ORGANIC LETTERS

2013
Vol. 15, No. 11
2672–2675

Metal-Free [2 + 2 + 1] Annulation of Alkynes, Nitriles, and Oxygen Atoms: Iodine(III)-Mediated Synthesis of Highly Substituted Oxazoles

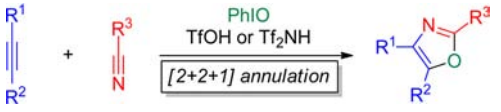
Akio Saito,*,† Akihiro Taniguchi,‡ Yui Kambara,† and Yuji Hanzawa‡

Division of Applied Chemistry, Institute of Engineering, Tokyo University of Agriculture and Technology, 2-24-16 Naka-cho, Koganei, Tokyo 184-8588, Japan, and Laboratory of Organic Reaction Chemistry, Showa Pharmaceutical University, 3-3165 Higashi-tamagawagakuen, Machida-shi, Tokyo 194-8543, Japan

akio-sai@cc.tuat.ac.jp

Received April 9, 2013

ABSTRACT



The metal-free [2 + 2 + 1] annulation of alkynes, nitriles, and O-atoms for the regioselective assembly of 2,4-disubstituted and 2,4,5-trisubstituted oxazole compounds has been achieved by the use of PhIO with TfOH or Tf_2NH. The present reaction could be applied to a facile synthesis of an anti-inflammatory drug.

Since oxazole derivatives have found widespread applications not only as biologically active compounds but also as synthetic intermediates,[1] much effort has been directed toward devising methods for the synthesis of substituted oxazoles.[2] Among them, oxidative [3 + 2] annulations of prefunctionalized ketones or aldehydes with nitriles[3,4] or amines[5] have been well studied as straightforward procedures. These procedures, however, have been constrained by the need to use heavy metal oxidants and/or by the limitation of the substrates. Recently, Zhang et al. reported an elegant assembling procedure for the preparation of 2,5-disubstituted oxazoles, which was achieved by the gold(I)-catalyzed [2 + 2 + 1] annulation of terminal alkynes, nitriles, and quinoline *N*-oxides as the oxygen source (Scheme 1a).[6] In similar approaches, Jiang et al. disclosed that 2,4,5-trisubstituted oxazoles were formed by the oxidative annulation of internal alkynes with nitriles under Cu(II)/O_2 systems.[7,8] To the best of our knowledge, however, there have been no reports about the formation

† Tokyo University of Agriculture and Technology.
‡ Showa Pharmaceutical University.

(1) (a) Turchi, I. J.; Dewar, M. J. S. *Chem. Rev.* **1975**, *75*, 389. (b) Wipf, P. *Chem. Rev.* **1995**, *95*, 2115. (c) Greenblatt, D. J.; Matlis, R.; Scavone, J. M.; Blyden, G. T.; Harmatz, J. S.; Shader, R. I. *Br. J. Clin. Pharmacol.* **1985**, *19*, 373. (d) Palmer, D. C., Ed. *Oxazoles: Synthesis, reactions, and spectroscopy, Part A*; J. Wiley & Sons: Hoboken, NJ, 2003; Vol. 60. (e) Palmer, D. C., Ed. *Oxazoles: Synthesis, reactions, and spectroscopy, Part B*; J. Wiley & Sons: Hoboken, NJ, 2004; Vol. 60.

(2) For recent examples: (a) Liu, X.; Cheng, R.; Zhao, F.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *Org. Lett.* **2012**, *14*, 5480. (b) Zhao, F.; Liu, X.; Qui, R.; Zhang-Negrerie, D.; Huang, J.; Du, Y.; Zhao, K. *J. Org. Chem.* **2011**, *76*, 10338. (c) Davies, P. W.; Cremonesi, A.; Dumitrescu, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8931. (d) Bartoli, G.; Cimarelli, C.; Cipolletti, R.; Diomedi, S.; Giovannini, R.; Mari, M.; Marsili, L.; Marcantoni, E. *Eur. J. Org. Chem.* **2012**, 630.

(3) Heavy metal oxidant-mediated reactions: (a) Lee, J. C.; Hong, T. *Tetrahedron Lett.* **1997**, *38*, 8959. (b) Lee, J. C.; Hong, T. *Tetrahedron Lett.* **1997**, *38*, 8959. (c) Kotani, E.; Kobayashi, S.; Adachi, M.; Tsujioka, T.; Nakamura, K.; Tobinaga, S. *Chem. Pharm. Bull.* **1989**, *37*, 606. (d) Nagayoshi, K.; Sato, T. *Chem. Lett.* **1983**, 1355.

(4) Iodine(III)-mediated reactions: (a) Varma, R. S.; Kumar, D. J. *Heterocycl. Chem.* **1998**, *35*, 1533. (b) Kawano, Y.; Togo, H. *Tetrahedron* **2009**, *65*, 6251. (c) Ishiwata, Y.; Togo, H. *Tetrahedron* **2009**, *65*, 10720. (d) Saito, A.; Hyodo, N.; Hanzawa, Y. *Molecules* **2012**, *17*, 11046.

(5) (a) Wan, C.; Zhang, J.; Wang, S.; Fan, J.; Wang, Z. *Org. Lett.* **2010**, *12*, 2338. (b) Xie, J.; Jiang, H.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2012**, *48*, 979. (c) Xu, Z.; Zhang, C.; Jiao, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 11367. (d) Wan, C.; Gao, L.; Wang, Q.; Zhang, J.; Wang, Z. *Org. Lett.* **2010**, *12*, 3902. (e) Xue, W.-J.; Li, Q.; Zhu, Y.-P.; Wang, J.-G.; Wu, A.-X. *Chem. Commun.* **2012**, *48*, 3485.

(6) He, W.; Li, C.; Zhang, L. *J. Am. Chem. Soc.* **2011**, *133*, 8482.

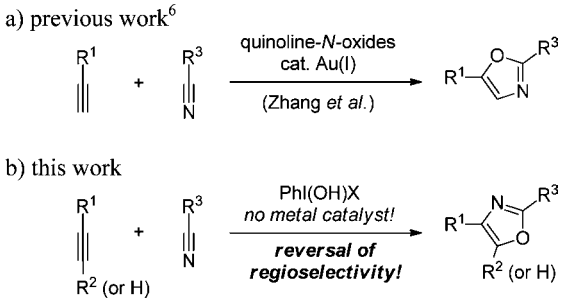
(7) Li, X.; Huang, L.; Chen, H.; Wu, W.; Huang, H.; Jiang, H. *Chem. Sci.* **2012**, *3*, 3463.

(8) Trisubstituted oxazoles have been reported to be formed by the oxidative annulation of internal alkynes and acetontrile using stoichiometric amounts of toxic PhTe(O)OTf. See: Fukumoto, T.; Aso, Y.; Otsubo, T.; Ogura, F. *J. Chem. Soc., Chem. Commun.* **1992**, 1070.

10.1021/ol4009816
Published on Web 05/22/2013

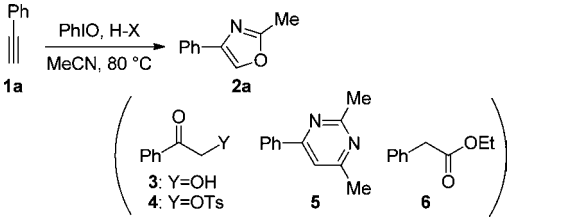
of 2,4-disubstituted oxazoles by oxidative annulation strategies[9] and applicable procedures to both terminal and internal alkynes until very recently. We herein describe the metal-free [2 + 2 + 1] synthesis of 2,4-disubstituted or 2,4,5-trisubstituted oxazoles from terminal or internal alkynes and nitriles with iodine(III) reagents (Scheme 1b).

Scheme 1. Comparison of Zhang's and Our Work for [2 + 2 + 1] Annulations of Alkynes, Nitriles, and O-Atoms



In modern organic chemistry with the increasing importance of greener synthetic processes, hypervalent iodine reagents have gained much attention as eco-friendly oxidants.[10] From this standpoint, we have developed the metal-free synthesis of heterocyclic compounds based on the activation of alkynes by iodine(III) reagents.[11] On the basis of our study for the iodine(III)-mediated heterocycle formation, we envisaged that the metal-free [2 + 2 + 1] annulation would be achieved through Ritter-type addition of nitriles to intermediates formed by alkynes and iodine(III) reagents PhI(OH)X, which is generated *in situ* from iodosobenzene (PhIO) and a Brønsted acid (H−X).[12] At the outset, we focused our initial efforts on the evaluation of oxidants, which were generated *in situ* from PhIO (1.2 equiv) and various Brønsted acids (H−X, 1.2 equiv) at ambient temperature for 30 min, in the reaction of ethynylbenzene (**1a**) and acetonitrile (MeCN) as the solvent (Table 1). The use of *p*-toluenesulfonic acid (TsOH) or triflic acid (TfOH) gave 2,4-disubstituted oxazole **2a** along with ketone **4** or pyrimidine **5** (entry 2 or 3). Since the formation of **5** from **1a** and MeCN is known to be catalyzed by TfOH,[13] the slight increase in the amount of PhIO was examined under similar conditions to those for entry 3. Thus, 1.5 equiv of PhIO with 1.2 equiv of TfOH afforded **2a** in 31% yield without forming **5** (entry 4). Furthermore, the treatment of PhIO with TfOH at 0 °C for a short time is crucial to the improved yield of **2a** (entries 5 and 6), and the yield of **2a** was increased to 80% using 1.8 equiv of PhIO with 1.5 equiv of TfOH (entry 7).[14,15] It should be mentioned that triflic imide (Tf_2NH) or HBF_4 led to the formation of **2a** at ambient temperature, albeit in a reduced yield (entry 8 or 9).

Table 1. Evaluation of Oxidants for the Formation of **2a** from **1a**



entry	PhIO (equiv)	H−X (equiv)	time (h)	yield (%)[a] 2a	other	
1	1.2	CF_3CO_2H (1.2)	20	0	**3**	38
2	1.2	TsOH (1.2)	22	4	**4**	7
3	1.2	TfOH (1.2)	14	7	**5**	25
4	1.5	TfOH (1.2)	8	31		
5[b]	1.5	TfOH (1.2)	8	56		
6[c]	1.5	TfOH (1.2)	8	63		
7[c]	1.8	TfOH (1.5)	8	80		
8[c]	1.8	Tf_2NH (1.5)	20[d]	60		
9[c]	1.8	HBF_4[e] (1.5)	18[d]	54	**6**	26

[a] The yield was determined by ^1H NMR analysis using toluene as the internal standard. Unless otherwise noted, PhIO was treated with H−X in MeCN at rt for 30 min before addition of **1a**. [b] PhIO was treated with H−X in MeCN at 0 °C for 5 min before addition of **1a**. [c] H−X was added to the mixture of PhIO and alkyne in MeCN at 0 °C. [d] Reaction temperature: rt. [e] Et_2O solution.

We next investigated the scope of alkynes and nitriles under the PhIO/acid-mediated conditions **A** (TfOH as acids) or **B** (Tf_2NH as acids) (Table 2). Both conditions could be applied to the [2 + 2 + 1] annulations of not only terminal alkynes **1a**−**c** but also internal alkynes **1d**−**j**, regardless of the kind of nitriles employed (MeCN, propionitrile, succinonitrile, benzonitrile). In addition to **1a**−**c**, **1d** and **1g**−**j** were regioselectively converted to the corresponding 2,4-disubstituted (**2a**−**c**, **7a**, and **9a**) and 2,4,5-trisubstituted oxazoles (**2d**, **2e**−**j**, **7d**, and **9d**) as a single isomer with the illustrated structures. Under conditions **B** as compared to conditions **A**,

(9) Very recently, oxidative [3 + 2] annulations of alkynes and carboxamides were reported for the formation of 2,4-disubstituted oxazoles; see: Luo, Y.; Ji, K.; Li, Y.; Zhang, L. *J. Am. Chem. Soc.* **2012**, *134*, 17412.

(10) Recent reviews: (a) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656. (b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. (c) Dohi, T.; Kita, Y. *Chem. Commun.* **2009**, *45*, 2073. (d) Miyamoto, K.; Ochiai, M. *J. Syn. Org. Chem., Jpn.* **2010**, *68*, 228. (e) Brand, J. P.; González, D. F.; Nicolai, S.; Waser, J. *Chem. Commun.* **2011**, *47*, 102. (f) Satam, V.; Harad, A.; Rajule, R.; Pati, H. *Tetrahedron* **2010**, *66*, 7659. (g) Zhdankin, V. V. *J. Org. Chem.* **2011**, *76*, 1185.

(11) (a) Saito, A.; Matsumoto, A.; Hanzawa, Y. *Tetrahedron Lett.* **2010**, *51*, 2247. (b) Saito, A.; Anzai, T.; Matsumoto, A.; Hanzawa, Y. *Tetrahedron Lett.* **2011**, *52*, 4658.

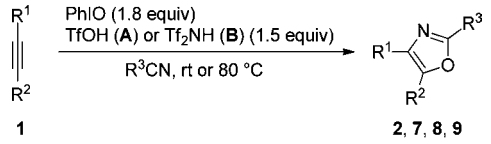
(12) (a) PhI(OH)OTf: Kitamura, T.; Furuki, R.; Taniguchi, H.; Stang, P. J. *Tetrahedron* **1992**, *48*, 7149. (b) PhI(OH)OTs (Koser's reagent): Koser, G. F. *Aldrich. Acta* **2001**, *34*, 89. (c) Koser's-type reagent: Dohi, T.; Ito, M.; Yamaoka, N.; Morimoto, K.; Fujioka, H.; Kita, Y. *Tetrahedron* **2009**, *65*, 10797. (d) PhI(OAc)NMs_2 and PhI(OAc-)NTs_2: Röben, C.; Souto, J. A.; González, Y.; Lishchynskyi, A.; Muñiz, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 9478.

(13) Garcia Martinez, A.; Herrera, A.; Martinez, R.; Teso, E.; Garcia, A.; Osio, J.; Pargada, L.; Unanue, R.; Subramanian, L. R.; Hanack, M. *J. Heterocycl. Chem.* **1988**, *25*, 1237.

(14) The addition of $AcNH_2$ (1.2 equiv) under similar conditions to entry 7 gave a trace amount of **2a**.

(15) The use of 10 equiv of MeCN in 1,2-dichloroethane instead of MeCN solvent reduced the yield of **2a** (9%), even at 80 °C for 14 h under similar conditions mediated by PhIO with TfOH.

Table 2. Formation of Oxazoles from Various Alkynes and Nitriles under the PhIO/Acid-Mediated Conditions **A** or **B**



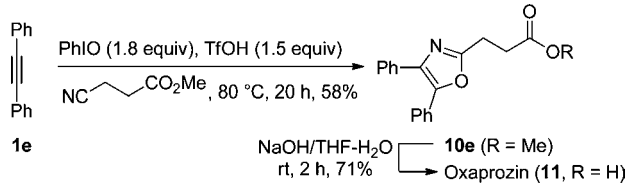
1 2, 7, 8, 9

					yield (%)[a]	
1	R^1	R^2	R^3CN	product	**A**[b]	**B**[b]
1a	Ph	H	MeCN	**2a**	81[c]	60
1b	$(CH_2)_2Ph$	H	MeCN	**2b**	74	80
1c	$(CH_2)_5Me$	H	MeCN	**2c**	48	52
1d	Ph	Me	MeCN	**2d**	82[c]	70
1e	Ph	Ph	MeCN	**2e**	61	73
1f	^{n}Pr	^{n}Pr	MeCN	**2f**	62	64
1g	Ph	COPh	MeCN	**2g**[d]	67	70
1h	Ph	COMe	MeCN	**2h**[d]	54	68
1i	Ph	CO_2Me	MeCN	**2i**[d]	37[e]	37
1j	Ph	Br	MeCN	**2j**	26	42
1a	Ph	H	EtCN	**7a**	74	57
1d	Ph	Me	EtCN	**7d**	77	76
1e	Ph	Ph	$(CH_2CN)_2$	**8e**	57	53
1a	Ph	H	PhCN	**9a**	48	40
1d	Ph	Me	PhCN	**9d**	51	52

[a] Isolated yields. [b] Conditions: (**A**) TfOH as acids, 80 °C; (**B**) Tf_2NH as acids, rt. [c] Reaction time: 8 h. [d] PhIO, 1.5 equiv; acid, 3.0 equiv. [e] Reaction time: 42 h.

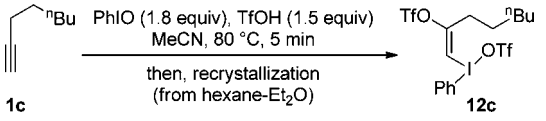
all the attempted reactions proceeded at ambient temperature and in some cases brought about improved product yields (**2e**, **2h**, and **2j**). In cases using other nitriles, except for MeCN, conditions **A** showed similar or superior results to conditions **B**. Conditions **A** provided a facile synthesis of an anti-inflammatory drug, Oxaprodine (**11**),[1c] from commercially available compounds in two steps (Scheme 2). Thus, in the presence of TfOH, **1e** treated with PhIO in methyl 3-cyanopropanoate gave oxazole **10e**, which was converted to **11** by hydrolysis.

Scheme 2. A Facile Synthesis of Anti-Inflammatory Drug **11**

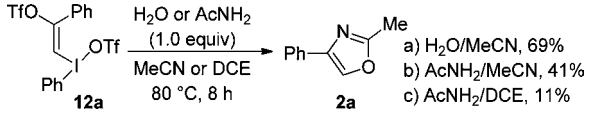


Observations of a precipitate formed during the early stage of the reaction time in many cases in the present reactions encouraged us to confirm the structure of the precipitate obtained from **1c** in MeCN under the PhIO/TfOH-mediated conditions at 80 °C for 5 min. As shown in Scheme 3, after the recrystallization of the precipitate from hexane/Et_2O, the obtained crystal was found to be alkenyliodonium triflate **12c** by single-crystal X-ray structure analysis.[16] Since **12c** has been known to be formed by the treatment of **1c** with PhI(OH)OTf in CH_2Cl_2,[12a] PhI(OH)-OTf and the alkenyliodonium intermediates **12** would be involved in the formation of oxazoles. This is supported by the formation of **2a** from the isolated **12a**. Thus, the treatment of **12a** with H_2O (1.0 equiv) in MeCN at 80 °C for 8 h gave **2a** in 69% yield (Scheme 4a). Since the addition of $AcNH_2$ instead of H_2O in MeCN or DCE also gave **2a**, albeit in reduced yields (Schemes 4b and 4c), $AcNH_2$ might be responsible in part for the formation of **2a** from **12a**.

Scheme 3. Formation of **12c** from **1c**



Scheme 4. Formation of **2a** from **12a**



On the basis of these results and previous reports regarding nucleophilic vinylic substitutions of (*β*-haloalkenyl)-iodonium species,[17] a plausible mechanism for the present oxazole formation is illustrated in Scheme 5. That is, **12** is formed through the iodooxidation of alkyne **1** activated by PhI(OH)OTf and the subsequent ligand exchange in **Int-A**.[18] And then, the nucleophilic vinylic substitution of **12** with R^3CN, which contributes to the Michael-acceptor ability of **12**,[17] leads to **Int-B**. The lower leaving abilities of CF_3COO and TsO groups might bring about the formation of ketone **3** or **4**, which would proceed via the α-iodanyl ketone formed by the hydrolysis or the related reaction of the analog of **Int-A** and/or **12** (CF_3COO or TsO instead of TfO group).[19] Subsequently, **Int-B** reacts with H_2O to generate **Int-C** and/or **Int-D**, which are converted to **Int-E**. The vinylic substitutions of **12** with R^3CONH_2 derived from R^3CN and H_2O might be possible as an alternative route to **Int-D**. Finally, the reductive elimination of **Int-E** gives the target oxazoles. Therefore, the regiochemistry of oxazoles depends on the outcome of the iodooxidation step,

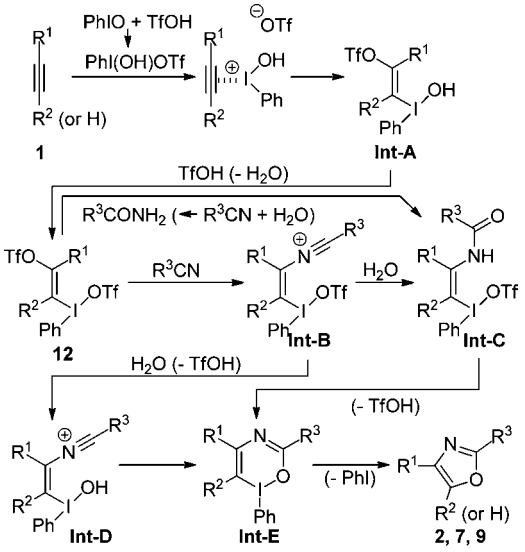
(16) CCDC 924418 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(17) Ochiai, M.; Kitagawa, Y.; Toyonari, M.; Uemura, K.; Oshima, K.; Shiro, M. *J. Org. Chem.* **1997**, *62*, 8001.

(18) Such ligand exchanges of OH at iodine have been known. See: Moriarty, R. M.; Vaid, R. K.; Koser, G. F. *Synlett* **1990**, 365.

(19) The formation of α-iodanyl ketone from (*β*-acetoxyalkenyl) iodonium species, see: Ochiai, M.; Kitagawa, Y.; Yamamoto, S. *J. Am. Chem. Soc.* **1997**, *119*, 11598.

Scheme 5. Proposed Mechanism for the Oxazole Formation



in which the bulky iodonium ion would bind to the less stercially hindered R^2 side of the alkyne carbon in **1a**−**c** (R^1 = Ph, $(CH_2)_2$Ph, or $(CH_2)_5CH_3$, R^2 = H) or **1d** (R^1 = Ph, R^2 = Me).

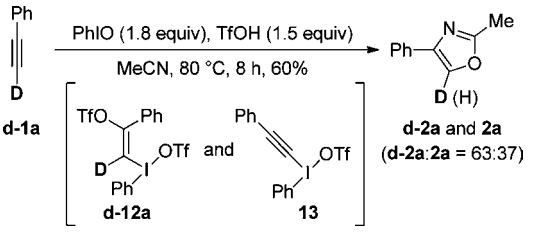
To gain a better understanding of the oxazole formation from the terminal alkynes, we examined the reaction of the deuterated **d-1a** in MeCN under the PhIO/TfOH-mediated conditions (Scheme 6). The reaction at 80 °C for 8 h gave the undeuterated **2a** along with **d-2a** (**d-2a:2a** = 62:38). Since the hydrogen/deuterium exchange of **d-2a** was not observed in the presence of TfOH under similar conditions, the formation of the undeuterated **2a** would be a result of an intervention of the alkynyliodonium intermediate **13**. Actually, **13** was treated with $AcNH_2$ in MeCN at 80 °C for 8 h giving rise to **2a** in 34% yield.[20] Similar observations have been reported in the synthesis of thiazoles from alkynyliodonium salts and thioamides by Wipf's[21] and Ochiai's groups.[22] For the synthesis of thiazoles, Ochiai et al. proposed a reaction mechanism that involves a

(20) The treatment of **13** with H_2O instead of $AcNH_2$ in MeCN under similar conditions did not afford **2a**.

(21) Wipf, P.; Venkatraman, S. *J. Org. Chem.* **1996**, *61*, 8004.

(22) (a) Miyamoto, K.; Nishi, Y.; Ochiai, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6896. (b) Ochiai, M.; Nishi, Y.; Hashimoto, S. *J. Org. Chem.* **2003**, *68*, 7887.

Scheme 6. Formation of **d-2a** and **2a** from **d-1a**



Michael addition of thioamides to alkynyliodonium salts.[22a] Thus, the oxazole formation from the terminal alkynes might take part in the Michael addition of R^3CONH_2 to alkynyliodonium intermediates besides the route via **12**.

In conclusion, we have developed a metal-free, regioselective procedure for [2 + 2 + 1] annulations of alkynes, nitriles, and O-atoms mediated by PhIO with TfOH or Tf_2NH. The present procedure could be applied to both terminal and inner alkynes with various nitriles, thereby leading to 2,4-di- and 2,4,5-trisubstituted oxazoles. Furthermore, a new route for the synthesis of a nonsteroidal anti-inflammatory drug was demonstrated. In light of the isolation of an alkenyliodonium triflate and experimental results, a plausible mechanism for the present oxazole formation was proposed. Particularly, a deuterium labeling experiment suggests that alkynyliodonium intermediates along with alkenyliodonium intermediates would be involved in cases of terminal alkyne substrates. We believe that the present study not only provides an attractive procedure for access to the highly substituted oxazoles but also broadens the reactivity of iodine(III) reagents.

Acknowledgment. This work was supported by a Grant-in-Aid for Young Scientists (B), MEXT Japan (No 24790024). We are grateful to Dr. Hiroyasu Satoh (Rigaku Co., Ltd.) for the support of X-ray structure analysis.

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

The authors declare no competing financial interest.