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1*H*-Benzotriazol-1-yl Methanesulfonate: A Regioselective *N*-Mesylating Reagent

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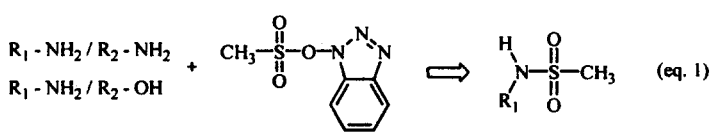
Abstrsct: 1*H*-Benzotriazol-1-yl methanesulfonate has been found to be an effective reagent in selective mesylation for differentiating amino groups from one another. In a molecule with both primary and secondary amino groups, mesylation only occurred at the primary amino group. When a compound contains both amino and hydroxy groups, the reagent selectively mesylated at the amino groups.

Keywords: benzotriazoles, amines, sulfonamides, regioselection

Sulfonyl groups have been widely used to protect amines and other nitrogeneous functionality in organic synthesis.[1] One of the most attractive features of sulfonamides is their stability to a wide array of reaction conditions. Recently, the arsenal of *N*-sulfonyl protecting groups has been improved by addition of new varieties amenable to mild removal.[2] The most widely used methanesulfonyl chloride is moisture sensitive and too reactive. As far as we are aware, there is no result on the scope of regioselective mesyl transfer reaction.

In connection with some on-going projects,[3] we have had occasion to study 1-hydroxybenzotriazole sulfonyl derivatives and found it a simple but very useful and powerful reagent for the selective mesylation of amino groups. In the present paper, 1*H*-benzotriazol-1-yl methanesulfonate (BMS) is described for selective mesylation in a series of structurally diverse amines (eq.1).



(eq. 1)

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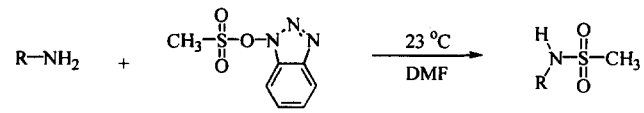
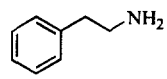
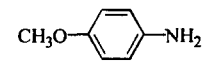
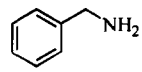
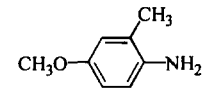
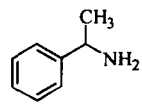
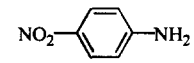
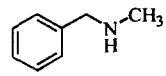
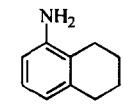
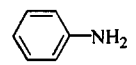
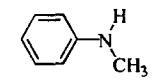
1-Hydroxybenzotriazole sulfonyl derivatives are of considerable importance as efficient coupling reagents in peptide chemistry.[4] However, these reagents have not been used for differentiating amino groups from one another. BMS is easily prepared in almost quantitative yield by the reaction of methanesulfonyl chloride with 1-hydroxybenzotriazole and triethylamine in methylene chloride at 0 °C for 2 h.[5] We first investigated the mesylating potential of BMS using various amino groups with the effect of solvents. Among the solvents employed, dimethylformamide was found to be the most effective. Ethanol was also effective, while the reaction did very slowly proceed in methylene chloride and diethyl ether. The byproduct 1-hydroxybenzotriazole could be removed easily from the reaction mixture by the usual aqueous workup. In general, the reaction was carried out with 1.0 equiv of BMS in dimethylformamide at room temperature.[6]

Table 1 includes some experimental results and illustrates the efficiency, the mildness, and the scope of this method.

Table 1. Mesylation of amino groups



entry	amine	time	yield	entry	amine	time	yield
1		0.5 h	83 %	6		2 h	81 %
2		0.5 h	87 %	7		6 h	81 %
3		1 h	82 %	8		48 h	(85 %)[a]
4		1 h	80 %	9		48 h	60 %
5		22 h	85 %	10		120 h	(83 %)[a]

[a] Yields of recovered starting materials

As shown in Table 1, primary and secondary, alkyl, and aryl amines all readily gave excellent yields of mesylated products. Alkyl amines such as benzylamine and phenethylamine, were readily mesylated to the corresponding sulfonamides in high yields within 0.5 h (entries 1, 2). The reaction of secondary amine such as *N*-methylbenzylamine proceeded slowly (entries 4). In case of arylamines, the mesylation occurred very slowly at room temperature. For example, the mesylation of aniline needed 22 h (entry 5). Employment of electron-donating groups at *p*-position of aniline (entry 6) accelerated the reaction, while introduction of electron-withdrawing (entry 8) or sterically hindered groups (entries 7, 9) decelerated the reaction. The

reaction with 1-amino-5,6,7,8-tetrahydronaphthalene proceeded in 60 % yield in 48 h (entry 9). With *p*-nitroaniline or *N*-methylaniline, the starting materials were recovered in 80 % yield even after 48 h and more (entries 8, 10).

The substantial difference in reaction rates in accordance with steric hindrance and nucleophilicity of the amino groups prompted us to examine selective mesylation of amines. We chose to investigate the selectivity in the mesylation of a mixture of two sterically or electronically different amines. Figure 1 shows these experimental results and illustrates the efficiency and the applicability of the present method.

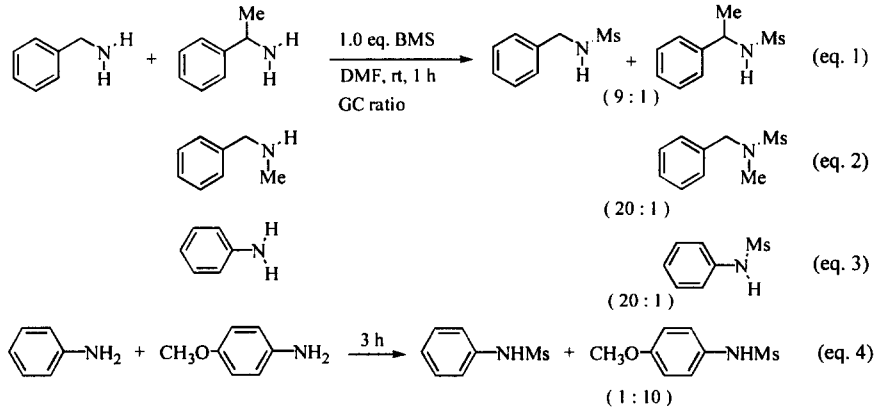
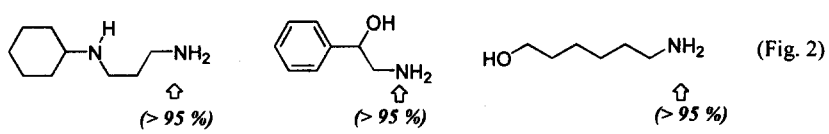


Figure 1. Selective Mesylation of the Amino Groups

The steric influence of substituents on the amino group is clearly demonstrated by competition experiments using benzylamine, α-methylbenzylamine, and *N*-methylbenzylamine. Indeed, the present mesylation system provided to be exceptionally chemoselective: The reaction of a 1:1 mixture of benzylamine and *N*-methylbenzylamine using 1.0 equiv of BMS resulted, after 1 h, in the complete mesylation of primary amine whereas virtually trace amount of secondary amine could be detected by GC (20:1 ratio, Figure 1, eq. 2). Similar high selectivity was observed in the mesylation of alkyl amine in the presence of aryl amine. A competition between benzylamine and aniline resulted in 20:1 ratio of benzylamine (Figure 1, eq. 3). As shown in the reaction of aniline and *p*-methoxyaniline (Figure 1, eq. 4), this reagent is also highly sensitive to electronic influence of the amino groups.

In order to explore the generality and scope of this method, we examined structurally diverse amines having two functional groups in the molecule as shown in Figure 2.



N-Cyclohexyl-1,3-propanediamine, containing a primary and secondary amino groups, with 1.0 equiv of BMS, underwent mesylation selectively at the primary amino groups in more than 19:1 ratio. In case of 2-amino-1-phenylethanol, containing both an amino and hydroxy group in the molecule, was also selectively mesylated at the amino group. This result could be applied to the one-step synthesis of precursor of chiral auxiliary, 3-mesyl-1,3-oxazolidine.[7]

In a conclusion, 1*H*-benzotriazol-1-yl methanesulfonate is a convenient mesylation reagent due to its facile preparation, easy handling, and stability. This reagent is highly sensitive to the steric and electronic influence of the amines and, therefore, promises a wide variety of applications in synthetic organic chemistry for selective amino groups functionalizations.

References and Notes

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(5) 1*H*-Benzotriazol-1-yl methanesulfonate: mp 91°C (from *n*-hexane/CH_2Cl_2); MS *m/z* 213 (M^+); ^1H NMR (200 MHz, $CDCl_3$) δ 3.58 (s, 3H), 7.61-7.67 (m, 3H), 8.05 (d, J = 7.7 Hz, 1H); IR (KBr): 3048, 3027, 1385, 1188cm^{-1}; Anal. Calcd for $C_7H_7N_3O_3S$: C, 39.43; H, 3.31; N, 19.71; O, 22.51; S, 15.04. Found: C, 39.13; H, 3.41; N, 19.33; O, 22.82; S, 15.30.

(6) Typical experimental procedure: To a solution of 1*H*-benzotriazol-1-yl methanesulfonate (213 mg, 1.0 mmol) in DMF (7 mL) was added benzylamine (112 mg, 1.0 mmol). The reaction mixture was stirred at room temperature for 1 h, diluted with Et_2O (20 mL), and washed with water (3×20 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was subjected to silica gel column chromatography with ethyl acetate/*n*-hexane (1:3) as an eluant to give *N*-benzyl methanesulfonamide (157 mg, 87 %) as colorless solid: R_f = 0.15 (ethyl acetate/n-hexane = 1:3); mp 63 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 2.86 (s, 3H), 4.31 (d, J=7.1 Hz, 2H), 4.73 (brs, 1H), 7.25-7.34 (m, 5H); MS *m/z* 185 (M^+); IR (KBr): 3233, 3019, 1301 cm^{-1}

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