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2-(1,3-Dioxan-2-yl)ethylsulfonyl Group: A New Versatile Protecting and Activating Group for Amine Synthesis

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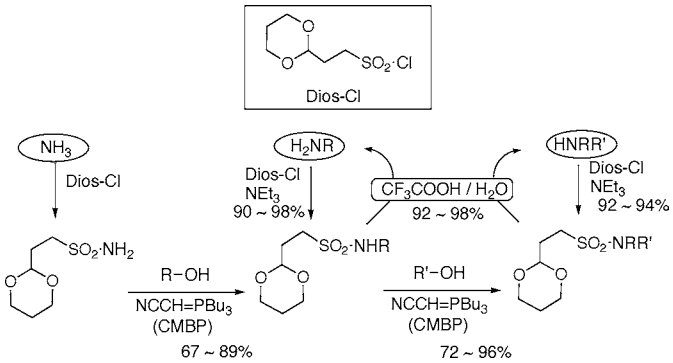
ABSTRACT



2-(1,3-Dioxan-2-yl)ethylsulfonyl (Dios) chloride was synthesized and used as a new versatile sulfonating agent for amines. Primary and secondary amines were sulfonated very easily in excellent yields with Dios chloride. N-Nonsubstituted and N-monosubstituted Dios-amides, activated amines, were alkylated satisfactorily under new Mitsunobu conditions utilizing (cyanomethylene)tributylphosphorane (CMBP). The Dios group is very stable under basic and reductive conditions and is removed by heating in a hot aqueous solution of trifluoroacetic acid.

Because many nitrogen-containing molecules possess a wide variety of interesting biological activities, the synthesis of such compounds has attracted much attention and has been accomplished with the development of efficient synthetic methods.[1] In synthesis, protection and/or activation of the nitrogen atom followed by deprotection procedures are often required to construct not only nitrogen functional groups but also other functional groups and carbon frameworks. Thus, many excellent protecting and/or activating groups have been developed and applied to various stages of organic syntheses.[2] Among them, sulfonamides such as tosylamide (Ts-amide) and β-trimethylsilylethylsulfonamide (SES-amide)[3] occupy an attractive position because of their sufficient stability toward various reagents under harsh conditions and their ease of handling. However, because of harsh cleavage conditions,[4] the traditional sulfonyl groups are often unable to satisfy the requirements for the synthesis of multifunctional

(1) (a) Sandler, R.; Karo, W. *Organic Functional Group Preparations*, 2nd ed.; Academic: New York, 1983; Chapter 13, pp 323−352. (b) Marson, C. M.; Hobson, A. D. *Comprehensive Organic Functional Group Transformations*; Katritzky, A., Meth-Cohn, O., Rees, C. W., Eds.; Pergamon: Oxford, 1995; Vol. 2, pp 297−332.

(2) For selected references, see: (a) Greene, T. W.; Wuts, P. G. *Protective Group in Organic Synthesis*, 3rd ed.; John Wiley and Sons: New York, 1998; pp 494−653. (b) Qian, L.; Sun, Z.; Mertes, M. P.; Mertes, K. B. *J. Org. Chem.* **1991**, *56*, 4904. (c) Vedejs, E.; Lin, S.; Klapars, A.; Wang, J. *J. Am. Chem. Soc.* **1996**, *118*, 9796. (d) Sun, P.; Weinreb, S. M. *J. Org. Chem.* **1997**, *62*, 8604.

(3) Weinreb, S. M.; Demko, D. M.; Lessen, T. A. *Tetrahedron Lett.* **1986**, *27*, 2099.

(4) For selected references about the Ts group, see: (a) Kovacs, J.; Ghatak, U. R. *J. Org. Chem.* **1966**, *31*, 119. (b) Paul, B. J.; Hobbs, E.; Buccino, P.; Hudlicky, T. *Tetrahedron Lett.* **2001**, *42*, 6433. (c) Ji, S.; Gortler, L. B.; Waring, A.; Battisti, A.; Bank, S.; Closson, W. D.; Wriede, P. *J. Am. Chem. Soc.* **1967**, *89*, 5311. (d) Opalka, C. J.; D'Ambra, T. E.; Faccone, J. J.; Bodson, G.; Cossement, E. *Synthesis* **1995**, 766. (e) Gold, E. H.; Babad, E. *J. Org. Chem.* **1972**, *37*, 2208. (f) Vedejs, E.; Lin, S. *J. Org. Chem.* **1994**, *59*, 1602. (g) Hill, D. C.; Flugge, L. A.; Petillo, P. A. *J. Org. Chem.* **1997**, *62*, 4864. (h) Nayak, S. K. *Synthesis* **2000**, 1575.

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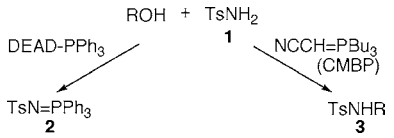
molecules. Thus, the Fukuyama method utilizing the *o*-nitrobenzenesulfonyl (Ns) group has been widely accepted and applied to amine synthesis.[5] Further, the *o*-anisylsulfonyl (Ans) group was recently developed as an alternative activating/protecting group of nitrogen function.[6]

Primary and secondary sulfonamides may be subjected to the Mitsunobu alkylation to synthesize pure primary and secondary amines, respectively.[7] However, the original Mitsunobu reagent (DEAD−PPh_3) mediates the alkylation with low to moderate yields, except the reaction of Ns-amide, because of the so-called "pK_a restriction" of nucleophiles.[8] Furthermore, the use of DEAD−PPh_3 fails in the alkylation of primary sulfonamides such as Ts-amide (**1**, pK_a = 10.2), which reacts with PPh_3 to form triphenylphosphine tosylimide **2** under the reaction conditions (Scheme 1).[9] These

Scheme 1. Reaction of $TsNH_2$ (**1**)

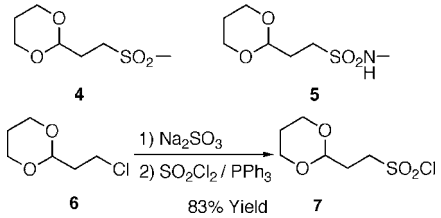


problems were overcome by using new Mitsunobu reagents developed by our group.[10] The reagents satisfactorily mediated the alkylation reaction of various nucleophiles with a pK_a of 11−23, such as *N*-methyltosylamide (pK_a = 11.7),[10a] geranyl phenyl sulfone (pK_a = 22.5 in DMSO),[10b] and others.[10c−e] In addition, the alkylation of tosylamide **1** was found to proceed smoothly with the use of only (cyanomethylene)tributylphosphorane (CMBP),[10a,11] one of the phosphorane types of new Mitsunobu reagents, to give the desired N-monosubstituted sulfonamides **3** in excellent yields (Scheme 1), establishing a new facile synthetic method to primary amines.[10f]

With this background, we decided to develop a new versatile sulfonyl group, which can be deprotected easily under acidic conditions. Thus, 2-(1,3-dioxan-2-yl)ethylsulfonyl (Dios) group **4** was proposed. The pK_a of Dios-amide **5**, an aliphatic sulfonamide, can be estimated to be the same as that of methanesulfonamides (e.g., MsNHMe: pK_a = 11.8).[12] This suggested that the Mitsunobu alkylation of Dios-amides could not be expected to proceed in high yield when using the original reagent as mentioned above. However, we can anticipate that the use of new reagents promotes the desired Mitsunobu alkylation significantly. In this paper, we would like to describe the results of the newly developed Dios chemistry.

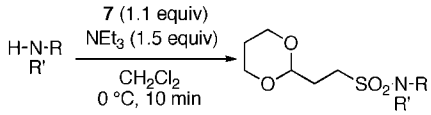
Dios chloride (Dios Cl) **7**, a sulfonyl agent, was prepared by the following reaction sequence: (1) Easily prepared 2-(2-chloroethyl)-1,3-dioxane (**6**)[13] was converted to the corresponding sodium 2-(1,3-dioxan-2-yl)ethylsulfonate (Na_2SO_3, DME−H_2O, reflux, 72 h), and then (2) the sulfonate was treated with 2.0 equiv of PPh_3 and 2.2 equiv of sulfuryl chloride (CH_2Cl_2, 0 °C, 2 h). The agent could be purified by rapid chromatography on silica gel and stored at −15 °C for long periods of time (Scheme 2).

Scheme 2. Dios Group and Its Preparation

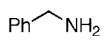
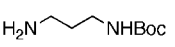
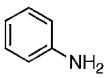


The reaction of **7** with ammonia afforded water-soluble N-nonsubstituted Dios-amide **8** in 90% yield (NH_3 aqueous, CH_3CN, 0 °C ∼ room temperature, 10 min). Primary and secondary amines were also sulfonated in excellent yields (1.1 equiv of **7**, 1.5 equiv of NEt_3, CH_2Cl_2, 0 °C, 10 min), as listed in Table 1.

Table 1. List of Amines and % Yield in the Sulfonylation



9: R ≠ H, R' = H
10: R, R' ≠ H

amine	% yield	amine	% yield
	97		90
	98 [a]		92
	95		94

[a] The reaction was carried out for 50 min.

The feature of the reaction of the Dios-amide **8** in the presence of CMBP was quite similar to that of Ts-amide **1**

(5) For a review of Ns chemistry, see: (a) Kan, T.; Fukuyama, T. *J. Synth. Org. Chem. Jpn.* **2001**, *59*, 779. (b) Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353, and references therein.

(6) Milburn, R. R.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 892.

(7) For example, see: (a) Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, G. D., Jr.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709. (b) Edwards, M. L.; Stemerick, D. M.; McCarthy, J. R. *Tetrahedron Lett.* **1990**, *31*, 3417.

(8) The acidic hydrogen in nucleophiles has to have a pK_a less than 11 for the reaction to proceed satisfactorily. See: (a) Mitsunobu, O. *Synthesis* **1981**, *1*. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335.

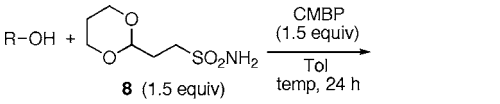
(9) Bittner, S.; Assaf, Y.; Krief, P.; Pomerantz, M.; Ziemnicka, B. T.; Smith, C. G. *J. Org. Chem.* **1985**, *50*, 1712. Also see ref 10f and 11.

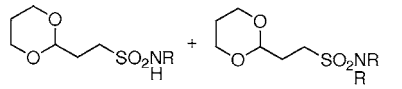
(10) (a) Tsunoda, T.; Ozaki, F.; Itô, S. *Tetrahedron Lett.* **1994**, *35*, 5081. (b) Uemoto, K.; Kawahito, A.; Matsushita, N.; Sakamoto, I.; Kaku, H.; Tsunoda, T. *Tetrahedron Lett.* **2001**, *42*, 905. (c) Itô, S.; Tsunoda, T. *Pure Appl. Chem.* **1999**, *71*, 1053. (d) Tsunoda, T.; Itô, S. *J. Synth. Org. Chem. Jpn.* **1997**, *55*, 631. (e) Tsunoda, T.; Kaku, H.; Itô, S. *TCIMail* **2004**, *123*, 2. (f) Tsunoda, T.; Yamamoto, H.; Goda, K.; Itô, S. *Tetrahedron Lett.* **1996**, *37*, 2457.

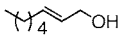
(11) Sakamoto, I.; Nishii, T.; Ozaki, F.; Kaku, H.; Tanaka, M.; Tsunoda, T. *Chem. Pharm. Bull.* **2005**, *53*, 1508.

reported previously.[10a,14] Thus, the Mitsunobu alkylation of **8** proceeded in satisfactory yields to give **9** even with secondary alcohol (Table 2), although benzylic and allylic

Table 2. List of Alcohols, Reaction Temperature, and % Yield of the Product in the Mitsunobu Alkylation of **8**





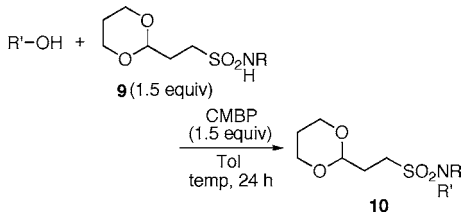
alcohol	temp (°C)	% yield
	rt	67 (22) [a]
	rt	80 (19) [a]
	rt	89
	80	86

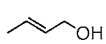
[a] The yield of double alkylation product **10** was shown in parentheses.

alcohols gave overreacted products **10a** and **10b** (double alkylation products) to some extent because of their high reactivity.

As shown in Table 3, N-monosubstituted Dios-amide **9** could also be subjected to the Mitsunobu alkylation utilizing

Table 3. List of Alcohols, Reaction Temperature, and % Yield of the Product in the Mitsunobu Alkylation of **9**



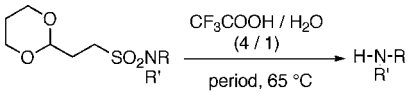
alcohol	-R	temp (°C)	% yield
	-CH_2Ph	rt	90
	-CH_2Ph	rt	96
	-CH_2Ph	rt	94
	-CH_2Ph	80	82 (88) [a]
	-Ph	80	91
	-$(CH_2)_3NHBoc$	rt	78

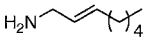
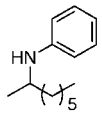
[a] Yield using CMMP was shown in parentheses.

CMBP. Although the reaction could be expected to be promoted with satisfactory results by (cyanomethylene)-trimethylphosphorane (CMMP),[10e,15] which is a more highly reactive Mitsunobu reagent than CMBP, the commercially available CMBP possessed sufficient reactivity to afford N,N-disubstituted Dios-amide **10** in excellent yields. The alkylation of **9** was also accomplished using alkyl halides under basic conditions. For example, benzyl bromide reacted with **9a** (R = Bn) (K_2CO_3, DMF, room temperature, 15 h), giving quantitative yield. However, the reaction of 2-bromooctane, a secondary alkyl halide, gave poor results owing to competitive elimination (NaH, DMF or THF, 0 °C ∼ room temperature).[16] On the contrary, a potential advantage of the Mitsunobu alkylation was that a secondary alkyl group could be introduced with complete Walden inversion on nitrogen effectively, as shown in Table 3.[17]

As expected, deprotection of N-monosubstituted and N,N-disubstituted Dios-amides **9** and **10** was achieved by acid-catalyzed hydrolysis of the acetal moiety to aldehyde in a hot aqueous solution of trifluoroacetic acid (TFA) followed by spontaneous retro-Michael reaction, giving the corresponding primary and secondary amines in high yields (Table 4).[18] N-Monosubstituted Dios-amides **9** could be cleaved

Table 4. List of Produced Amines, Reaction Period, and % Yield in the Desulfurization of **9** and **10**

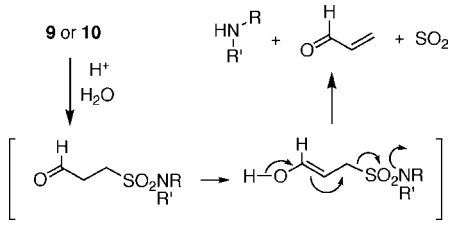


produced amine	period (min)	% yield	produced amine	period (min)	% yield
	50	89		80	99
	40	93			
	90	93		100	95

more easily than N,N-disubstituted Dios-amides **10**. A plausible reaction pathway is shown in Scheme 3. Acrolein generated as a coproduct did not react with amines produced under these aqueous conditions.

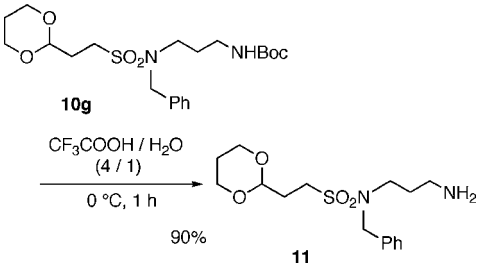
(12) King, J. F.; Rathore, R.; Lam, J. Y. L.; Guo, Z. R.; Klassen, D. F. *J. Am. Chem. Soc.* **1992**, *114*, 3028.
(13) Gil, G. *Tetrahedron Lett.* **1984**, *25*, 3805.
(14) The results of the reaction of **8** using other Mitsunobu reagents are shown in the Supporting Information as a Table.
(15) Sakamoto, I.; Kaku, H.; Tsunoda, T. *Chem. Pharm. Bull.* **2003**, *51*, 474.
(16) The results of the reaction of **9** with primary and secondary alkyl halides under basic conditions are described in the Supporting Information.
(17) The reaction of (2*S*)-2-octanol with **9** and a route for preparation of an authentic sample are shown in the Supporting Information as a Scheme. LC analysis of the product and the authentic sample shown in the Supporting Information reveal that the reaction of **9** proceeded with the complete configurational inversion of (2*S*)-2-octanol.
(18) Deprotection of the Dios group could also be achieved under other acidic conditions, which were often employed for the hydrolysis of 1,3-dioxanes.

Scheme 3. Reaction Pathway of Desulfurization



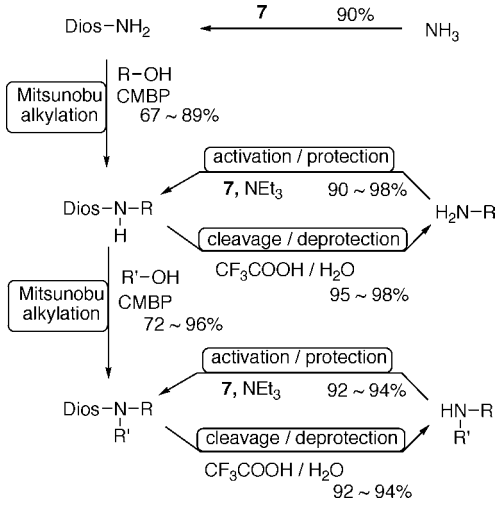
This newly developed Dios group was highly stable unless the cyclic acetal was hydrolyzed (e.g., 6 N HCl aqueous/THF = 2:1, room temperature, 47 h, very slow reaction). Additionally, the chemistry and the stability of 1,3-dioxanes are well-known and well-established.[19] For example, N,N-disubstituted Dios-amide was inert under several conditions, such as: (1) LAH, room temperature, 12 h; (2) 2 N KOH, 95 °C in a sealed tube, 12 h; (3) *n*-BuLi, −78 °C ∼ room temperature, 12 h; (4) EtMgBr, −78 °C ∼ room temperature, 12 h.[20] Because the Dios group was more stable than a Boc group in acidic conditions, the treatment (TFA/H_2O = 4:1) of **10g** at 0 °C achieved selective deprotection of the Boc group to give **11** in 90% yield (Scheme 4). Thus, the Dios group can be utilized not only as an activating group but also as a new amine-protecting group.

Scheme 4. Selective Deprotection of the Boc Group



To conclude, the complete reaction sequence is illustrated in Scheme 5. The Dios group was introduced onto an amino group, and the resulting Dios-amide was alkylated under the new Mitsunobu conditions. Finally, the Dios group was cleaved/deprotected under acidic conditions. Thus, because the Dios group can be used as a versatile activating/protecting group of amines, the reactions presented herein would be widely employed as useful methodologies in the synthesis of nitrogen-containing molecules.

Scheme 5. Conclusion of Dios Methodology



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Supporting Information Available: Experimental procedures, compound characterization data, LC analysis, and ^1H spectra of all the products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL052545+

(19) Greene, T. W.; Wuts, P. G. *Protective Group in Organic Synthesis*, 3rd ed.; John Wiley and Sons: New York, 1998; pp 307−326.

(20) The results of the reaction of Dios-amide under these conditions are shown in the Supporting Information.