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N,N′-Ditosylhydrazine: A Convenient Reagent for Facile Synthesis of Diazoacetates†

Tatsuya Toma, Jun Shimokawa, and Tohru Fukuyama*

Graduate School of Pharmaceutical Sciences, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

fukuyama@mol.f.u-tokyo.ac.jp

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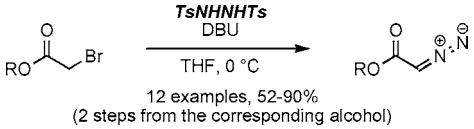
ABSTRACT

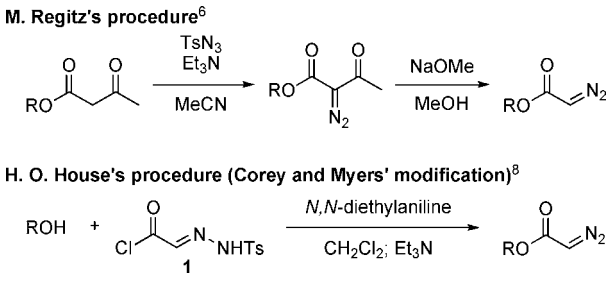


A novel entry to the synthesis of diazoacetates is disclosed. A variety of diazoacetates were synthesized from the corresponding bromoacetates by treatment with *N,N′*-ditosylhydrazine in moderate to high yields. Ease of operation with the stable crystalline reagent as well as a short reaction time offer a useful alternative to the conventional methods.

Diazocarbonyl compounds are useful in organic synthesis because of their unique and powerful reactivities.[1] Over the past several decades, the synthetic utility of diazocarbonyl compounds has been greatly expanded by the advent of such important reactions as cyclopropanations,[2] C−H insertion reactions,[3] Wolff rearrangements,[4] etc.[5] This expansion in use is due mainly to the development of the appropriate metal reagents, which offer improved chemoselectivity and stereoselectivity, and in certain cases, high enantioselectivity. We describe herein a novel synthetic method for the preparation of a variety of diazoacetates from the corresponding bromoacetates by treatment with *N,N′*-ditosylhydrazine and DBU.

To date, diazoacetates have been prepared mainly by diazotransfer reactions with sulfonyl azides under basic conditions (Scheme 1).[6] However, this strategy calls for an appropriate activation of the acetate group such as acetoacetates for lowering the pK_a of the methylene proton.[7] A

Scheme 1



† This paper is dedicated to the memory of Professor Yoshihiko Ito whose untimely death on December 23, 2006, was a great loss to the chemical community in the world.

(1) For reviews, see: (a) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091. (b) Padwa, A.; Austin, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1797. (c) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919. (d) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds from Cyclopropanes to Ylides*; Wiley-Interscience: New York, 1998.

(2) For a review of cyclopropanation, see: Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977.

(3) (a) Kurosawa, W.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 8112. (b) For a recent review of C−H activation using diazo compounds, see: Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861.

(4) (a) Sarpong, R.; Su, J. T.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 13624. (b) For a review, see: Kirmse, W. *Eur. J. Org. Chem.* **2002**, 2193.

(5) (a) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223. (b) Padwa, A. *Chem. Commun.* **1998**, 1417. (c) Padwa, A.; Austin, D. J.; Hornbuckle, S. F.; Price, A. T. *Tetrahedron Lett.* **1992**, *33*, 6427. (d) Padwa, A.; Austin, D. J.; Hornbuckle, S. F. *J. Org. Chem.* **1996**, *61*, 63. (e) Kitagaki, S.; Anada, M.; Kataoka, O.; Matsuno, K.; Umeda, C.; Watanabe, N.; Hashimoto, S.-I.; *J. Am. Chem. Soc.* **1999**, *121*, 1417.

(6) Regitz, M. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 733.

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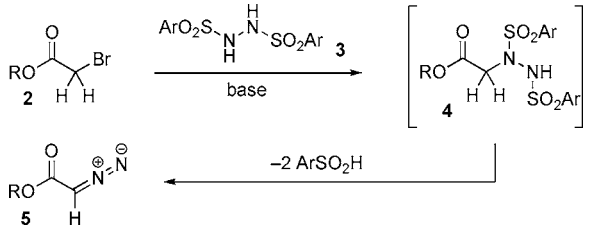
need for removing the activating group under basic conditions after the introduction of the diazo group precludes its application to base-sensitive substrates.

House and co-workers reported an alternative procedure, which employs *p*-toluenesulfonylhydrazone of glyoxylic acid chloride (**1**).[8] While a one-pot conversion of an alcohol to the corresponding diazoacetate can be performed with this procedure, it takes two steps to prepare the reagent from glyoxylic acid. Thus, we initiated efforts to develop a novel method for the synthesis of diazoacetates from the corresponding alcohols.

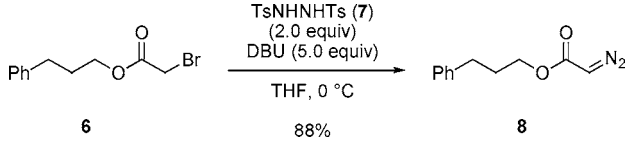
Scheme 2



As illustrated in Scheme 2, in view of the ease of elimination of a sulfonyl group as a sulfinic acid, we envisioned the possibility of employing disulfonylhydrazine **3** as a precursor to the diazo group. Namely, elimination of two molecules of sulfinic acid from **4** would lead to the formation of diazoacetate **5**.

In our initial studies, we employed a *tosyl* group due to the availability of inexpensive *p*-toluenesulfonyl hydrazide and *p*-toluenesulfonyl chloride. Much to our delight, 3-phenylpropyl 2-bromoacetate (**6**) underwent a facile conversion to the corresponding diazoacetate (**8**) upon treatment with *N*,*N*′-ditosylhydrazine (**7**)[9] and DBU at 0 °C (88% yield, Scheme 3).[10]

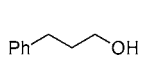
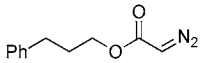
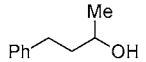
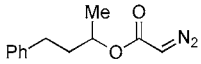
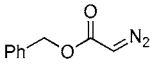
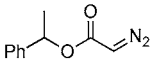
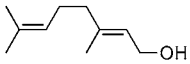
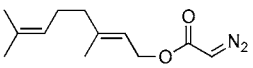
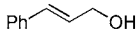
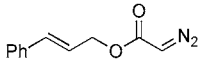
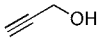
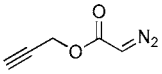
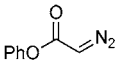
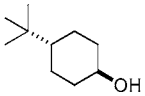
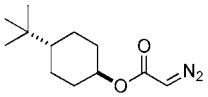
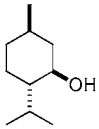
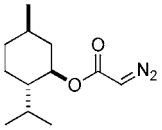
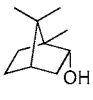
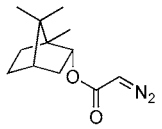
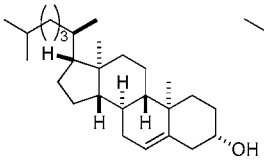
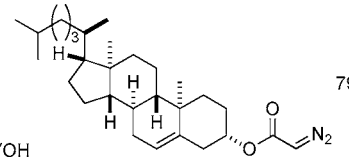
Scheme 3



In an effort to optimize this novel transformation, we next investigated a series of disulfonylhydrazines and bases. After various attempts with other sulfonylhydrazines, *N*,*N*′-ditosylhydrazine proved to be the best reagent with regard to ease of handling, stability, and ease of preparation.[11,12] The use of other bases such as Et_3N, *i*-Pr_2NEt, *N*-methylmorpholine, pyridine, and K_2CO_3 did not give better results.

To examine the scope and limitations of this method, we next investigated the diazoacetylation of a range of alcohols. As shown in Table 1, various diazoacetates were synthesized from the corresponding alcohols via the bromoacetates in moderate to good yields. In the case of menthol, the yield

Table 1. Two-Step Diazoacetylation of Alcohols

entry	bromoacetate precursor	product	yield[a]
1			88
2			71
3			90
4			64
5			62
6			78
7			67[b]
8	PhOH		74
9			77
10			52
11			72
12			79

[a] Yields for the two steps after purification by column chromatography on neutral silica gel. [b] Yield was low due to the volatile nature of the product.

(7) Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V; Pearson M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958. (b) Regitz, M.; Hocker, J; Liedhegener, A. *Organic Synthesis*; Wiley: New York, 1973; Collect. Vol. V, p 179. (c) Doyle, M. P.; Austin, R. E.; Bailey, A. S.; Dwyer, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Kwan, M. M. Y.; Liras, S.; Oalmann, C. J.; Pieters, R. J.; Protopopova, M. N.; Raab, C. E.; Roos, G. H. P.; Zhou, Q.-L.; Martin, S. F. *J. Am. Chem. Soc.* **1995**, *117*, 5763.

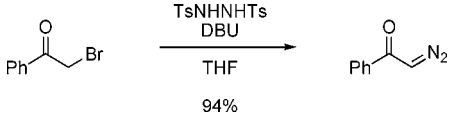
(8) (a) House, H. O.; Blankley, C. J. *J. Org. Chem.* **1968**, *33*, 53. (b) Blankley, C. J.; Sauter, F. J.; House, H. O. *Organic Synthesis*; Wiley: New York, 1973; Collect. Vol. V, p 258. (c) Corey and Myers reported the improved modification of this procedure: Corey, E. J.; Myers, A. G. *Tetrahedron Lett.* **1984**, *25*, 3559.

(9) Jennings, K. F. *J. Chem. Soc.* **1957**, 1172.

of the diazoacetate was lower and formation of more byproducts were observed, presumably due to the steric hindrance exerted by the nearby isopropyl group (entry 10). In addition, this protocol could be successfully applied to the formation of a diazoketone when the α-bromomethyl ketone was used as a substrate (Scheme 4).

In conclusion, we have developed a general method for synthesizing diazoacetates from the corresponding bromoacetates by treatment with *N*,*N*′-ditosylhydrazine and DBU. Because of the ease of handling of the stable crystalline reagent and the ready accessibility of a variety of bromoacetates from the corresponding alcohols, this method is likely to find widespread use in organic synthesis.

Scheme 4



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Supporting Information Available: Experimental details and spectroscopic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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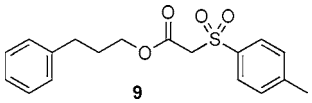
(10) From the TLC analysis of the reaction mixture, we found a small amount of a byproduct (<5%) which was characterized as sulfone **9**, formed by the nucleophilic attack of *p*-toluenesulfinic acid to the bromoacetate.



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(11) Attempts to prepare bis(2-nitrobenzenesulfonyl)hydrazine were unsuccessful due to their decreased stability in the presence of a weak base such as pyridine.

(12) *N*,*N*′-Ditosylhydrazine can be recrystallized easily from MeOH. It is stable at room temperature and melts at 209 °C with decomposition. No appreciable decomposition occurred after storage for 6 months at room temperature.