

5-Nitro-3*H*-1,2-benzoxathiole *SS*-Dioxide, a New Reagent for Coupling in Peptide Synthesis

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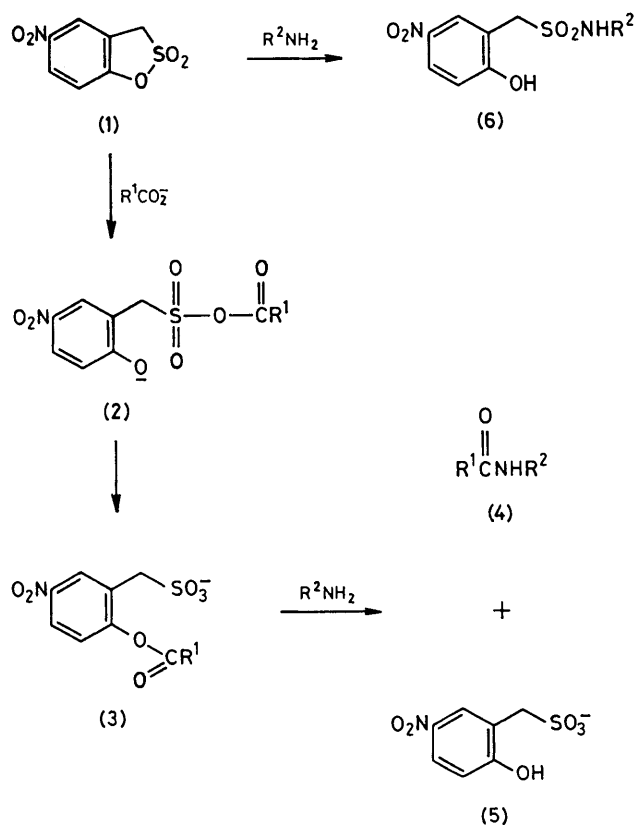
Summary Peptides are rapidly prepared and isolated by a two-step, one-pot reaction using 5-nitro-3*H*-1,2-benzoxathiole *SS*-dioxide (**1**), a strained sultone, as a condensation agent.

STRAINED five-membered cyclic sulphate and sulphonate esters show a greatly enhanced reactivity at sulphur compared with their acyclic analogues.¹ Furthermore, weak catalysis of the alkaline hydrolysis of the sultone (**1**)² by acetate ion has been observed.^{1c}

TABLE. Yields and m.p.s of the peptides (4).

Acid	Amine	Method ^a (solvent)	Peptide (4)	
			M.p. ^b (t/°C)	% Yield
Z-Gly	Gly-OEt	A (MeCN or DMF)	80 (79—80)	55
		B (MeCN)		53
Z-Gly	Ala-OMe	A (MeCN)	90 (62—64)	60
Z-Gly	Ser-OMe	A (MeCN)	95.5 (96—97)	60
Boc-Gly	Gly-OEt	A (MeCN)	Oil (Oil)	55
Z-Phe	Gly-OEt	A (MeCN)	110 (109—111)	52
Z-Pro	Gly-OEt	A (MeCN)	Oil (Oil)	63
Z-Met	Gly-OEt	A (THF)	94 (92—93)	63
Z-Val	Gly-OEt	A (THF)	162 (162—164)	55
Z-Asn	Gly-OEt	A (DMF)	185 (185—187)	40
Z-Ser	Gly-OEt	A (THF)	102 (98—100)	49
Z-Gly	Phe	C (THF-Pyr-H ₂ O)	125 (125—126)	70
Z-Phe	Gly-Pro	C (MeCN-Pyr-H ₂ O)	208—209 (205—206)	40
Z-Gly-Phe	Gly-OEt	A (DMF)	116.5 (116—119)	80
		B (THF)		56

^a Method A: to a stirred solution (THF or DMF) or a suspension (MeCN) of 1 mmol of (1) in 3 ml of solvent a mixture of RCO₂H and Et₃N (1 mmol each in 3 ml of solvent) is added. After 2 h a solution of the amine (or its hydrochloride + Et₃N; 1 mmol in 1 ml of solvent) is added. After a further 30 min the solvent is evaporated off. After addition of 20 ml of saturated aqueous NaHCO₃ the peptide is filtered off or extracted into EtOAc and sometimes purified by filtration through a short column of Florisil (5 g) using EtOAc as eluant. Method B: as Method A, but using the tetrabutylammonium salt (T. Mukaiyama, N. Morito, and Y. Watanabe, *Chem. Lett.*, 1979, 1305). Method C: see text (Pyr = pyridine). ^b Lit. m.p.s in parentheses (G. R. Pettit, 'Synthetic Peptides,' vols. 4 and 5, Elsevier, Amsterdam, 1976 and 1980).



SCHEME

In an aprotic medium nucleophilic attack by carboxylate ion on the sultone (1) would be expected to lead to the mixed carboxylic sulphonic anhydride (2).[†] An intramolecular acyl transfer reaction analogous to that we observed previously with a phosphate ester³ would then give the ester (3), aminolysis of which can be assisted by the neighbouring sulphonate anion (Scheme). Moreover isolation of the amide (4) should be easy, the sulphonate by-product (5) being soluble in water. Our expectations here have been borne out in practice.

A carbonyl absorption at 1770 cm⁻¹ rapidly appears during the reaction of triethylammonium acetate with (1) [1 mmol each in 3 ml of dry tetrahydrofuran (THF)]. On adding 1 equiv. of benzylamine this ester band rapidly disappears (< 5 min) and an amide band is observed at 1675 cm⁻¹. Under the same conditions aminolysis of *p*-nitrophenyl acetate takes about 90 min for completion.

The sultone (1) has been used for coupling the triethylammonium (method A) or tetrabutylammonium salts (method B) of *N*-protected amino-acids with amino-esters in dimethylformamide (DMF), MeCN, or THF (Table). Aminolysis of the ester (3) is very much faster than that of the sultone (1) and the formation of the sulphonamide (6) is not observed. The condensation does not seem to be very sensitive to the steric hindrance of either the acid or the amine component.

Our coupling reactions were done on a millimolar scale. Yields were not optimized and are better on a larger scale. Generally, there is no side reaction; t.l.c. of the crude reaction mixture (SiO₂, EtOAc as eluant) shows the presence of the sulphonate (5) and small amounts of unchanged acid and reagent (1). However, in the case of *Z*-Asn and *Z*-Ser

[†] Simple *p*-nitrophenyl sulphonates are inefficient for coupling but sulphonates of acidic *N*-hydroxy-compounds have been found to be good coupling reagents: M. Itoh, H. Nojima, J. Notani, D. Hagiwara, and K. Takai, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 3320; K. Horiki and A. Murakami, *Heterocycles*, 1978, **10**, 185; Y. A. Davidovitch and U. Ragnarsson, *Acta Chem. Scand., Ser. B*, 1979, **33**, 311.

minor by-products are formed, and the peptide was purified by thick layer chromatography.

The method can also be easily applied to coupling reactions with salts of amino-acids or peptides (method C): the ester (**3**) prepared in THF or MeCN is slowly added to a pyridine-H₂O solution of the salt while the pH of the reaction mixture is kept constant (8.5) by addition of 5 N NaOH.

In order to examine the usefulness of the reagent for fragment condensation, the Anderson peptide (Z-Gly-Phe-Gly-OEt) has been prepared. Less than 0.7% of racemate was isolated using method A in DMF or method B in THF.

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¹ (a) E. T. Kaiser, *Acc. Chem. Res.*, 1970, **3**, 145; (b) E. T. Kaiser, 'Organic Chemistry of Sulfur,' ed. S. Oae, Plenum, New York, 1977, p. 649; (c) T. Deacon, A. Steltner, and A. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1975, 1778; (d) E. Izbicka and D. W. Bolen, *J. Am. Chem. Soc.*, 1978, **100**, 7625; (e) A. Laleh, R. Ranson, and J. G. Tillett, *J. Chem. Soc., Perkin Trans. 2*, 1980, 610.

² W. Marckwald and H. H. Frahne, *Ber.* 1898, **31**, 1854; E. T. Kaiser and Kwok-Wing Lo, *J. Am. Chem. Soc.*, 1969, **91**, 4912.

³ M. Wakselman and F. Acher, *Tetrahedron Lett.*, 1980, **21**, 2705.