ORGANIC LETTERS

2008
Vol. 10, No. 21
5039−5042

Metal-Free Oxidative Cyclization of Urea-Tethered Alkenes with Hypervalent Iodine

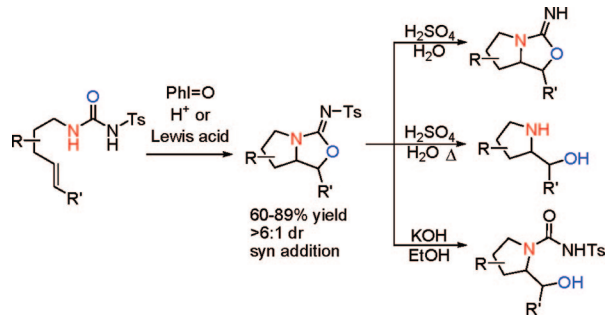
Brian M. Cochran and Forrest E. Michael*

Department of Chemistry, University of Washington, Box 351700, Seattle, Washington 98195-1770

fmichael@chem.washington.edu

Received September 22, 2008

ABSTRACT



A metal-free oxidative cyclization of ureas onto unactivated alkenes using iodosylbenzene and an acid promoter is described. The products isolated are predominantly bicyclic isoureas resulting from an intramolecular oxyamination reaction. The acid type and urea substitution have a strong effect on the product formed. A variety of substrates form the isourea with high diastereoselectivity via syn addition including di- and trisubstituted alkenes. Hydrolysis of the isourea gives access to new diastereomerically pure prolinol derivatives.

Transition-metal-catalyzed oxidative amination reactions of alkenes are powerful methods for the selective formation of new carbon−nitrogen bonds. In many of these transformations, a hypervalent iodine(III) reagent, such as $PhI(OAc)_2$ or PhI=NTs, serves as the oxidant. Common examples of such reactions include aziridinations,[1] oxyaminations,[2] and diaminations.[3] For example, $PhI(OAc)_2$ has been used as an oxidant in Pd-catalyzed intramolecular aminoacetoxylation[2b] and diamination reactions of sulfonamides and ureas.[3]

Given the toxicity and cost issues associated with transition-metal catalysts, the development of metal-free alternatives is of significant interest. In the absence of metal catalysts, hypervalent iodine reagents can be effective in oxidizing a variety of electron-rich functional groups,[4] including sulfides, amines, aromatic and heteroaromatic rings,[5a−d] and alkynes.[5e−g] The direct oxidation of unacti-

(1) (a) Review: Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905–2919. (b) Guthikonda, K.; Wehn, P. M.; Caliando, B. J.; DuBois, J. *Tetrahedron* **2006**, *62*, 11331–11342. (c) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Org. Chem.* **1991**, *56*, 6744–6746.

(2) (a) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 7179–7181. (b) Alexanian, E. J.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 7690–7691. (c) Desai, L. V.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 5737–5740.

(3) (a) Muñiz, K.; Streuff, J.; Hövelmann, C. H.; Núñez, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7125–7127. (b) Steuff, J.; Hövelmann, C. H.; Nieger, M.; Muñiz, K. *J. Am. Chem. Soc.* **2005**, *125*, 14586–14587. (c) Muñiz, K.; Hövelmann, C. H.; Streuff, J. *J. Am. Chem. Soc.* **2008**, *130*, 763–773.

(4) For reviews, see: (a) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523–2584. (b) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123–1178. (c) Kitamura, T.; Fujiwara, Y. *Org. Prep. Proc. Int.* **1997**, *29*, 409–458. (d) Kita, Y.; Takada, T.; Tohma, H. *Pure Appl. Chem.* **1996**, *68*, 627. (e) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893–2903. (f) Varvoglis, A. *Synthesis* **1984**, 709–726. (g) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656–3665.

(5) (a) Lee, K.; Kim, D. Y.; Oh, D. Y. *Tetrahedron Lett.* **1988**, *29*, 667–668. (b) Dohi, T.; Ito, M.; Morimoto, K.; Iwata, M.; Kita, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 1301–1304. (c) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Sugita, K. *J. Am. Chem. Soc.* **2002**, *124*, 2212–2220. (d) Dohi, T.; Morimoto, K.; Kiyono, Y.; Tohma, H.; Kita, Y. *Org. Lett.* **2005**, *7*, 537–540. (e) Kitamura, T.; Furuki, R.; Taniguchi, H.; Stang, P. J. *Tetrahedron* **1992**, *48*, 7149–7156. (f) Kitamura, T.; Furuki, R.; Taniguchi, H.; Stang, P. J. *Tetrahedron Lett.* **1990**, *31*, 703–704. (g) Serna, S.; Tellitu, I.; Domingues, E.; Moreno, I; SanMartin, R. *Org. Lett.* **2005**, *7*, 3073–3076.

10.1021/ol8022165 CCC: $40.75
Published on Web 10/09/2008

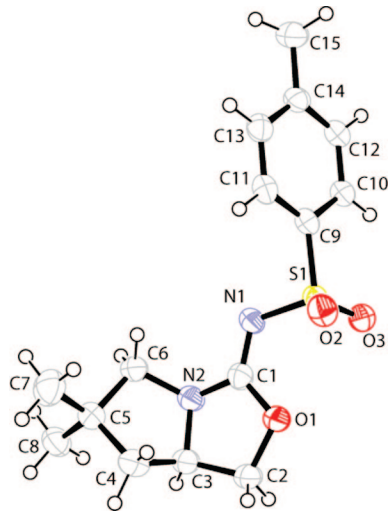
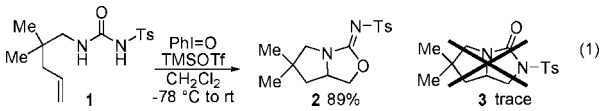


Figure 1. ORTEP of **2** with thermal ellipsoids shown at 50% probability.

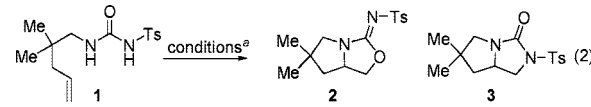
vated alkenes with iodine(III) reagents, however, is generally limited to the vicinal disubstitution of the double bond with 2 equiv of the counterion to form dihalides or bis(sulfonates).[6,7] There have been few reports of unactivated alkenes undergoing oxidative intramolecular cyclizations with these iodine reagents.[8] Herein, we report a *metal-free* oxidative cyclization of unactivated alkenes promoted by simple Brønsted and Lewis acids to directly generate vicinal amino alcohol derivatives from alkenes.[9]

In the above-mentioned diamination report,[3b] oxidative cyclization of urea-tethered alkene **1** to cyclic urea **3** using $PhI(OAc)_2$ required catalytic $Pd(OAc)_2$. In contrast, when substrate **1** was treated with PhI═O and TMSOTf under metal-free conditions (eq 1), complete consumption of the starting material was observed, but only trace amounts of the expected diamination product **3** were formed. The major product proved to be isourea **2**, which was isolated by column chromatography in 89% yield and its identity confirmed spectroscopically and by X-ray crystallography (Figure 1). Commercially available $PhI(OAc)_2$ also facilitated the reaction in the presence of TMSOTf. When the reaction was performed in the absence of acid, only starting material was observed. Toluene, MeCN, and Et_2O were also competent solvents.



A wide variety of Brønsted and Lewis acids were effective at promoting oxidative cyclization (Table 1). The use of

Table 1. Acid-Promoted Oxidative Cyclization



entry	acid	% conversion[b]	ratio **2**:**3**[b]
1	TMSOTf	100	10:1
2	TIPSOTf	100	8:1
3	TfOH	95	>20:1
4	Tf_2O	100	7:1
5	Tf_2NH	100	6:1
6	$HBF_4{\cdot}Et_2O$	100	>20:1
7	$BF_3{\cdot}Et_2O$	100	9:1
8	(*R*)-CSA[c]	100	>20:1
9	*rac*-(BINOL)PO_2H	100	1.5:1
10	$Sc(OTf)_3$	84	1.3:1
11	$Zn(OTf)_2$	80	1.3:1
12	TFA	77	1:1.3
13	BzOH	20	1:>20
14	AcOH	10	1:>20

[a] 1.2 equiv of acid, 1.2 equiv of PhI═O, CH_2Cl_2 (0.1 M), −78 °C to rt, 1 d. [b] Determined by ^1H NMR. [c] Product was racemic by chiral HPLC.

strong acids (entries 1−8) resulted in complete consumption of **1** and predominant or exclusive formation of isourea **2**. (*R*)-Camphorsulfonic acid ((*R*)-CSA) was also competent in generating **2**; however, no enantioselectivity was observed. Weaker acids also promoted oxidative cyclization, albeit more slowly and with a change in chemoselectivity (entries 9−14). Interestingly, a clear trend of reactivity vs chemoselectivity was seen: as the strength of the acid decreased, the reaction favored formation of diamination product **3** at the cost of conversion.

The effects of substitution at the distal urea nitrogen were then examined (Table 2). When the tosyl substituent was replaced with 3-trifluoromethylphenyl (**4**) or hydrogen (**5**), the only products isolated were isoureas **9** and **10**, respectively. Substituting a benzoyl group (**6**) on the urea also led to the formation of isourea **11** as the major product, though the diamination product **12** was isolated in moderate yield. Treatment of alkyl-substituted ureas **7** and **8** under the same conditions, however, generated a new class of products. These were identified as seven-membered ring isoureas **13** and **14**, where 1 equiv of the triflate counterion had been incorporated. From these limited examples, it appears that subtle electronic effects of the urea substituent control the mode of reactivity, namely, electron-withdrawing groups favor the formation of bicyclization products (**2**, **9**−**12**), whereas electron-donating groups promote formation of the monocyclic isourea (**13** and **14**).

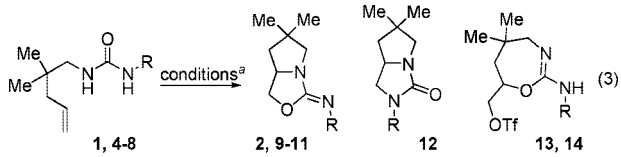
(6) (a) Zefirov, N. S.; Zhdankin, V. V.; Dan'kov, Y. V.; Sorokin, V. D.; Semerikov, V. N.; Koz'min, A. S.; Caple, R.; Berglund, B. A. *Tetrahedron Lett.* **1986**, *27*, 3971–3974. (b) Rieke, R. D.; Li, P. T-J.; Burns, T. P.; Uhm, S. T. *J. Org. Chem.* **1981**, *46*, 4324–4326. (c) Hembre, R. T.; Scott, C. P.; Norton, J. R. *J. Org. Chem.* **1987**, *52*, 3650–3654.

(7) NaN_3 or $TMSN_3$ can be used in with iodine(III) reagents to generate the 1,2-diazide. (a) Moriarty, R. M.; Khosrowshahi, J. S. *Tetrahedron Lett.* **1986**, *27*, 2809–2812. (b) Magnus, P.; Roe, M. B.; Hulme, C. *J. Chem. Soc., Chem. Commun.* **1995**, 263–265.

(8) (a) Kim, H-J.; Schlecht, M. F. *Tetrahedron Lett.* **1987**, *28*, 5229–5232. (b) Serna, S.; Tellitu, I.; Domingues, E.; Moreno, I; SanMartin, R. *Tetrahedron* **2004**, *60*, 6533–6539.

(9) In the course of preparing this manuscript, the following publication using IPy_2BF_4 to oxidatively cyclize tosylurea substrates appeared. Though the isourea products were isolated as byproducts from their reactions, in all cases the imidazolidinone (e.g., **3**) was the major product. Muñiz, K.; Hövelmann, C. H.; Campos-Gómez, E.; Barluenga, J.; González, J. M.; Streuff, J.; Nieger, M. *Chem. Asian J.* **2008**, *3*, 776–788.

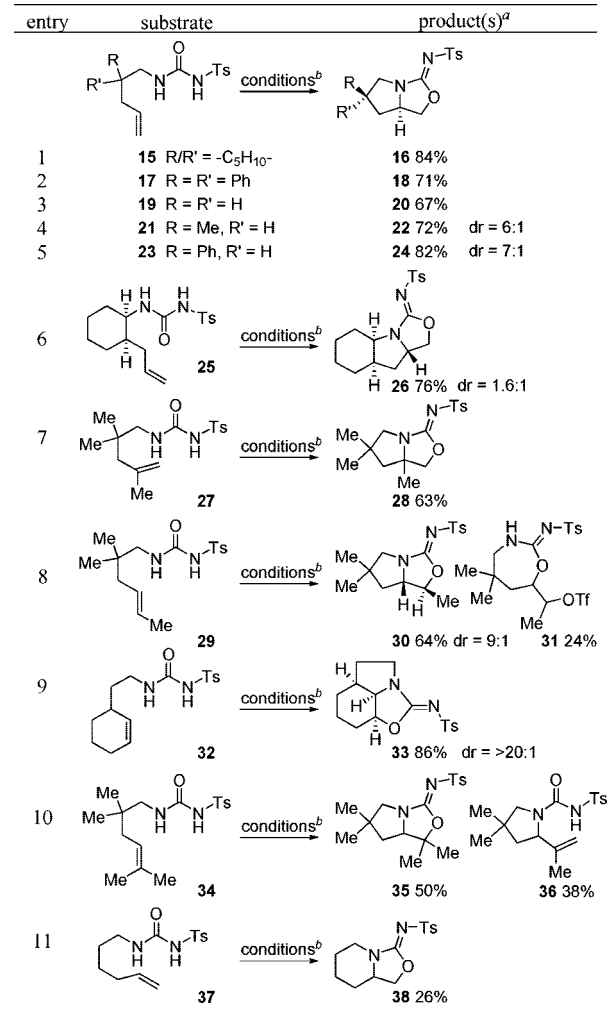
Table 2. Effect of Urea Substitution



R		products (yield, %)[b]		
Ts	**1**	**2** (89)	trace	trace
3-CF_3Ph	**4**	**9** (74)	trace	trace
H[c]	**5**	**10** (78)	trace	trace
Bz	**6**	**11** (61)	**12** (20)	trace
Bn	**7**			**13** (53)
*t*Bu	**8**			**14** (85)

[a] 1.2 equiv of TMSOTf, 1.2 equiv of PhI=O, CH_2Cl_2 (0.1 M), −78 °C to rt. [b] Isolated yields. [c] 1.5 equiv of TMSOTf, 1.5 equiv of PhI=O, CH_2Cl_2 (0.1 M), 0 °C to rt.

Table 3. Oxidative Cyclization of Tosyl-Substituted Ureas



[a] Isolated yields. Diastereoselectivity was determined by ^{1}H NMR. [b] 1.2 equiv of TMSOTf, 1.2 equiv of PhI=O, CH_2Cl_2 (0.1 M), −78 °C to rt.

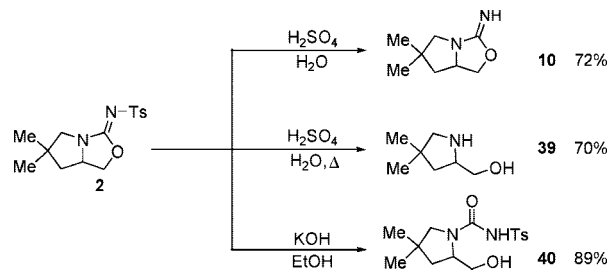
The reactivities of a variety of alkene tethers were examined using the tosyl-substituted urea (Table 3). When the *gem*-dimethyl substituent was replaced with a spirocyclohexyl (**15**) or *gem*-diphenyl group (**17**), or removed completely (**19**), isoureas **16**, **18**, and **20** were isolated in good yields. Substrates containing a single substituent on the backbone also led to the formation of isoureas **22** and **24** in good yields and good diastereoselectivity for the cis product. The cis-1,2-disubstituted cyclohexane **25** also afforded tricyclic isourea **26** in good yield, but modest diastereoselectivity.

More highly substituted alkenes were also reactive under these conditions. The 1,1- and 1,2-disubstituted alkenes **27**, **29**, and **32** were all converted to the expected isoureas (**28**, **30**, **33**) in good yields. The formation of trans product **30** from trans alkene **29** and cis product **33** from cis substrate **32** reveals that the cyclization takes place by selective syn addition of the urea. In the former case, a small amount of 7-membered ring byproduct **31** was also formed as a single diastereomer. Trisubstituted alkene **34** gave the expected isourea **35** as well as allylic oxidation product **36**. The formation of the 6-membered ring isourea **38** was also successful albeit in modest yield.

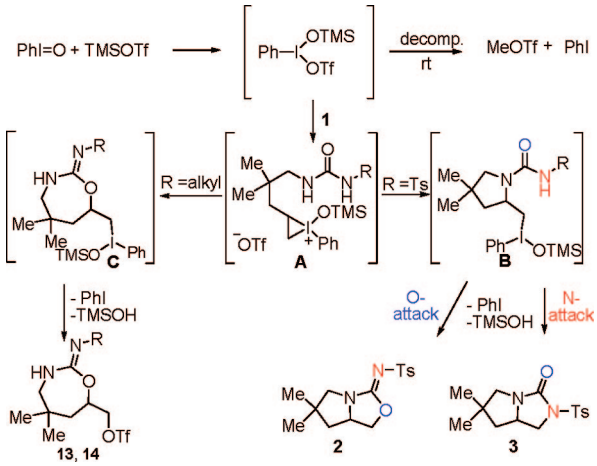
The isourea functionality can be further transformed in several ways (Scheme 1). When isourea **2** was treated with KOH/EtOH at room temperature, partial hydrolysis to the β-hydroxyurea **40** was observed. Conversion to product **40** can also be accomplished from alkene **1** in a one-pot procedure in 86% yield. Complete deprotection of the isourea to give prolinol **39** could be accomplished by heating **2** in H_2SO_4/H_2O. Surprisingly, at room temperature the tosyl group can be selectively removed to give the unsubstituted isourea **10** in 72% yield.

Based on the products isolated from the reaction of the urea-tethered alkenes and some initial NMR studies, a plausible reaction mechanism is depicted in Scheme 2. TMSOTf reacts with PhI=O to give the highly electrophilic PhI(OTf)(OTMS). Support for this complex is based by ^{1}H NMR on newly formed aryl peaks downfield of PhI. In the absence of other reagents, this complex rapidly decomposes to form MeOTf and PhI. However, in the presence of compound **1**, the reagent can coordinate to the alkene to give iodonium ion **A**. This intermediate normally undergoes a 5-exo cyclization through the nitrogen of the urea to give intermediate **B**. The iodine of intermediate **B** is displaced

Scheme 1. Further Transformations of Isourea **2**



Scheme 2. Proposed Reaction Mechanism



intramolecularly by the oxygen of the urea to give oxyamination product **2**, or through the nitrogen to give diamination product **3**, with the former being preferred under strongly acidic conditions due to greater nucleophilicity of the oxygen atom. Alternatively, alkyl ureas seem to prefer 7-exo cyclization to form intermediate **C**. Since further intramolecular attack is impossible, the iodine of intermediate **C** is instead displaced with a triflate anion to give products **13** and **14**. This double-displacement mechanism also explains the selective syn addition observed in compounds **30** and **33**.[6]

In summary, urea-tethered alkenes undergo oxidative cyclization reactions with PhI═O in the absence of metal catalysts to generate a variety of new oxidative amination products. Activation of the iodine reagent with strong acids leads to the oxyamination product while weaker acids favor the diamination product. The substitution pattern of the urea and the alkene influences the product selection in subtle ways. A variety of substrates, including di- and trisubstituted alkenes, can be cyclized in good diastereoslectivity to form isoureas and/or β-amino alcohols.

Acknowledgment. Werner Kaminsky and John Freudenthal (University of Washington) are acknowledged for X-ray crystallography, and the University of Washington and the American Chemical Society Petroleum Research Fund are acknowledged for financial support.

Supporting Information Available: Detailed reaction conditions and experimental data for synthesis of all new starting materials, cyclization products, and details of the X-ray crystal structures of compounds **2** and **40**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL8022165