ORGANIC LETTERS

2008
Vol. 10, No. 24
5585−5588

New Metal-Free One-Pot Synthesis of Substituted Allenes from Enones

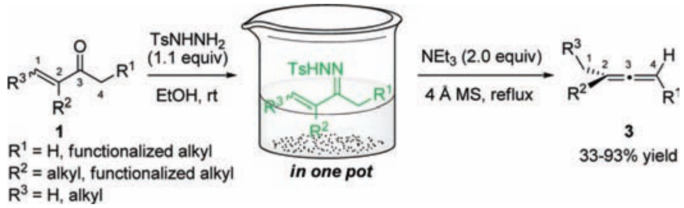
Meng Tang, Chun-An Fan, Fu-Min Zhang, Yong-Qiang Tu,* Wen-Xue Zhang, and Ai-Xia Wang

State Key Laboratory of Applied Organic Chemistry and Department of Chemistry, Lanzhou University, Lanzhou 730000, P. R. China

tuyq@lzu.edu.cn

Received October 23, 2008

ABSTRACT



A new metal-free, one-pot synthesis of substituted allenes from enones was discovered for the first time, in which a tertiary amine as a base was found to be an effective promoter in such novel transformations. The present synthetic protocol proceeded readily with high compatibility of sensitive functional groups, and it provides a new efficient way to access a series of synthetically important allenes without the use of metallic reagents or catalysts.

Allenes are important molecules in modern organic chemistry, and their extraordinary chemical structure is found in many bioactive natural products and pharmaceuticals.[1] The interesting reactivities of allenic structures have been widely explored for selective functional group transformations, and they have proven useful as versatile building blocks in organic synthesis.[2−4] Since the prediction of allenes by Van't Hoff in 1875,[5a] many efforts have been made to develop various synthetic methods for the synthesis of this kind of structurally unique molecule. The first documented synthesis was disclosed by Burton and von Pechmann in 1887.[5b] Throughout the past century, a variety of compounds including functionalized alkynes, alkenes, and carbonyls have been exploited in the synthesis of allenes.[6] Most of the useful synthetic methods have depended upon the use of the main

---

(1) Hoffman-Röder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196.

(2) (a) *Allenes in Organic Synthesis*; Schuster, H. F., Coppola, G. M., Ed.; John Wiley & Sons: New York, 1984. (b) *The Chemistry of Ketenes, Allenes, and Related Compounds Part 1*; Patai, S., Ed.; John Wiley & Sons: New York, 1980. (c) *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Ed.; Wiley-VCH: Weinheim, 2004. (d) Cumulenes and Allenes In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Krause, N., Ed.; Georg Thieme Verlag: Stuttgart, Germany, 2008; Vol. 44.

(3) For reviews, see: (a) Ma, S. *Chem. Rev.* **2005**, *105*, 2829. (b) Brandsma, L.; Nedolya, N. A. *Synthesis* **2004**, 735. (c) Sydnes, L. *Chem. Rev.* **2003**, *103*, 1133. (d) Ma, S. *Acc. Chem. Res.* **2003**, *36*, 701. (e) Tius, M. A. *Acc. Chem. Res.* **2003**, *36*, 284. (f) Wei, L.-L.; Xiong, H.; Hsung, R. P. *Acc. Chem. Res.* **2003**, *36*, 773. (g) Bates, R.; Satcharoen, V. *Chem. Soc. Rev.* **2002**, *31*, 12. (h) Ma, S. Carbopalladation of Allenes. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; John Wiley & Sons: New York, 2002; pp 1491−1521. (i) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535. (j) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067. (k) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3590. (l) Marshall, J. *Chem. Rev.* **2000**, *100*, 3163. (m) Wang, K. K. *Chem. Rev.* **1996**, *96*, 207.

(4) (a) Ma, S. Pd-Catalyzed Two- or Three-Component Cyclization of Functionalized Allenes. In *Topics in Organometallic Chemistry*; Tsuji, J., Ed.; Springer-Verlag: Heidelberg, 2005; pp 183−210. (b) Ma, S. *Aldrichimica Acta* **2007**, *40*, 91.

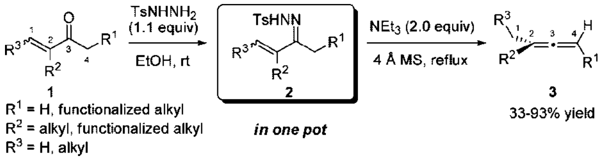
(5) (a) Van't Hoff, J. H. *La Chimie dans l'Espace*; Bazendijk, P. M. (publisher): Rotterdam, 1875. (b) Burton, B. S.; Pechman, H. v. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 145.

(6) For reviews, see: (a) Bruneau, C., Renaud, J.-L. Allenes and Cumulenes. In *Comprehensive Organic Functional Group Transformations II*; Katritzky, A. R., Taylor, R. J. K., Ed.; Elsevier: 2005; Vol. 1, pp 1019−1081. (b) Bruneau, C.; Dixneuf, P. H. Allenes and Cumulenes. In *Comprehensive Organic Functional Group Transformations I*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Elsevier: 1995; Vol. 1, pp 953−995. (c) Brummond, K. M.; DeForrest, J. E. *Synthesis* **2007**, 795. (d) Miesch, M. *Synthesis* **2004**, 746. (e) Krause, N.; Hoffmann-Röder, A. *Tetrahedron* **2004**, *60*, 11671. (f) Hoffmann-Röder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 2933. (g) Rossi, R.; Diversi, P. *Synthesis* **1973**, 25. (h) Taylor, D. R. *Chem. Rev.* **1967**, *67*, 317.

10.1021/ol802445p CCC: $40.75

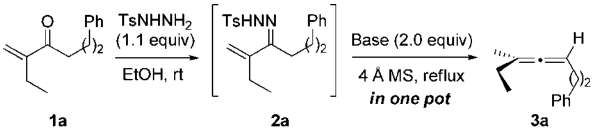
group metal reagents and/or transition metal catalysts.[3c,6e,f] Recently, however, we discovered a new, metal-free, one-pot synthesis of multisubstituted allenes that commence from enones[7] (Scheme 1). To the best of our knowledge, the present method constitutes the first example of an allenic synthesis that exploits in situ generated α,*β*-unsaturated tosylhydrazones[8−11] under mild Lewis basic conditions.[10] Moreover, this metal-free synthetic protocol proceeds readily with regioselective double bond migration and delivers various trisubstituted and 1,1-disubstituted allenes under conditions that are compatible with many functional groups. Herein we will present our preliminary results on this chemistry.

Scheme 1. One-Pot Synthesis of Allenes from Enones



Our initial study was performed with enone **1a** as a model substrate in the presence of $TsNHNH_2$.[12] The typical procedure used was as follows: a solution of **1a** (1.0 equiv) and $TsNHNH_2$ (1.1 equiv) in analytically pure EtOH was stirred at room temperature until **1a** disappeared. Molecular sieves (4 Å) and a base (2.0 equiv) were subsequently added, and the mixture was heated at reflux for the indicated time. During the initial optimization of this novel allenic synthesis (Table 1), it was found that the type of base, as well as the use of 4 Å molecular sieves, played a key role in the current transformation. Of the bases screened, NEt_3 proved to be the most effective for this reaction (83% yield, entry 1). Of special significance was the fact that a lower yield of product (56%) was obtained in the absence of 4 Å molecular sieves (entry 2). Among other tertiary amines examined, Hünig's base (entry 3) and DABCO (entry 4) gave moderate yields of the desired allene **3a**, while only a very low yield (26%) was obtained using pyridine as a base (entry 5). Compared with acyclic tertiary amines (entries 1−3), the use of cyclic DABCO reduced the reaction time to 12 h, but it always led to a much lower yield of product (56%). Further investigations with other bases (entries 6 and 7) revealed that secondary organic amines were far less effective, the expected product **3a** being delivered in around 40% yield. By the way of contrast, employing inorganic Brønsted bases (e.g., NaOH, NaOMe, and Na_2CO_3) led to isolation of a totally different product: 4-ethyl-5-(3-phenylpropyl)-pyrazole (entries 8−10),[9,13] which was consistent with previous reports on the thermal decomposition of α,*β*-unsaturated tosylhydrazone sodium salts.[9]

Table 1. Base-Promoted Allenic Synthesis from Enone **1a**[a]



entry	base	time (h)[b]	yield (%)[c]
1	NEt_3	20	83
2[d]	NEt_3	20	56
3	*i*Pr_2NEt	45	52
4	DABCO	12	56
5	pyridine	70	26
6	$NHEt_2$	20	41
7	$NHiPr_2$	45	37
8	NaOMe	8	0[e]
9	NaOH	12	0[e]
10	Na_2CO_3	20	trace[e]

[a] Typical procedure: a mixture of **1a** (100.0 mg, 0.5 mmol) and $TsNHNH_2$ (102.0 mg, 5.5×10^{-1} mmol) in EtOH (2 mL) was stirred at room temperature until **1a** disappeared, and then EtOH (2 mL), 4 Å molecular sieves (0.5 g), and base (1.0 mmol) were added sequentially. The resulting mixture was heated to reflux for the indicated time. [b] Refluxing time. [c] Isolated yield. [d] Without use of 4 Å MS. [e] For entries 8−10, 4-ethyl-5-(3-phenylpropyl)-pyrazole was isolated in 90, 92, and 67% yield, respectively.[9,13]

Intrigued by the above data, the generality and scope of this reaction were investigated under the optimized conditions. As shown in Table 2, various unsaturated ketones of

---

(7) Enolates prepared from enones through 1,4-addition can be converted into allenes. For reference, see: Brummond, K. M.; Dingess, E. A.; Kent, J. L. *J. Org. Chem.* **1996**, *61*, 6096.

(8) For the reductive rearrangement of α,*β*-unsaturated tosylhydrazones to alkene through 1,3-transposition, see: (a) Qi, W.; Mclntosh, M. C. *Org. Lett.* **2008**, *10*, 357. (b) Silvestri, M. G.; Bednarski, P. J.; Kho, E. *J. Org. Chem.* **1985**, *50*, 2798. (c) Kabalka, G. W.; Summer, S. T. *J. Org. Chem.* **1981**, *46*, 1217. (d) Hutchins, R. O.; Natale, N. R. *J. Org. Chem.* **1978**, *43*, 2299. (e) Kabalka, G. W.; Yang, D. T. C.; Baker, J. D., Jr. *J. Org. Chem.* **1976**, *41*, 574. (f) Hutchins, R. O.; Kacher, M.; Rua, L. *J. Org. Chem.* **1975**, *40*, 923. (g) Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1973**, *95*, 3662. For a review, see: (h) Ripoll, J.-L.; Vallée, Y. *Synthesis* **1993**, 659.

(9) α,*β*-Unsaturated tosylhydrazones have been used in the synthesis of pyrazoles for a long time. For the related references, see: (a) Aggarwal, V. K.; Alonso, E.; Bae, I.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Patel, M.; Porcelloni, M.; Richardson, J.; Stenson, R. A.; Studley, J. R.; Vasse, J.-L.; Winn, C. L. *J. Am. Chem. Soc.* **2003**, *125*, 10926. (b) Doyle, M. P.; Yan, M. *J. Org. Chem.* **2002**, *67*, 602. (c) Sharp, J. T.; Findlay, R. H.; Thorogood, P. B. *J. Chem. Soc., Perkin Trans. 1* **1975**, 102. (d) Closs, G. L.; Böll, W. A. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 399. (e) Closs, G. L.; Closs, L. E.; Böll, W. A. *J. Am. Chem. Soc.* **1963**, *85*, 3796.

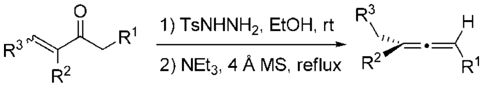
(10) Johnson et al. have reported the formation of allene and other products from α,*β*-unsaturated tosylhydrazone via radical carbene intermediate. For references, see: (a) Klett, M. W.; Johnson, R. P. *J. Am. Chem. Soc.* **1985**, *107*, 3963. (b) Stierman, T. J.; Johnson, R. P. *J. Am. Chem. Soc.* **1985**, *107*, 3971. (c) Price, J. D.; Johnson, R. P. *J. Am. Chem. Soc.* **1985**, *107*, 2187. (d) Stierman, T. J.; Johnson, R. P. *J. Am. Chem. Soc.* **1983**, *105*, 2492.

(11) For other representative examples on the synthetic application of α,*β*-unsaturated tosylhydrazones, see: (a) Baptistella, L. H. B.; Aleixo, A. M. *Synth. Commun.* **2002**, *32*, 2937. (b) Sato, T.; Homma, I. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1885. (c) Duerr, H. *Chem. Ber.* **1970**, *103*, 369. (d) Dauben, W. G.; Lorber, M. E.; Vitmeyer, N. D.; Shapiro, R. H.; Duncan, J. H.; Tomer, K. *J. Am. Chem. Soc.* **1968**, *90*, 4762.

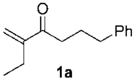
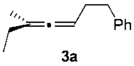
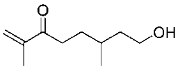
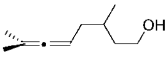
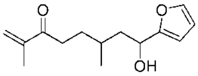
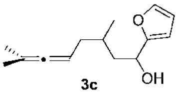
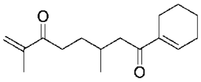
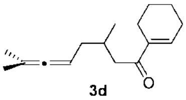
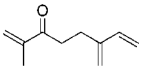
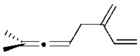
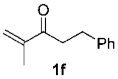
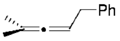
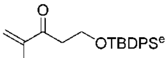
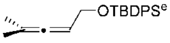
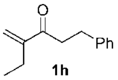
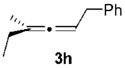
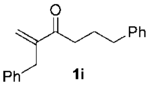
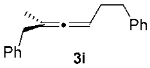
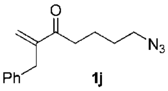
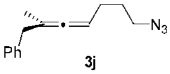
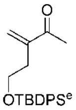
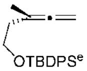
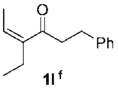
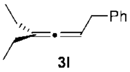
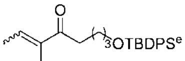
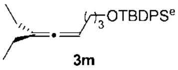
(12) Substituted benzenesulfonyl hydrazine has been used in allene synthesis from propargylic alcohols and their derivatives. For references, see: (a) Movassaghi, M.; Ahmad, O. K. *J. Org. Chem.* **2007**, *72*, 1838. (b) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492. (c) Danheiser, R. L.; Carini, D. J.; Fink, D. M.; Basak, A. *Tetrahedron* **1983**, *39*, 935. (d) Kabalka, G. W.; Newton, R. J., Jr.; Chandler, J. H.; Yang, D. T. C. *J. Chem. Soc., Chem. Commun.* **1978**, 726.

(13) For details on its analytical data, see page 13 in Supporting Information.

Table 2. Synthesis of Allenes from Various Enones[a]



1 **3**

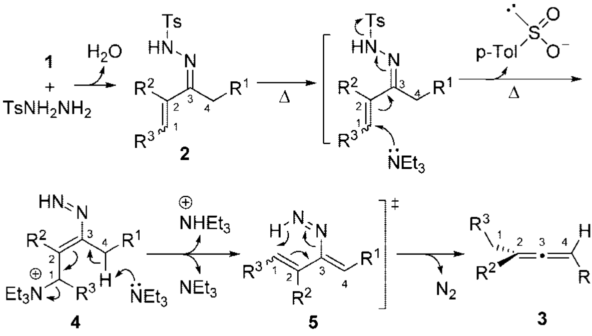
Entry	Substrate **1**	Product **3**	Time(h)[b]	Yield (%)[c]
1	 **1a**	 **3a**	20	83
2	 **1b**	 **3b**	10	93
3	 **1c**	 **3c**	12	75[d]
4	 **1d**	 **3d**	12	85
5	 **1e**	 **3e**	12	85
6	 **1f**	 **3f**	12	86
7	 **1g**	 **3g**	16	86
8	 **1h**	 **3h**	20	80
9	 **1i**	 **3i**	24	75
10	 **1j**	 **3j**	12	64
11	 **1k**	 **3k**	30	67
12	 **1l**[f]	 **3l**	96	34[g]
13	 **1m**[h]	 **3m**	96	33[i]

[a] For experimental procedure, see Supporting Information. [b] Refluxing time. [c] Isolated yield. [d] About 1:1 dr measured by ^{13}C NMR. [e] TBDPS = *t*-butyldiphenylsilyl. [f] *Z*:*E* = > 99:<1. [g] 59% yield was obtained on the basis of the recovered hydrazone. [h] *Z*:*E* = 56:44. [i] 54% yield was obtained on the basis of the recovered hydrazone.

general structure **1** were subjected to this reaction, and a series of trisubstituted and 1,1-disubstituted allenes **3** were obtained in generally good yield. Remarkably, our reaction conditions show good compatibility with different functional groups in this region. Hydroxyls (entries 2 and 3), a bulky enone (entry 4), a conjugated diene (entry 5), silyl groups (entries 7, 11, and 13), and the azide group (entry 10) all remain unaffected. The reaction of **1d** (entry 4) is especially noteworthy since this reaction shows an interesting regioselective hydrazonation of one of two enone moieties, in which the less bulky ketone reacted preferentially with 1.1 equiv of TsNHNH$_2$. Moreover, from the results in Table 2, it can be seen that the substituents R^1 and R^2 in **1** have little influence on this reaction, demonstrating its generality. However, the substituent R^3 could apparently affect the transformation. In comparison with **1h** of entry 8 (R^3 = H), the reaction of **1l** (R^3 = Me, entry 12) proceeded quite slowly, with around 60% conversion after 4 days. With **1m** as substrate (entry 13), a similar result was obtained. It demonstrates that the bulk of substitute R^3 has unfavorable influence on this transformation. Attempts to access 1,3-disubstituted and tetrasubstituted allenes by using enone **1** (R^1 = phenylpropyl, R^2 = H, R^3 = H) and 2-benzyl-4-methyl-1-penten-3-one did not give positive results at this stage, possibly due to the undesired competitive 1,4-addition of TsNHNH$_2$ to enones.[14]

To address this unusual NEt$_3$-promoted allenic synthesis, a plausible reaction pathway has been proposed in Scheme 2 although the detailed mechanism remains unclear at this stage. With in situ formation of the hydrazone **2** from **1** and TsNHNH$_2$,[15] the nucleophilic addition of NEt$_3$ as an organic Lewis base onto α,*β*-unsaturated tosylhydrazone **2** and loss of the *p*-toluenesulfinic acid anion is thought to yield the diazene cationic intermediate **4**.[16] Then, a base-induced 1,4-elimination took place, resulting in the formation of the diazenyl diene intermediate **5**. Under reflux conditions, an intramolecular 1,5-hydrogen reductive rearrangement, with the double bond migration from C1,2 to C2,3, gives the desired allene **3** by the release of N$_2$.[8] From this proposed mechanism, various experimental observations can be un-

Scheme 2. Proposed Pathway in NEt$_3$-Promoted Allenic Synthesis



---

(14) Magnus, P.; Roe, M. B. *Tetrahedron Lett.* **1995**, *36*, 5479.

(15) When the isolated hydrazone **2a** in Table 1 was separately subjected to the reaction system (4 Å molecular sieves, 2.0 equiv of NEt$_3$, EtOH, reflux), the desired allene **3a** could also be obtained in around 80% yield. This fact clearly demonstrates that hydrazone **2** is involved in the current allenic synthesis.

derstood. For example, when using inorganic Brønsted bases (entries 8−10, in Table 1), the deprotonation of the NHTs moiety in **2** of Scheme 2 preferentially took place, giving an α,β-unsaturated tosylhydrazone sodium salt, which quickly underwent elimination−cyclization to furnish the pyrazole.[9] This reactivity was clearly differentiated from the nucleophilicity observed using organic amines as Lewis bases (entries 1−7, in Table 1) toward the unsaturated tosylhydrazones **2** in Scheme 2. Additionally, the unfavorable steric hindrance during the nucleophilic addition of NEt_3 to **2** in Scheme 2 might be one of the reasons for the low conversions and yields, when R^3 was methyl, not hydrogen (entries 12 and 13, Table 2).

In conclusion, a new metal-free, one-pot protocol for the synthesis of various trisubstituted and 1,1-disubstituted allenes from enones has been discovered, and a series of allenes with sensitive functional groups have been synthesized in good yield. Further investigations into the detailed mechanism and toward developing an asymmetric variation are currently underway in our laboratory.

Acknowledgment. We thank the NSFC (Nos. 20621091, 20672048, and 20732002) and the Chang Jiang Scholars Program for financial support.

Supporting Information Available: Experimental procedures, characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802445P

---

(16) Ito, K.; Maruyama, J. *Chem. Pharm. Bull.* **1983**, *31*, 3014.