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A General Procedure for the Esterification of Carboxylic Acids with Diazoalkanes Generated in Situ by the Oxidation of *N*-*tert*-Butyldimethylsilylhydrazones with (Difluoroiodo)benzene

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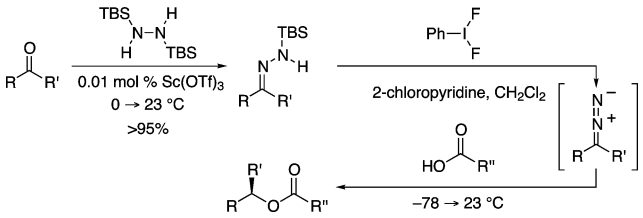
The bimolecular reaction of carboxylic acids with diazoalkanes to form esters is among the mildest and most efficient of organic transformations but is seldom used in synthesis beyond the important case of methyl esterification.[1] This is largely a consequence of the inaccessibility and poor stability of higher diazoalkanes as substrates.[2] In this work we describe a new method for the synthesis of diazoalkanes by the oxidation of *N*-*tert*-butyldimethylsilylhydrazones (TBSHs) with (difluoroiodo)benzene,[3] a reagent heretofore unexplored in the context of hydrazone oxidation. When conducted in the presence of a carboxylic acid substrate, the oxidation leads to efficient esterification in situ (Scheme 1). In addition to greatly extending the range of diazoalkanes that are now available for esterifications, this new protocol offers significant advantages with regard to safety, for diazo intermediates are neither isolated nor achieve appreciable concentrations during the reaction.[4]

Substituted diazoalkanes such as aryldiazomethanes are usually prepared by the thermal decomposition of salts of *N*-tosylhydrazones (Bamford−Stevens reaction),[5] or by the base-induced rearrangement of *N*-alkyl *N*-nitroso-*p*-toluenesulfonamides.[1,6] Many diazoalkanes cannot be synthesized by these methods, however, for they decompose during preparation and/or isolation.[7] These methods can also pose a substantial laboratory safety hazard,[8] particularly when gas-phase manipulations of diazo intermediates are involved, such as in the Bamford−Stevens reaction.[9] Diazo compounds have also been prepared by the oxidation of hydrazones;[2,10] however, aside from stabilized species such as diaryldiazomethanes,[11] few diazoalkanes can be synthesized efficiently in this manner, primarily because both the substrates (hydrazones)[12] and products are unstable under the reaction conditions (both are prone to decompose to form azines).[13] With the development of a method for the highly efficient synthesis of TBSH derivatives and the demonstration that they are more stable than hydrazones yet react efficiently in a parallel series of hydrazone-based transformations (Wolff−Kishner-type reduction, vinyl iodide synthesis, etc.),[12] we sought to extend the utility of TBSHs by developing them as diazo precursors. Toward this end, we surveyed a series of oxidants for their ability to transform benzaldehyde TBSH (1 equiv) and benzoic acid (1 equiv) into benzyl benzoate. In our initial screen, hypervalent iodine reagents afforded promising results, and following a more in depth survey of oxidants of this type, we arrived at conditions for the esterification of a wide variety of carboxylic acids by the oxidation of aldehyde- and ketone-derived TBSHs using (difluoroiodo)benzene (Table 1). In the optimized procedure, 2-chloropyridine (5 equiv) and a carboxylic acid substrate (1 equiv, neat or in solution) were added in sequence to a freshly prepared solution of (difluoroiodo)-benzene (2.3 equiv) in dichloromethane at −78 °C. Addition of a solution of an appropriate TBSH diazo precursor (1.5 equiv) in dichloromethane (∼2 M) initiated the reaction; after stirring at −78 °C for 4 h, the reaction flask was allowed to warm gradually to 23 °C. The ester products were isolated by an aqueous workup procedure followed by flash column chromatography.

Scheme 1



As is evident from the data of Table 1, good yields of esters are obtained by this method using a wide range of different carboxylic acids and diazo precursors. The yields shown are optimized with regard to the amount of the diazo precursor that was used (typically, 1.5 or 3 equiv). The greater excess (3-fold) was sometimes necessary when the diazo compound or the carboxylic acid was sterically hindered, and in the cases of podocarpic acid (entry 11) and cyclohexane hexacarboxylic acid (entry 12), still larger amounts of the diazo precursor were necessary to achieve maximal conversion and yield. These substrates were also poorly soluble in dichloromethane; in both cases, the addition of a cosolvent such as ethyl acetate (entry 11) or triethylamine (entry 12) proved to be beneficial (see also entry 9, gibberellic acid). Moisture did not appear to be an important factor in any of the reactions examined. For example, special precautions to dry the reaction solvents did not improve the yields and, in fact, the inclusion of as much as 5 equiv of water during the benzylation of benzoic acid (entry 10) did not lead to a detectable reduction in the yield of the product. Equally noteworthy is the fact that hydroxyl and phenol groups (entries 9 and 11) of carboxylic acid substrates do not react and thus do not require protection during the esterification.[14] Many other functional groups (nitro, ketone, lactone, alkene, etc.) were also found to be unaffected under the conditions of esterification. The reaction conditions can be considered to be essentially neutral, insofar as a number of acetals and ketals were efficiently transformed (entries 4, 7, 15), as was the exceedingly base-labile substrate (diazo precursor) of entry 5.

To learn more about the details of the esterification reaction, we conducted a variable-temperature ^{1}H NMR experiment, following the transformation of entry 10. Combination of (difluoroiodo)-benzene (1.5 equiv), 2-chloropyridine (3 equiv), benzoic acid (1 equiv), and benzaldehyde TBSH (1 equiv) in CD_2Cl_2 in an NMR tube showed little evidence of reaction below −40 °C; however, above this temperature (warming to −10 °C over 1 h in 10 °C increments) the substrates were smoothly consumed as benzyl benzoate was formed (∼65% yield). Significantly, the concentration of phenyldiazomethane was undetectably low throughout the experiment. In a control experiment, we confirmed that phenyldiazomethane was formed (above −40 °C) in the absence of the

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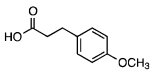
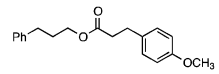
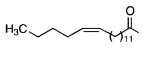
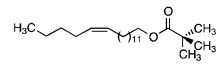
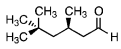
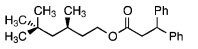
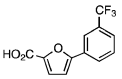
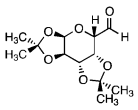
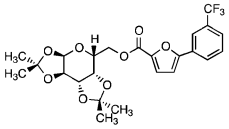
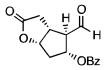
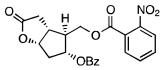
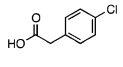
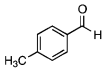
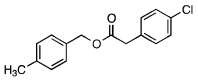
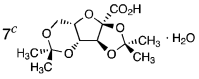
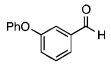
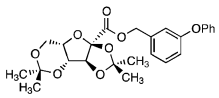
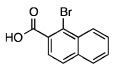
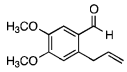
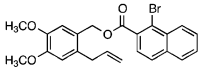
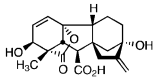
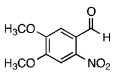
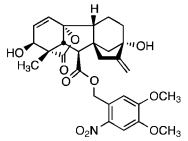
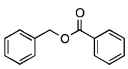
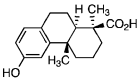
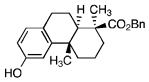
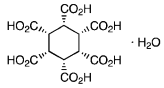
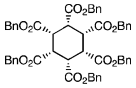
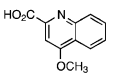
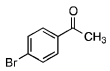
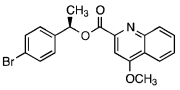
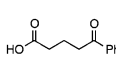
Table 1. Esterification of Carboxylic Acids with Diazoalkanes Generated in Situ by the Oxidation of *N-tert*-Butyldimethylsilylhydrazones (TBSHs) with (Difluoroiodo)benzene[a]

entry	acid	diazo precursor	product	yield (%)[b]
1				86
2				83
3				81
4[c]				92
5[c]				84
6				92
7[c]				89
8				90
9[c,d]				82
10				90
11[e]				82
12[f]				53
13[c]				86
14[c]				85
15[c]				87

[a] Standard conditions for TBSH formation: 1 equiv of carbonyl-containing substrate, 1.05 equiv of 1,2-bis(*tert*-butyldimethylsilyl)hydrazine, 0.01 mol % $Sc(OTf)_3$, neat, 0 → 23 °C (volatile byproducts, including TBSOH, were removed in vacuo prior to esterification). Standard conditions for esterification: 1.5 equiv of TBSH (0.1 M), 1 equiv of carboxylic acid (~0.07 M), 2.3 equiv of $PhIF_2$ (~0.15 M), 5 equiv of 2-chloropyridine (~0.3 M), CH_2Cl_2, −78 → 23 °C. [b] Yield after purification by column chromatography on silica gel. [c] Esterification conducted with 3 equiv of TBSH derivative. [d] Esterification run in 1:1 CH_2Cl_2/EtOAc. [e] Esterification run in 9:1 CH_2Cl_2/EtOAc with 9 equiv of TBSH derivative. [f] Esterification run in 99:1 CH_2Cl_2/Et_3N with 18 equiv of TBSH derivative.

carboxylic acid substrate. In that experiment, the diazo intermediate was transformed into benzaldehyde azine, which was also the primary byproduct in the presence of substrate (~20% yield). This competing reaction (diazo compound ⟹ azine)[13] is believed to form the basis for the requirement that excess diazo precursor be used to achieve high yields in the esterifications. The important conclusion from the spectroscopic studies is that the diazo intermediate is consumed as it is formed and thus poses little or no safety hazard.

In summary, we have developed a general method for the esterification of carboxylic acids with diazoalkanes prepared in situ by the oxidation of TBSH derivatives with (difluoroiodo)benzene. The procedure appears to be widely applicable with regard to both diazo precursors and carboxylic acid substrates. Although there are many options for ester bond formation in synthesis, the reaction of carboxylic acids with diazo intermediates holds a special place in fine chemical synthesis. The example of the transformation of gibberellic acid to form the photochemically labile nitroveratryl ester (entry 9, Table 1) perhaps best illustrates the type of application where the present methodology may be useful.

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Supporting Information Available: Detailed experimental procedures and complete spectroscopic data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Reviews: (a) Pizey, J. S. In *Synthetic Reagents*; Wiley: New York, 1974; Vol. 2, pp 65−142. (b) Black, T. H. *Aldrichimica Acta* **1983**, *16*, 3−10. (c) Sammakia, T. Diazomethane. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons, Ltd.: Chichester, England, 1995; Vol. 4, pp 1512−1519.

(2) Regitz, M.; Maas, G. *Diazo Compounds: Properties and Synthesis*; Academic Press: London, 1986; pp 65−198.

(3) (a) Bockemüller, W. *Chem. Ber.* **1931**, *64*, 522−530. (b) Sawaguchi, M.; Ayuba, S.; Hara, S. *Synthesis* **2002**, 1802−1803.

(4) For examples of the generation and trapping of diazo compounds in situ in other chemical transformations, see: (a) Angle, S. R.; Neitzel, M. L. *J. Org. Chem.* **2000**, *65*, 6458−6461. (b) May, J. A.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 12426−12427. (c) Aggarwal, V. K.; de Vicente, J.; Bonnert, R. V. *J. Org. Chem.* **2003**, *68*, 5381−5383. (d) Aggarwal, V. K.; Fulton, J. R.; Sheldon, C. G.; de Vicente, J. *J. Am. Chem. Soc.* **2003**, *125*, 6034−6035. (e) 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*, 10926−10940. (f) Zhu, S.; Liao, Y.; Zhu, S. *Org. Lett.* **2004**, *6*, 377−380.

(5) (a) Bamford, W. R.; Stevens, T. S. *J. Chem. Soc.* **1952**, 4735−4740. (b) Creary, X. *Org. Synth., Coll. Vol.* **1990**, *7*, 439−443.

(6) De Boer, T. J.; Backer, H. J. *Org. Synth., Coll. Vol.* **1963**, *4*, 250−253.

(7) See: (a) Shapiro, R. H. *Org. React.* **1976**, *23*, 405−507. (b) Grot, C.; Pfiel, E.; Weinrich, E.; Weissel, O. *Justus Liebigs Ann. Chem.* **1964**, *679*, 42−50.

(8) Review: Gutsche, C. D. *Org. React.* **1954**, *8*, 364−429.

(9) For example, see: Sammakia, T. Phenyldiazomethane. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons, Ltd.: Chichester, England, 1995; Vol. 4, pp 3969−3971.

(10) Curtius, T. *Ber. Dtsch. Chem. Ges.* **1889**, *22*, 2161−2165.

(11) (a) Lapatsanis, L.; Milias, G.; Paraskewas, S. *Synthesis* **1985**, 513−515. (b) McLaren, K. L. *J. Org. Chem.* **1995**, *60*, 6082−6084. (c) Curini, M.; Rosati, O.; Pisani, E. *Tetrahedron Lett.* **1997**, *38*, 1239−1240. (d) Bates, R. W.; Fernández-Megía, E.; Ley, S. V.; Rück-Braun, K.; Tilbrook, D. M. G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1917−1925. (e) Zhao, H.; van der Donk, W. A. *Org. Lett.* **2001**, *3*, 593−596. (f) Xu, Z.; Peng, Y.; Ye, T. *Org. Lett.* **2003**, *5*, 2821−2824.

(12) Furrow, M. E.; Myers, A. G. *J. Am. Chem. Soc.* **2004**, *126*, 5436−5445.

(13) Bethell, D.; Whittaker, D. *J. Chem. Soc. B* **1966**, 778−782.

(14) Use of an excess of (difluoroiodo)benzene relative to the TBSH substrate led to diminished yields of product in the case of the phenolic substrate podocarpic acid, which may be an indication of the occurrence of phenolic oxidation under those circumstances.

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