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Thiophenol-Mediated Hydrogen Atom Abstraction: An Efficient Tin-Free Procedure for the Preparation of Cyclopentane Derivatives

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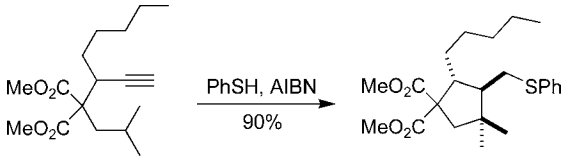
ABSTRACT



An efficient procedure for running a cascade reaction involving 1,5-abstraction of a hydrogen atom followed by a radical cyclization is reported. Alkenyl radicals are generated from easily available terminal alkynes and thiophenol. This procedure eliminates the need of using the toxic tributyltin hydride and gives a greater amount of radical translocation products.

Radical reactions represent a very useful tool for synthetic organic chemistry.[1] Their complementarity to ionic or concerted processes and their ability to be involved in cascade reactions makes them particularly attractive. The use of hydrogen atom abstraction is of particular interest since it has no classical counterpart and allows functionalization of remote unreactive positions.[2] Alkenyl radicals are known to produce five-membered rings via a hydrogen atom transfer followed by a cyclization.[3] This process, thoroughly investigated by Curran,[4] is depicted in Scheme 1. The alkenyl radical is generated from the corresponding bromide **1a′** by reaction with a stannyl radical. After a 1,5-hydrogen atom abstraction, the translocated radical cyclizes via a 5-exo-trig mode and is reduced by tin hydride to afford cyclopentane derivatives **2a′**.

To minimize the amount of uncyclized product **3a′** (direct reduction), tin hydride is generated in situ from a catalytic amount of tributyltin chloride according to the method developed by Stork.[5] Several applications of this reaction have been reported.[6,7] However, the usefulness of this process is hampered by the formation of uncyclized product and by tin contamination of the final products.[8]

Intermolecular addition of radicals to terminal alkynes offers an attractive alternative for the generation of alkenyl

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(3) Heiba, E. I.; Dessau, R. M. *J. Am. Chem. Soc.* **1967**, *89*, 3772.

(4) (a) Curran, D. P.; Kim, D.; Ziegler, C. *Tetrahedron Lett.* **1991**, *47*, 6189. (b) Curran, D. P.; Shen, W. *J. Am. Chem. Soc.* **1993**, *115*, 6051.

(5) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303.

(6) (a) Lathbury, D. C.; Parsons, P. J.; Pinto, I. *J. Chem. Soc., Chem. Commun.* **1988**, 81. (b) Borthwick, A. D.; Caddick, S.; Parsons, P. J. *Tetrahedron* **1992**, *48*, 10655. (c) Brown, C. D. S.; Simpkins, N. S.; Clinch, K. *Tetrahedron Lett.* **1993**, *34*, 131. (d) Bertrand, M. P.; Crich, D.; Nouguier, R.; Samy, R.; Stien, D. *J. Org. Chem.* **1996**, *61*, 3588. (e) Stien, D.; Crich, D.; Bertrand, M. P. *Tetrahedron* **1998**, *54*, 10779. (f) Gimisis, T.; Chatgilialoglu, C. *J. Org. Chem.* **1996**, *61*, 1908. (g) Chatgilialoglu, C.; Gimisis, T.; Spada, G. P. *Chem. Eur. J.* **1999**, *5*, 2866. (h) Robertson, J.; Peplow, M. A.; Pillai, J. *Tetrahedron Lett.* **1996**, *37*, 5825. (i) Kittaka, A.; Tanaka, H.; Yamada, N.; Kato, H.; Miyasaka, T. *Nucleosides Nucleotides* **1997**, *16*, 1423. (j) Kittaka, A.; Asakura, T.; Kuze, T.; Tanaka, H.; Yamada, N.; Nakamura, K. T.; Miyasaka, T. *J. Org. Chem.* **1999**, *64*, 7081.

(7) Renaud, P.; Beaufils, F.; Feray, L.; Schenk, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 4230.

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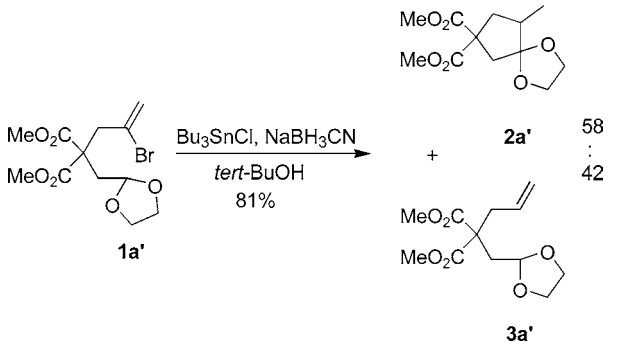
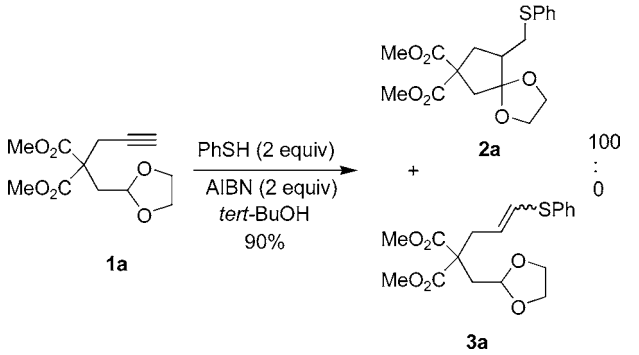
Scheme 1



radicals.[3,9] A few examples of sequential reactions involving intermolecular radical addition to alkyne−hydrogen atom abstraction−cyclization have been reported.[3,9d−i,10] Burke has reported a radical translocation−cyclization process mediated by thiophenol.[11] However, this particular example involves the formation of a highly stable captodative radical, and even with this highly favorable system, the formation of the nontranslocated product could not be avoided.[12] Montevecchi[13] has investigated the mechanistic aspect of the addition of the phenylthiyl radical to terminal alkynes, and Broka[9a] reported that the reaction of oct-1-en-7-yne with thiophenol was not leading to any cyclized products either via a direct 6-exo cyclization process or via a translocation−cyclization reaction. Recently, we reported an isolated example of an efficient H-abstraction−cyclization process using an acetal derived from indanol.[7] We report here that this method is applicable to a wide range of substrates for radical translocation−cyclization cascade processes. Activation of unreactive C−H bonds is described. A detailed investigation of the thiophenol method as well as a comparative study with Curran's tin hydride procedure is reported.

In a first series of experiments, alkenyl radicals were generated by radical addition of thiophenol to terminal alkynes, and their efficiency in undergoing a tandem hydrogen abstraction−cyclization process was examined. For this purpose, the substrate **1a** was investigated (Scheme 2).

Scheme 2



Benzene, the most common solvent for radical reactions, is not the best choice for this cascade process. Indeed, unidentified products resulting from the addition of vinyl radicals to benzene are observed. The best results are obtained in refluxing *tert*-butanol by using syringe pump addition of thiophenol (2 equiv) over 20 h under AIBN initiation. Interestingly, the amount of the initiator plays a crucial role in this process. The use of 2 equiv of AIBN proved to be the best compromise between conversion and the ratio of cyclized/uncyclized products **2a**/**3a** (90% yield, **2a**/**3a** 100:0).

A stoichiometric amount of AIBN is required for the reaction to go to completion, indicating that, under our reaction conditions, the chain process is not very efficient. Dimerization of the thiyl radical leading to diphenyl disulfide could explain this inefficiency.[14] Further investigation of the mechanism is currently underway.

The optimized reaction procedure has been compared with Curran's tin hydride procedure. A first series of experiments with substrates **1a**/**1a′**−**1c**/**1c′** that lead after radical translocation to heteroatom stabilized radicals have been performed according to Scheme 3. The results, summarized in Table 1 (entries 1−3), clearly demonstrate the superiority of the thiophenol over the tin hydride procedure.[15] Indeed, in all three examples, the thiophenol method leads exclusively to the cyclic compounds **2** in good to excellent yields. The formation of reduced compounds **3** was not observed. The tin hydride procedure gives significant amounts of uncyclized product **3′**.

A second series of experiments was run with substrates **1d**/**1d′**−**1f**/**1f′** bearing substituents that stabilize the translocated radicals by conjugation. The results are summarized in entries 4−6 of Table 1. With phenyl (entries 4), cyano

(8) For review articles on tin-free radical reactions, see: (a) Baguley, P. A.; Walton, J. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3072. (b) Studer, A.; Amrein, S. *Synthesis* **2002**, *7*, 835.

(9) (a) Broka, C. A.; Reichert, D. E. C. *Tetrahedron Lett.* **1987**, *28*, 1503. (b) Miyata, O.; Naito, T. *C. R. Acad. Sci. Paris, Chem.* **2001**, *4*, 401. (c) Kyoko, N.; Koichiro, O.; Kiitiro, U. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3465. (d) Bosch, E.; Bachi, M. D. *J. Org. Chem.* **1993**, *58*, 5581. (e) Alcaide, B.; Rodriguez-Campos, I. M. Rodriguez-Lopez, J.; Rodriguez-Vicente, A. *J. Org. Chem.* **1999**, *64*, 5377. (f) Wille, U.; Jargstorff, C. *Eur. J. Org. Chem.* **2003**, 3173. (g) Wille, U. *J. Am. Chem. Soc.* **2002**, *124*, 14. (h) Wille, U. *Tetrahedron Lett.* **2002**, *43*, 1239. (i) Wille, U.; Lietzau, L. *Tetrahedron* **1999**, *55*, 10119. (j) Wille, U.; Lietzau, L. *Tetrahedron* **1999**, *55*, 11465. (k) Wille, U.; Plath, C. *Liebigs Ann.* **1997**, 111.

(10) More examples involving intramolecular radical addition to alkynes have been reported: (a) Gross, A.; Fensterbank, L.; Bogen, S.; Thouvenot, R.; Malacria, M. *Tetrahedron* **1997**, *40*, 13797. (b) Bogen, S.; Fensterbank, L.; Malacria, M. *J. Org. Chem.* **1999**, *64*, 819. (c) Bogen, S.; Fensterbank, L.; Malacria, M. *J. Org. Chem.* **1999**, *64*, 819. (d) Martinez-Grau, A.; Curran, D. P. *Tetrahedron Lett.* **1997**, *53*, 5679. (e) Sannigrahi, M.; Mayhew, D. L.; Clive, D. L. *J. Org. Chem.* **1999**, *64*, 2776. (f) Clive, D. L.; Yang, W.; MacDonald, A. C.; Wang, Z.; Cantin, M. *J. Org. Chem.* **2001**, *66*, 1966. See also ref 6c.

(11) Burke, S. D.; Jung, K. W. *Tetrahedron Lett.* **1994**, *35*, 5837.

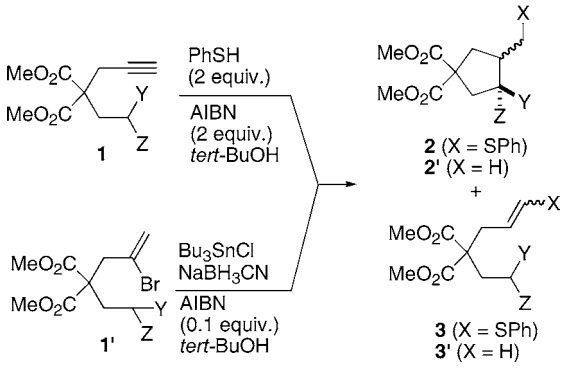
(12) A rate constant for the reduction of alkyl radicals by thiophenol of 1.3×10^8 M^{-1} s^{-1} has been reported: Franz, J. A.; Bushaw, B. A.; Alnajjar, M. S. *J. Am. Chem. Soc.* **1989**, *111*, 268.

(13) (a) Benati, L.; Montevecchi, P. C.; Spagnolo, P. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1659. (b) Capella, L.; Montevecchi, P. C.; Navacchia, M. L. *J. Org. Chem.* **1996**, *61*, 6783.

(14) No reaction takes place between alkynes **1** and PhSSPh with AIBN as an initiator.

(15) We believe that this is a fair comparison of two optimized methods since slow addition of tin hydride using a syringe pump does not give reproducible results with vinyl bromides. Under such conditions, the radical precursors are partially recovered unreacted: Curran, D. P.; Kim, D.; Liu, H. T.; Shen, W. *J. Am. Chem. Soc.* **1988**, *110*, 5900.

Scheme 3



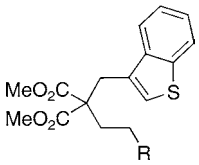
(entries 5), and ester (entries 6) substituents, a clear enhancement of the amount cyclized versus uncyclized products is observed when using the thiophenol-mediated process. For the phenyl and the cyano group, the overall yield is also improved with thiophenol relative to tin hydride. In the case of the ester group, only a moderate yield (57%) of cyclized product is obtained.[16]

Table 1. Thiophenol versus Tin Hydride for the Generation of Radicals via 1,5-Hydrogen Transfer According to Scheme 3

	substrate **1** or **1′**:Y,Z	PhSH **2**/**3** (yield)	Bu_3SnH[a] (**2′**/**3′**) (yield)
1	**a**: OCH_2CH_2O	100:0 (90%)	58:42 (81%)
2	**b**: OTBS, H	100:0 (89%)[b]	88:12 (87%)
3	**c**: PhS, H	100:0 (88%)[c]	
4	**d**: Ph, H	100:0 (85%)[d]	78:22 (76%)
5	**e**: CN, H	100:0 (70%)[e,f]	69:31 (61%)
6	**f**: CO_2Et, H	100:0 (57%)[g]	76:24 (83%)
7	**g**: Me, Me	100:0 (83%)	87:13 (65%)
8	**h**: Et, H	57:17[h,i] (−)	48:52 (73%)[j]
9	**i**: H, H	0:90[k] (54%)	

[a] Taken from ref 4b. [b] Dr 62:38. [c] Dr 69:31. [d] Dr 78:22. [e] *gem*-Diethyl esters were used. [f] Dr 69:31. [g] Dr 76:24. [h] Benzothiophenyl derivative **4a** (26%). [i] Dr not determined. [j] Y = Me, Z = H. [k] Benzothiophenyl derivative **4i** (10%).

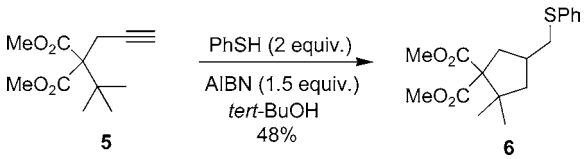
Finally, the generation of simple alkyl radicals bearing no extra stabilizing group was examined with substrates **1g**/**1g′**−**1i**/**1i′** (entries 7−9, Table 1). The generation of a tertiary alkyl radical from **1g**/**1g′** proves again to be more efficient with the thiophenol method than with the tin hydride method (entry 7). However, when attempting to generate secondary alkyl radicals from **1h** (entry 8), some reduced compound **3h** is obtained together with the benzothiophene derivative **4h** resulting from an intramolecular addition of the alkenyl radical to the aryl moiety.[13] The tin hydride method starting from **1h′** was also described to be inefficient for this process. Not surprisingly, very similar results are obtained when attempting to generate a primary alkyl radical from **1i** and **1i′** using both methods (entries 9). The formation of benzothiophene derivatives such as **4i** and **4h** demonstrates that thiophenol does not allow running of a very slow hydrogen atom transfer. The only reaction that takes place, at least partially under tin hydride conditions, is performed with thiophenol.



4h (R = Et)
4i (R = H)

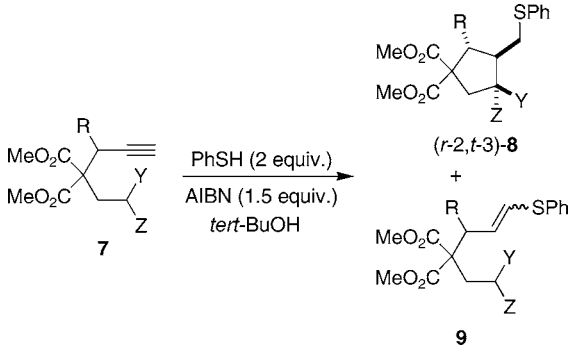
It was, however, possible to generate a nonstabilized primary alkyl radical using the thiophenol method starting from dimethyl 2-*tert*-butyl-2-propargylmalonate **5** (Scheme 4). The cyclized product **6** is isolated as a single product in 48% yield.

Scheme 4



Substrates bearing an alkyl substituent at the propargylic position were investigated next (Scheme 5).[17] Interestingly,

Scheme 5



most of these substrates give very high yields of hydrogen transfer. For instance, the generation of tertiary alkyl radicals from **7a** affords the cyclic compounds **8a** in 90% yield. Secondary alkyl radicals are efficiently generated from **7b** with this system, and the cyclized product **8b** is isolated in 90% yield without formation of the benzothiophene deriva-

(16) Fragmentation of the translocated radical to ethyl acrylate and a malonyl radical cannot be excluded for this system.

(17) For the stereochemistry nomenclature used in this paper, see: Panico, R.; Powell, W. H.; Richer, J.-C. *A Guide to IUPAC Nomenclature of Organic Compounds, Recommendation 1993*; Blackwell: Oxford, 1993.

tive (compare with substrate **1h**, entry 8 in Table 1). It is also worth mentioning that hydrogen atom abstraction starting from **7a** and **7b** is completely regioselective. The regioselectivity is explained by the presence of *gem*-diester substituents (Thorpe−Ingold effect[18]) in the cyclic transition state leading to **8a** and **8b**. Even the product **8c**, resulting from the cyclization of a primary alkyl radical generated from **7c** could be observed. However, in this particular case, the major product is the noncyclized product **9c**. The ester-subtituted substrate **7d** gives the expected translocation−cyclization product **8d** in much better yield than **1f**, the substrate nonsubstituted at the propargylic position (Table 1, entry 6). The four examples of Table 2 demonstrate clearly that a propargylic substituent has a very beneficial effect on the rate of hydrogen transfer. The presence of vicinal substituents (the propargylic substituent and the *gem*-diesters) is at the origin of a rate acceleration similar to the one observed by Jung in related *vic*-disubstituted systems.[19]

Table 2. Effect of the Propargylic Effect on the Thiophenol-Mediated H-Abstraction−Cyclization Process According to Scheme 5

starting material	R	Y	Z	ratio	yield
7a	nC$_5$H$_{11}$	CH$_3$	CH$_3$	100:0	90%[a]
7b	nC$_5$H$_{11}$	nC$_5$H$_{11}$	H	100:0	90%[b]
7c	iC$_3$H$_7$	H	H	20:80	c
7d	iC$_3$H$_7$	CO$_2$Et	H	100:0	97%[d]

[a] (*r*-2,*t*-3)/(*r*-2,*c*-3) 88:12.[16] [b] Mixture (45:45:5:5) of diastereomers; (*r*-2,*t*-3,*c*-4 and *t*-4)/(*r*-2,*c*-3,*c*-4 and *t*-4) 90:10. [c] Yield not determined. [d] (*r*-2,*t*-3,*c*-4/(*r*-2,*t*-3,*t*-4) 85:15.

In summary, we have developed an efficient procedure for running cascade reactions involving 1,5-abstraction of a hydrogen atom followed by a radical cyclization. Such reactions are classically run under tin hydride conditions starting from haloalkenes. In the procedure presented here, alkenyl radicals are generated from easily available terminal alkynes and thiophenol. This procedure eliminates the need of using the toxic tributyltin hydride and gives a greater amount of radical translocation products. Finally, the products bear a phenylthio substituent that offers many opportunities for further transformation. By proper design of *gem*- and *vic*-disubstituents effects, it is possible to generate efficiently nonstabilized radicals via 1,5-hydrogen transfers. We believe that this procedure strongly enhances the synthetic potential of the translocation−cyclization reaction developed by Curran. Application of this procedure for the preparation of natural products containing fused and spirocycles is currently under investigation.

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Supporting Information Available: Experimental procedures and characterizations of compounds **1**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Jung, M. E. *Synlett* **1999**, 843.