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A NEW SULFONATING AGENT ON HETERO ATOMS

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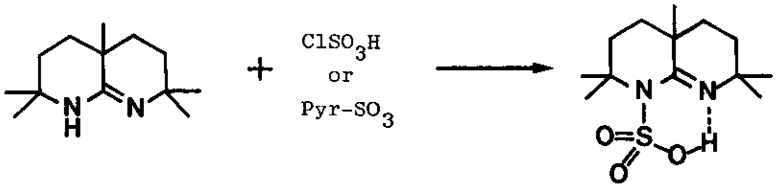
Abstract —— The novel amidine-N-sulfonic acid (2) was prepared from 3,3,6,9,9-pentamethyl-2,10-diazabicyclo[4.4.0]-1-decene (1) and chlorosulfonic acid. Reaction of 2 with the azetidinone (4) and different hydroxy compounds under rather mild conditions yielded corresponding N- and O-sulfonic acid PDBD salts, which could be purified by the usual column chromatography on silica gel and/or recrystallization.

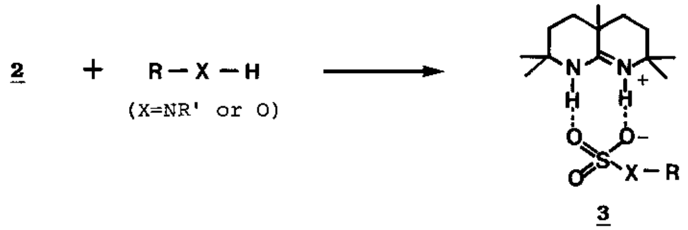
In connection with our synthetic efforts directed toward monocyclic β-lactam antibiotics, we required an N-sulfonating agent having the following properties: 1) ability to react at N-1 position of azetidinones under the mild and neutral conditions, 2) the sulfonated adducts are able to be purified by the usual column chromatography on silica gel and/or recrystallization, 3) stability on storage for a long period. While several methods (pyridine-SO_3[1], dioxane-SO_3[2], DMF-SO_3[3], etc.[4]) for the sulfonation of hetero atoms are known, they are unsatisfactory because of their drastic reaction conditions and subsequent transformations. The use of the amidine-sulfur trioxide complex was therefore investigated. Preliminary experiments utilizing DBU indicated that sulfur trioxide complex was formed by the reaction with chlorosulfonic acid, but the resulting complex was found to be unstable and the yield was low. On the other hand, the amidine-N-sulfonic acid 2 was readily obtained from 3,3,6,9,9-pentamethyl-2,10-diazabicyclo[4.4.0]-1-decene (PDBD) (1)[5] by sulfonation with chlorosulfonic acid or pyridine-sulfur trioxide complex in 61 % and 88 % yields, respectively (Scheme 1).[6]

Scheme 1



1 (PDBD)   2

Scheme 2



Compound 2 was found to be a stable solid which fully satisfies all of our requirements. The reaction process of 2 with hetero atoms is illustrated in Scheme 2. The principal advantage of this reaction compared with that using other sulfonating agents is that compound 2 and the products 3 are soluble in most of the organic solvents. For instance, the azetidinone 4 reacted stoichiometrically with 2 at 65 ∿ 70°C in several aprotic solvents, of which tetrahydrofuran/dioxane (1:1) gave the best result as shown in Table 1. The desired PDBD-salt was isolated in nearly quantitative yield by a simple silica gel purification.[7]

A typical experimental procedure is as follows; a solution of the azetidinone 4[8] (216 mg, 1 mmol) and the amidine-N-sulfonic acid 2 (318 mg, 1.1 mmol) in THF/dioxane (1:1, 2 ml) was stirred at 65 ∿ 70°C (bath temperature) for 20 min. After cooling, the solvent was removed *in vacuo* and the residue was passed through a short silica gel column. Elution with chloroform/acetone/methanol (91:3:6) gave the analytically pure sulfonate 5 as a colorless solid. Yield, 502 mg (99 %).

Sulfonation of different hydroxy compounds using 2 was also found to be simple process that can be carried out under a wide variety of conditions, a part of which

Scheme 3

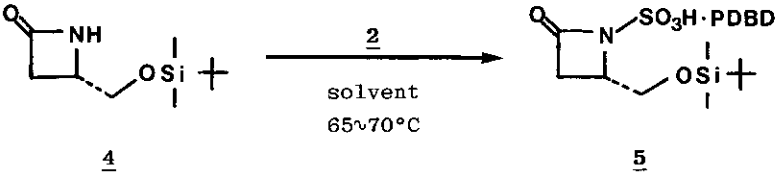


Table 1. Reaction Conditions and Yields of Sulfonation of 4

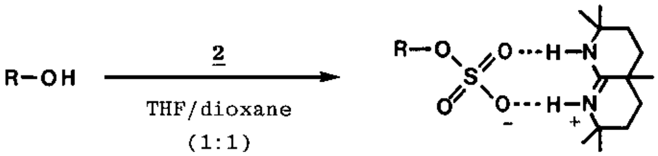
Solvent	Reaction Time (min)	Yield (%)[a)]
acetonitrile	180	61
THF	30	80
dioxane	90	85
benzene	90	97
THF/dioxane(1:1)	20	99

a) Isolated yields.

is summarized in Table 2. In the case of the sulfonation of ethyl acetoacetate, ethyl 3-oxo-2-sulfobutyrate was obtained as a sole product, the structure of which was characterized from NMR and IR spectra.

In conclusion, it was found that this novel sulfonating method was useful and applicable to the various N- and O-sulfonic acid synthesis. Further investigations for the monocyclic β-lactam antibiotics will be published elsewhere.

Table 2. Sulfonation of Hydroxy Compounds Using 2



ROH	Reaction Time (min)	Temp. (°C)	Yield (%)[a]
Benzyl alcohol	30	50∿55	96
2-Naphthol	160	15∿20	95
Benzoic acid	90	50∿55	72
Ethyl acetoacetate	120	50∿55	89[b]

a) Isolated yields. b) C-Sulfonated product.

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5. F. Heinzer, M. Soukup, and A. Eschenmoser, Helv. Chim. Acta, 61, 2851 (1978). This amidine base is abbreviated PDBD in this paper.
6. Compound 2, mp 146∿147°C; IR($CHCl_3$): 1607, 1244, 1045 cm^{-1}; NMR($CDCl_3$) δ : 1.36, 1.38, 1.44, 1.67, 1.77 (each 3H, s, CH_3), 1.20∿2.40 (8H, m, $-CH_2-$), and 9.47 (1H, br, SO_3H).
7. Trace amount of PDBD-H_2SO_4 salt was formed under this reaction conditions presumably by the action of 2 with water contaminated in the reaction medium.
8. The azetidinone 4 was obtained from known (4S)-4-hydroxymethyl-2-azetidinone[9] in two steps [(i) 2 equiv $(CH_3)_3CSi(CH_3)_2Cl$, NEt_3, DMF, (ii) 1 equiv KF, MeOH].
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