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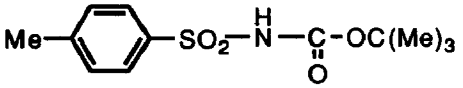
Facile Preparation of N-(Sulfonyl)carbamates

Bernard R. Neustadt

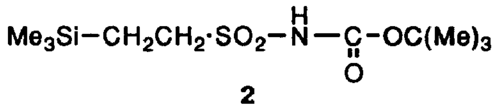
Schering-Plough Research Institute
Kenilworth, NJ 07033-0539

Abstract: N-(Sulfonyl)carbamates, useful N-nucleophiles in the Mitsunobu reaction, can be prepared readily by reaction of sulfonamides with chloroformates (or dicarbonates) catalyzed by 4-(dimethylamino)pyridine.

N-(Sulfonyl)carbamates have shown significant utility as N-nucleophiles for the Mitsunobu reaction.[1,2,3] The use of N-(Boc)-toluenesulfonamide **1**[1,2] and N-(Boc)-2-(trimethylsilyl)ethanesulfonamide **2**[3] have been described recently. N-(Boc)-methanesulfonamide **3**,[3] itself useful for the Mitsunobu reaction, is employed as an intermediate in the synthesis of **2**. Preparation of **3** involves a number of inconvenient reaction conditions (BuLi, KH, TMEDA, -78°C, Boc-azide). This note describes exceptionally convenient access to this class of sulfonamides.

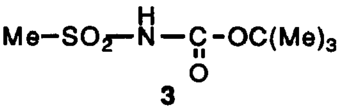


1



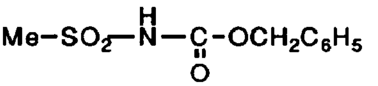
$Me_3Si{-}CH_2CH_2{\cdot}SO_2{-}\overset{H}{N}{-}\underset{\underset{O}{\|}}{C}{-}OC(Me)_3$

2



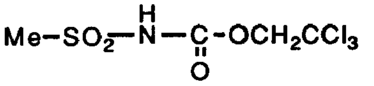
$Me{-}SO_2{-}\overset{H}{N}{-}\underset{\underset{O}{\|}}{C}{-}OC(Me)_3$

3



$Me{-}SO_2{-}\overset{H}{N}{-}\underset{\underset{O}{\|}}{C}{-}OCH_2C_6H_5$

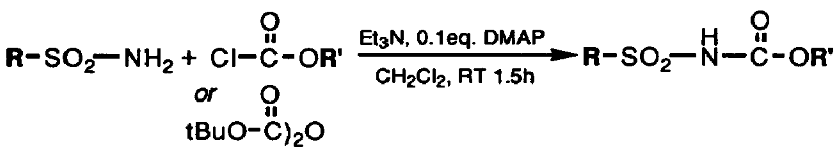
4



$Me{-}SO_2{-}\overset{H}{N}{-}\underset{\underset{O}{\|}}{C}{-}OCH_2CCl_3$

5

N-Acylation of sulfonamides has frequently employed heating or use of a strong base.[4] In contrast, the catalyzed acylation described here is very facile. The catalytic effect of 4-(dimethylamino)pyridine (DMAP) in the reaction is quite evident. When this acylation catalyst (0.1eq.) is added to a mixture of methanesulfonamide, Et3N, and di-(*t*-butyl) dicarbonate in CH2Cl2, vigorous gas evolution occurs, with clean formation of carbamate **3**. In a more convenient variant, the dicarbonate is added to the other reagents. This process works equally well with *p*-toluenesulfonamide, providing **1**[5] in high yield (see Table). N-(Cbz)-methanesulfonamide **4** and N-(Troc)-methanesulfonamide **5** can likewise be prepared by utilizing the corresponding chloroformates.[6] In all cases, pure sulfonamide is readily obtained by recrystallization. The procedure is convenient for large-scale preparations. Under the reaction conditions employed, no reaction takes place with a less reactive acylating agent such as dimethylcarbamoyl chloride.



$$R{-}SO_2{-}NH_2 + \begin{array}{c} Cl{-}\overset{O}{\overset{\|}{C}}{-}OR' \\ or \\ tBuO{-}\overset{O}{\overset{\|}{C}})_2O \end{array} \xrightarrow[CH_2Cl_2,\ RT\ 1.5h]{Et_3N,\ 0.1eq.\ DMAP} R{-}SO_2{-}\overset{H}{N}{-}\overset{O}{\overset{\|}{C}}{-}OR'$$

Table: Yields and Characterization of N-(Sulfonyl)carbamates

Entry	R	R'	Yield, %[a]	m.p., °C	NMR ($CDCl_3$)
1	Me	*t*-Bu	91 (88)	108-9	δ1.52 (9H, s), 3.27 (3H, s)
2	Me	$CH_2C_6H_5$	74 (57)	112-4	δ3.29 (3H, s), 5.23 (2H, s), 7.39 (5H, m)
3	Me	CH_2CCl_3	74 (58)	94-6	δ3.36 (3H, s), 4,84 (2H, s)
4	*p*-Tolyl	*t*-Bu	97 (88)	117-9	δ1.40 (9H, s), 2.46 (3H, s), 7.34 (2H, d), 7.90 (2H, d)

a. Crude yield of hexane-washed product, >95% purity by NMR. Values in parentheses are for recrystallized material (ether-hexane).

Preparation of **3**: Methanesulfonamide (3.80g=40mmol, dried under vacuum) was suspended in CH_2Cl_2 (50ml) containing Et_3N (4.40g=44mmol) and DMAP (0.49g=4.0mmol). A solution of di-(*t*-butyl) dicarbonate (99%, 10.0g=46mmol) in CH_2Cl_2 (80ml) was added dropwise with stirring over 8min. After 2h, the solution was concentrated *in vacuo* and the residue treated with EtOAc (240ml) and 1N HCl (160ml). The EtOAc was washed successively with water and brine, dried ($MgSO_4$), and concentrated to leave a solid. Heating with hexane (40ml), cooling to RT, and filtration provided **3** as an off-white solid (7.1g=91%), m.p. 106-8°C. Recrystallization from Et_2O-hexane furnished colorless rods (6.9g=88%), m.p. 108-9°C (lit.[3] m.p. 107.5-108°C).[7]

In a known method,[8] sulfonamides can be N-acylated with carboxylic acids by activating the acid with carbonyl-diimidazole. The method reported here allows facile acylation with readily available di-(*t*-butyl) dicarbonate and with chloroformates, thereby increasing the availability of these useful Mitsunobu N-nucleophiles.

References and Notes

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3. Campbell, J.A.; Hart, D.J. *J. Org. Chem.* **1993**, *58*, 2900.
4. (a) K_2CO_3, acetone, 8h reflux: Nieforth, K.A.; Jenkins, G.L.; Knevel, A.M. *J. Pharm. Sci.* **1964**, *53*, 73;
   (b) K_2CO_3, EtOH, 6h reflux: Lanyi, K.; Szabo, Z. *Acta Chim. Acad. Hung.* **1961**, *29*, 85;
   (c) KH, THF, 30h RT: Belletire, J.L.; Spletzer, E.G. *Tetrahedron Lett.* **1986**, *27*, 131.
5. This material is available commercially from Aldrich Chemical Co. It can also be prepared conveniently by reaction of toluenesulfonyl isocyanate with *t*-butanol according to reference 1.
6. For reaction with chloroformates, the use of 1.3eq. Et_3N gave higher yields.
7. All recrystallized materials gave correct CHN combustion analyses.
8. Drummond, J.T.; Johnson, G. *Tetrahedron Lett.* **1988**, *29*, 1653.

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