Tetrahedron Letters No. 35, pp 3089 - 3092, 1974. Pergamon Press. Printed in Great Britain.

SOME SULFONATES OF STRONGLY ACIDIC N-HYDROXY COMPOUNDS AS NOVEL COUPLING REAGENTS

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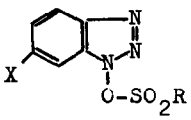
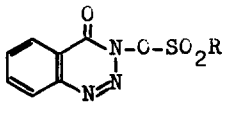
(Received in Japan 11 July 1974; received in UK for publication 18 July 1974)

The applications of strongly acidic N-hydroxy compounds for racemization suppression[1,2] and for esterification of carboxylic acids[3] have previously been reported.

Recently, the present authors noticed that ethyl 2-methanesulfonyloximino-2-cyanoacetate (I) possessed potential activity as a coupling reagent, while the methanesulfonates of strongly acidic phenols showed far less activity. Being encouraged by these results, we prepared a wide variety of sulfonates of possible N-hydroxy compounds and examined their potentials. Some of the sulfonates, which have enough activity, are listed in Table 1. These are

Table 1.

Sulfonates			Mp (°C)	Recrystd. from
$H_3C-SO_2-ON=C(CN)-COOEt$	I		79- 81.5	C_6H_6/pet. ether
	II	a:X= H, R=CH_3	88- 91	C_6H_6/pet. ether
		b:X= H, R=C_6H_5	84- 85	EtOAc/n-hexane
		c:X=Cl, R=C_4H_9(n)	72- 74	CCl_4/pet. ether
		d:X=Cl, R=C_6H_5	110-110.5	C_6H_6/n-hexane
		e:X=Cl, R=C_6H_4Cl(p)	125-127	C_6H_6/pet. ether
	III	a:R=CH_3	132-134	C_6H_6/pet. ether
		b:R=C_6H_5	132-134	C_6H_6

easily prepared by the reaction of alkyl- or arylsulfonyl chlorides with the corresponding N-hydroxy compounds under the condition of Schotten-Baumann reaction in aqueous or organic solvent. The sulfonates are stable crystalline materials unless these are exposed to moisture for long time, and could be stored in a closed brown bottle without decomposition over one year.

Amides can be prepared by two procedures using these coupling reagents; the active ester formation from a carboxyl component with a coupling reagent before the addition of an amine component (method A), and the direct addition of the coupling reagent to a mixture of carboxyl and amine components (method B). The use of an equimolar amount of tertiary base is essential in both methods.

$$R^1\text{-COOH} + H_2N\text{-}R^2 + R^3\text{-}SO_2\text{-}ON\langle^{R^4}_{R^5} \xrightarrow{\text{Base}} R^1\text{-CONH}R^2 + R^3\text{-}SO_3H \text{ Base} + HON\langle^{R^4}_{R^5}$$

In method A, the active ester formation is rapid and usually completed within one hour using triethylamine (TEA) in chloroform or ethyl acetate (EtOAc). When pyridine is used as a base, it requires the use of polar solvent such as acetonitrile to carry out the reaction smoothly. If it is desired, the active esters can be isolated in good yield. Aminolysis of the active esters is also completed within a few hours. A typical example of method A is as follows. To a stirred solution of N-benzyloxycarbonyl-L-phenylalanine (1.50 g, 5 mM) and TEA (0.70 ml, 5 mM) in dry tetrahydrofuran (20 ml) was added 1-methanesulfonyloxybenzotriazole (IIa, 1.10 g, 5 mM) at room temperature. After being stirred for 1 hour, 28% ammonium hydroxide solution (3.0 ml) was added to the mixture under ice-cooling. Stirring was continued for 2 hours at room temperature, and the mixture was allowed to stand overnight. After evaporation of the solvent, crystals of N-benzyloxycarbonyl-L-phenylalanine amide were filtered, washed with H_2O, and dried; mp 158-160°C, 1.15 g (77.2%). (Lit.[4]: mp 161-162°C).

In method B, there is some possibility of sulfonylamide formation from an amine component with the coupling reagent, although aminolysis of the coupling reagents was very slow and it was not noticeable in most cases. When strong amines such as phenethylamine (pKa 9.83) were acylated using

IId and TEA, considerable amount of p-chlorobenzenesulfonylphenethylamine was obtained. In this case, the use of the alkylsulfonates were much safer than the arylsulfonates, and the use of N-methylmorpholine (NMM) or pyridine in the place of TEA remarkably suppressed the side reaction even if the arylsulfonates were used. For the completion of coupling reaction, it requires generally 6 to 8 hours in chloroform or EtOAc, and 2 to 3 hours in acetonitrile. A typical example of method B is as follows. To an ice-cooled solution of N-benzyloxycarbonyl-L-proline (1.25 g, 5 mM), ethyl L-leucinate hydrochloride (1.00 g, 5 mM) and NMM (1.10 ml, 10 mM) in dry EtOAc (10 ml) was added 6-chloro-1-p-chlorobenzenesulfonyloxybenzotriazole (IIe, 1.72 g, 5 mM) with stirring. The mixture was stirred for 8 hours, and the product was extracted with EtOAc. The extract was washed with H_2O, N-$NaHCO_3$ (4 times), H_2O, N-HCl, and H_2O (2 times) and dried over $MgSO_4$. Evaporation of the solvent gave crystalline product; mp 65-67°C, 1.60 g (81.8%). (Lit.[5] mp 68-69°C).

Some representative amides prepared are presented in Table II. The sulfonate-type coupling reagents have some advantages over the most widely utilized reagent, dicyclohexylcarbodiimide (DCC). That is, less side reaction occurs using these reagents. By-products, sulfonic acid and acidic N-hydroxy compound, are washed off by sodium bicarbonate solution so easily that these will not contaminate the product. It is noteworthy that the sulfonates do not dehydrate from the ω-amide group of N-protected glutamine or asparagine at all, and afford the desired product in high yield. The authors recommend the use of IIe, especially of a combination of IIe and NMM in method B, for the preparation of amides, because IIe is the most stable and reactive one among the tested reagents.

Preliminary examination of racemization during coupling reaction showed that the sulfonates were superior than DCC, and more detailed investigation is now on the way.

We are grateful to Dr. Hiroshi Nakano, director of this laboratories, Drs. Takashi Kamiya and Kazuo Kariyone of this laboratories, for their kind advices and encouragements.

Table II.

Carboxylic Acid	Amine	Coupling Reagent	Method	Base (equiv.)	Solvent	Yield(%)
CH_3-COOH	H_2N-C_6H_5	I	A	TEA (1)	EtOAc	96
	"	I	B	" (1)	"	86
"	"	IId	"	" (1)	"	88.6
Z-Phe-OH	H-Leu-OEt·HCl	IIa	A	" (2)	$CHCl_3$	83
"	"	IIb	"	" (2)	CH_2Cl_2	80.5
Z-Pro-OH	"	IIc	B	Pyr (2)	"	77.4
"	"	IIIa	"	NMM (2)	$CHCl_3$	66.7
"	"	IIIb	"	" (2)	"	61.4
Z-Val-OH	H-Gly-OEt·HCl	IIe	"	Pyr (2)	CH_2Cl_2	82.1
"	H-Val-OEt·HCl	IIa	"	TEA (2)	"	80.4
"	"	IId	"	" (2)	$CHCl_3$	84.0
Z-Gln-OH	H-His-OMe·2HCl	IIc	"	" (3)	"	82.8
"	"	IIe	"	NMM (2)	MeCN	80.9
"	H-Tyr-OBzl·Ts-OH	IIc	A	TEA (2)	"	71.8
BOC-Asn-OH	H-Phe-OEt·HCl	IIe	B	" (2)	$CHCl_3$	70.0
Z-Arg(NO_2)-OH	H-Gly-OEt·HCl	IIe	"	NMM (2)	MeCN	71.2
BOC-Arg(NO_2)-OH	H-Tyr-OBzl·Ts-OH	IIa	"	TEA (2)	$CHCl_3$	70.3
Z-Gly-Phe-OH	H-Gly-OEt·HCl	IIa	"	" (2)	"	73.0*

Z= Benzyloxycarbonyl, BOC= t-Butyloxycarbonyl, Pyr= pyridine.

* No racemate was detected. Products were identified by comparing their physical constants with those of authentic samples.

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