazard's Lab for the DSC and ARC studies.

**Supporting Information Available:** The X-ray structure data for **2**, as well as experimental procedures and characterization data for **3a**, **3b**, **3c**, and **3d**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0168162

(14) (a) Sonogashira, K. *In Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 5. (b) Brandsma, L.; Vasilevsky, S. F.; Verkruijsse, H. D. *Application of Transition Metal Catalysts in Organic Synthesis*; Springer-Verlag: Berlin, 1998; Chapter 10. (c) Rossi, R.; Carpita, A.; Bellina, F. *Org. Prep. Proc. Int.* **1995**, *27*, 127−160. (d) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 3, Chapter 2.4.

(15) $^1H$ NMR and $^{13}C$ NMR and MS date are included in the Supporting Information.

(16) For reviews, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168. (c) Miyaura, N. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI: London, 1998; Vol. 6, pp 187−243. (d) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 2. (e) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263−303.

(17) (a) Batori, S.; Doepp, D.; Messmer, A. *Tetrahedron* **1994**, *50*, 4699. (b) Belgodere, E.; Bossio, R.; Sio, F. D.; Marcaccini, S.; Pepino, R. *Heterocycles* **1983**, *20*, 501.

(18) (a) Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821. (b) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263. (c) Miller, J. A.; Farrell, R. P. *Tetrahedron Lett.* **1998**, *39*, 6441.

(19) (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771.