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

By MICHEL WAKSELMAN and FRANCINE ACHER
(*C.E.R.C.O.A.-C.N.R.S., 2, rue Henry Dunant, 94320 Thiais, France*)

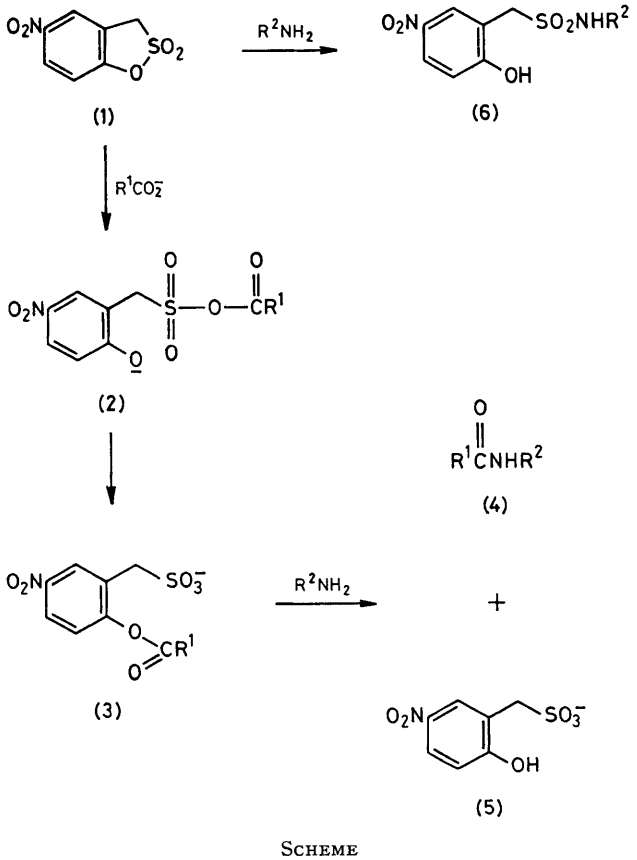
Summary Peptides are rapidly prepared and isolated by a two-step, one-pot reaction using 5-nitro-3*H*-1,2-benzoxathiole *SS*-dioxide (**1**), a strained sultone, as a condensation agent.

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)	Peptide (**4**) % 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_2O)	125 (125—126)	70
Z-Phe	Gly-Pro	C (MeCN–Pyr–H_2O)	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 RCO_2H and Et_3N (1 mmol each in 3 ml of solvent) is added. After 2 h a solution of the amine (or its hydrochloride + Et_3N; 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 $NaHCO_3$ 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 ester[3] 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 (SiO_2, 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–H_2O 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.