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PEPTIDE AND ACTIVE ESTER FORMATION BY MEANS OF DIARYL SULFITES IN PYRIDINES

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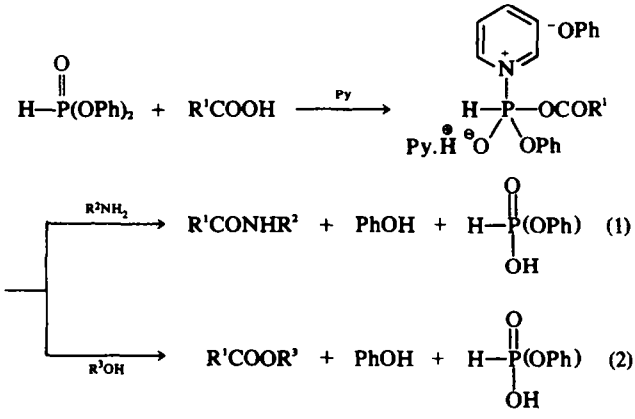
Abstract—Peptides and active esters of amino acids were obtained under mild conditions by mixing sulfites with a mixture of carboxyl and amino or hydroxyl components in tertiary amines. Of several sulfites and tertiary amines examined, diphenyl sulphite and pyridine and 3- or 4-methylpyridines were most effective. The reaction mechanism is discussed.

We have previously shown that the N-phosphonium salts of pyridine, formed by the oxidation of phosphorous acid and its esters in pyridines[1-3] or by dephenoxylation of diphenyl phosphite, can activate carboxyl groups to yield the corresponding amides and esters followed by aminolysis and alcoholysis (Eqs 1 and 2).



Considering that the chemical reactivity of sulfites is similar to that of phosphites, we have attempted the substitution of diphenyl sulfite for diphenyl phosphite in the coupling reactions between carboxylic acids and amines or hydroxyl compounds in the presence of tertiary amines such as pyridine, and have found that the amides and esters are in fact produced in good yields (Eqs 3 and 4).

$$O{=}S(OPh)_2 + R^1COOH + R^2NH_2 \xrightarrow{Py} R^1CONHR^2 + 2\,PhOH + SO_2 \quad (3)$$

$$O{=}S(OPh)_2 + R^1COOH + R^3OH \xrightarrow[Py]{} R^1COOR^3 + 2\,PhOH + SO_2. \quad (4)$$

Iselin *et al.*[5] demonstrated the formation of esters from carboxylic acids and aryloxy groups on sulfites (Eq 5).

$$O{=}S(OR)_2 + R^1COOH \rightarrow R^1COOR + ROH + SO_2. \quad (5)$$

The present paper deals with detailed studies on these reactions which have been extended to the preparation of peptides and active esters of amino acids using various sulfites in tertiary amines, especially diphenyl sulfite in pyridine.

RESULTS AND DISCUSSION

When a pyridine solution of equimolar amounts of benzyloxycarbonyl-glycine (Z-glycine), ethyl glycinate hydrochloride and triethylamine was treated at room temperature for 12 h with diphenyl sulfite, ethyl Z-glycylglycinate was obtained in 63% yield. Triethylamine was used as a HCl scavenger in the reaction. Similarly, this procedure was applied to the preparation of active esters of amino acids in the absence of triethylamine.

Several peptides and active esters were prepared in good yields by simply mixing the reactants accor-

ding to Eqs 3 and 4. The results are given in Tables 1 and 2.

In order to examine the effect of the ester residues in the sulfites, the reaction of Z-glycine with aniline was carried out using various sulfites in pyridine (Table 3). The results show that except for the cyclic sulfite of catechol, sulfites having nucleophilic aryloxy groups are favorable for the reaction; of the sulfites examined, the diphenyl ester was the most effective. Lack of reactivity of the catechol sulfite may be due to conformational restriction imposed on the formation of an N-sulfonium salt such as 1 in the scheme. Diethyl sulfite failed to give the anilide, since the sulfite is unable to form the salt because of the low nucleophilicity of the ethoxy group. No significant difference between the yield of the anilide with monosubstituted phenyl and naphthyl derivatives was observed, indicating that the reaction is not affected by the bulkiness of the ester residues in the sulfites. Prolonged reaction did not increase the yield (see di-m-tolyl sulfite).

Table 1. Preparation of peptides by means of diphenyl sulfite in pyridine[a]

Peptides	Reaction conditions temp, °C	time, h	Yield, %	m.p., °C
Z-Gly-Gly-OEt	40	6	65	80
Z-Gly-Tyr-OEt(L)	40	6	72	125–126
Z-Phe-Gly-OEt(L)	r.t.	12	60	108–109
Z-Phe-Gly-OEt(L)	40	6	65	108–109
Z-Met-Gly-OEt(DL)	40	6	65	72–73
Z-Gln-Gly-OEt(L)	40	6	63	168–170

[a] The reaction was carried out in pyridine using an equivalent of diphenyl sulfite.

Table 2. Preparation of active esters of amino acids by means of diphenyl sulfite in pyridine[a]

Active esters	Yield, %[b]	m.p., °C
Z-Gly—O—C$_6$H$_4$—NO$_2$	70	128
Z-Gly—O—C$_6$H$_4$—COOCH$_3$	72	121
Z-Gly—S—C$_6$H$_5$	56	71–72
Z-Phe—O—C$_6$H$_4$—NO$_2$	52	125–126

[a] The reaction was carried out at 40°C for 12 h in pyridine.
[b] Based on amino acids used.

Table 3. Preparation of Z-glycinanilide by means of several sulfites in pyridine[a]

Sulfites		pKa of ester residues	Yield, %
$(C_6H_5O)_2S{=}O$		9·998	78
$(CH_3C_6H_4O)_2S{=}O$	(o-)	10·287	54
	(m-)	10·091	54(59)[b]
	(p-)	10·264	59
$(ClC_6H_4O)_2S{=}O$		9·378	59
$(CH_3OC_6H_4O)_2S{=}O$		10·209	54
$(C_6H_4O_2)S{=}O$		—	51
$(CH_2O)_2S{=}O$		—	0
$(C_2H_5O)_2S{=}O$		—	0

[a] The reaction was carried out at 40°C for 3 h.
[b] The yield obtained at 40°C for 15 h.

Tertiary amines influenced the reaction markedly. This effect was investigated in the reaction of Z-glycine with aniline in acetonitrile using two equimolar amounts of several tertiary amines (Table 4). The results show that the basicity of the amines, revealed in pKa value, does not influence the yield. Pyridine and its 3- and 4-methyl derivatives gave better results than the 2-methyl and 2,6-dimethyl derivatives which have larger steric hindrance around the nitrogen atom in the pyridine

Table 4. Preparation of Z-glycinanilide in the presence of various tertiary amines[a]

Tertiary amines	pKa	Yield (%) of the anilide
None	—	11
Pyridine	5·23	78
3-Methylpyridine	5·52	82
2-Methylpyridine	5·97	28
4-Methylpyridine	6·02	79
2,6-Dimethylpyridine	6·99	25
Imidazole	7·12	42

[a] The reaction was carried out at 40°C for 3 h in acetonitrile using two equivalents of the amine.

nucleus. Imidazole was relatively less effective. The results can be explained in terms of the influence of the amines upon the competitive reactions producing the amide (Eq 3) and the phenyl ester (Eq 5), in a similar manner to those for diphenyl phosphite.[4]

The variation of the yield of peptide with the amounts of pyridine and diphenyl sulfite employed was examined by varying the molar ratios of pyridine and the sulfite over the carboxyl component. The results, shown in Fig 1, indicate an increase of the yield of Z-glycinanilide until the ratios of pyridine and the sulfite over the carboxyl component reach a limiting value of 1. Above this value, no substantial effect of further addition of pyridine or sulfite could be found.

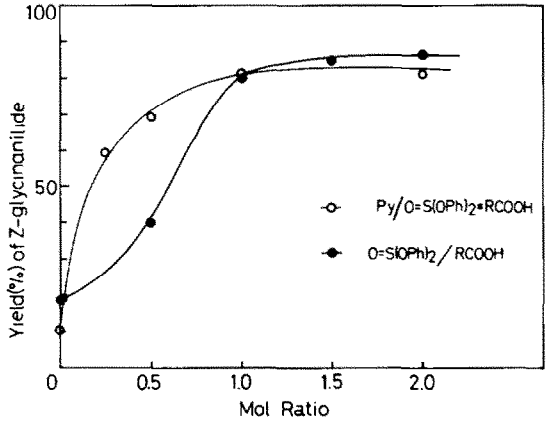
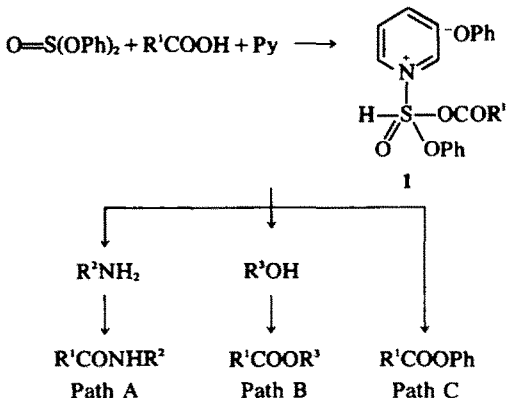


Fig 1. Variation of peptide yield with pyridine/diphenyl sulfite and diphenyl sulfite/Z-glycine mole ratios.

Based on the experimental results obtained, the reaction may be explained by assuming that an acyloxy N-sulfonium salt of pyridine (1) is initially formed by release of a phenolate anion from the sulfite according to a similar mechanism to that for diphenyl phosphite.[4] The salt undergoes two types of reaction, amide and ester formation by intermolecular reaction with the incoming amino or hydroxyl components (Paths A and B), and phenyl ester formation by intramolecular reaction with a phenolate anion released from the sulfite (Path C).

Path C may be governed by the tertiary amine employed in the reaction.



SCHEME 1

EXPERIMENTAL

Sulfites used in this study were prepared according to the literature.[6] Diethyl sulfite was obtained from a commercial source.

Preparation of Peptides and Active Esters of Amino Acids. Diphenyl sulfite (12·5 mmole) was added to a mixture of equimolar amounts of a Z-amino acid (12·5 mmole), an amino acid ethyl ester hydrochloride and triethylamine in 40 ml of pyridine. The mixture was stirred at ambient temperature for 12 h or at 40°C for 6 h, and then evaporated to a syrup *in vacuo*. From the residue the peptide was obtained according to a reported procedure.[4] Active esters were obtained similarly by the reaction of diphenyl sulfite (12·5 mmole) with equimolar amounts of a Z-amino acid (12·5 mmole) and a hydroxyl component in pyridine in the absence of triethylamine at 40°C for 12 h. Preparation of Z-glycinanilide was carried out in 40 ml of acetonitrile at 40°C for 3 h in the presence of two equivalents of several tertiary amines, and by varying the amounts of pyridine and diphenyl sulfite. The reaction was carried out using several sulfites in pyridine under identical conditions.

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