SYNTHESES OF 3-NITRO-2-PYRIDINESULFENATES

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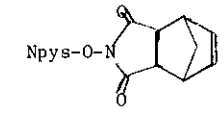
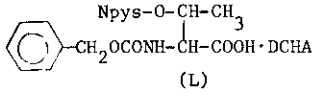
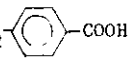
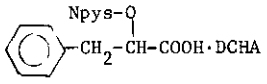
In the presence of tertiary amine under anhydrous conditions 3-nitro-2-pyridinesulfenyl (Npys) chloride reacts smoothly with hydroxy compounds, including various alcohols and hydroxy acids, to give the corresponding sulfenates.

The few known pyridinesulfenyl halides[1] are stable only in anhydrous solution. They decompose in air to give disulfides. Recently, the synthesis of 3-nitro-2-pyridinesulfenyl halides has been reported.[2] They have been found to be extraordinarily stable solids that can be safely stored at least one year in a refrigerator. A mild and efficient method for the esterification of cephalosporanic acids has been developed by the use of the sulfenyl chloride,[3] and Npys groups of amino acids have been utilized as activatable protecting groups for peptide synthesis.[4]

This paper reports the preparation of Npys sulfenates of various types of hydroxy compounds. Under anhydrous conditions Npys halides react readily and smoothly with alcohols in the presence of tertiary amine to afford sulfenates. In a typical experiment, 3-nitro-2-pyridinesulfenyl chloride (10 mmol) was added at 0°C to a stirred mixture of equimolar amounts (10 mmol) each of methanol and triethylamine in 200 ml of methylene chloride. The resulting mixture was stirred for 1 hr and washed with 5% citric acid and water. The solvent was removed _in vacuo_, and the residue was dissolved in a small amount of methanol and applied to a Sephadex LH-20 column in methanol after removal of the insoluble 3,3'-dinitro-2,2'-dipyridyl disulfide by filtration. The first yellow fractions were collected and evaporated _in vacuo_. Pure methyl 3-nitro-2-pyridinesulfenate was obtained by crystallization from ether-petroleum ether, 1.45 g (78%), mp 95-96°C. _Anal_. Found: C, 38.97; H, 3.17; N, 14.89; S, 17.22%. Calcd. for $C_6H_6N_2O_3S$: C, 38.70; H, 3.25; N, 15.05; S, 17.22%. NMR (δ in $CDCl_3$): 4.12 (3H, s, CH_3), 7.64 (1H, dd, J = 4.6 and 8.2 Hz, H-5 of pyridine), 8.92 (1H, dd, J = 1.4 and 8.2 Hz, H-4 of pyridine), 9.33 (1H, dd, J = 1.4 and 4.6 Hz, H-6 of pyridine). The 3-nitro-2-pyridinesulfenates of various kinds of hydroxy compounds prepared in this work are listed in Table I.

TABLE I

3-Nitro-2-pyridinesulfenates of Various Hydroxy Compounds

Compound[a]	Yield (%)	mp,°C	$[\alpha]_D^{22}$ °(c1, methanol)
1. Npys-OCH_3	78	95-96	
2. Npys-OCH_2CH_3	71	58-60	
3. Npys-OCH_2CH_2-N(C_2H_5)(C_2H_5)	54	176-178	
4. 	70	190-192	
5. $(CH_3)_3$-C-O-CONH-CH(Npys-O)-CH$_2$-COOH (L)	72	122-124	-23.7
6. 	58	92-94	-47.9
7. Npys-OCH_2-  -COOH	68	173-174	
8. 	72	158-159	-53.8

[a]DCHA indicates the dicyclohexylamine salt.

Compound 4, N-(3'-nitro-2'-pyridinesulfenyloxy)-5-norbornene-2,3-dicarboximide, was prepared for use in the mild and selective protection of amino functions by the Npys group in the presence of hydroxyl functions. For example, the reaction of equimolar amounts of compound 4, H-Pro-Thr-OMe and triethylamine overnight at room temperature gave Npys-Pro-Thr-OMe in 72% yield, mp 96∿98° C, $[\alpha]_D^{22}$- 14.6° (c1, methanol).

3-Nitro-2-pyridinesulfenyl chloride was found to react selectively with hydroxyl functions in the presence of carboxyl functions, and the derivatives of hydroxy acids were prepared in a similar manner under anhydrous conditions. In a typical experiment, 3-nitro-2-pyridinesulfenyl chloride (12 mmol) was added at 0°C to a stirred mixture of 4-(hydroxymethyl)phenylacetic acid

(10 mmol) and triethylamine (12 mmol) in 400 ml each of methylene chloride and ethyl acetate. The resulting mixture was stirred for one hour at room temperature, and the solvent was evaporated in vacuo. Ethyl acetate was added to the residue and the insoluble material was removed by filtration. Three ml of dicyclohexylamine was added to the filtrate, and the mixture was kept overnight in a refrigerator. The precipitate was collected by filtration and suspended in ethyl acetate and acidified with 5% citric acid, followed by washing with water and drying over sodium sulfate. The resultant solution was concentrated, and addition of petroleum ether gave pure 4-(3'-nitro-2'-pyridinesulfenyloxymethyl)phenyl acetic acid, compound 7, 2.18 g (68% yield), mp 173-174°C. Anal. Found: C, 52.30; H, 3.87; N, 8.88; S, 9.86%. Calcd for $C_{14}H_{12}N_2O_5S$: C, 52.49; H, 3.78; N, 8.75; S, 10.01%. NMR (δ in $CDCl_3$): 3.59 (2H, s, $-CH_2-CO-$), 4.65 (2H, s, $-O-CH_2-$), 7.08 (4H, m, phenyl), 7.31 (1H, dd, J = 4.6 and 8.2 Hz, H-5 of pyridine), 8.33 (1H, dd, J = 1.4 and 8.2 Hz, H-4 of pyridine), 8.72 (1H, dd, J = 1.4 and 4.6 Hz, H-6 of pyridine).[5] This compound has been employed as a key intermediate for the introduction of the trifluoroacetic acid resistant 4-(oxymethyl)phenylacetoamido linking group on the resin in solid phase peptide synthesis.[6] Other derivatives of hydroxy acids prepared from 3-nitro-2-pyridinesulfenyl chloride, such as Compound 8, are being studied as modifying agents for enzyme active sites.

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5. The structure of this compound was confirmed to be a sulfenate and not a sulfoxide by the following experiment. The compound gave 4-(hydroxymethyl)phenylacetic acid quantitatively by treatment with triphenylphosphine in aqueous methanol or treatment with 2-pyridinethiol 1-oxide which cleave S-O bonds but do not cleave $-\overset{\downarrow}{S}-$ bonds.
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7. This article is dedicated to Professor T. Kametani.

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