Reductive Cyclisation of 2-Azidophenyl Esters to 2-Substituted Benzoxazoles

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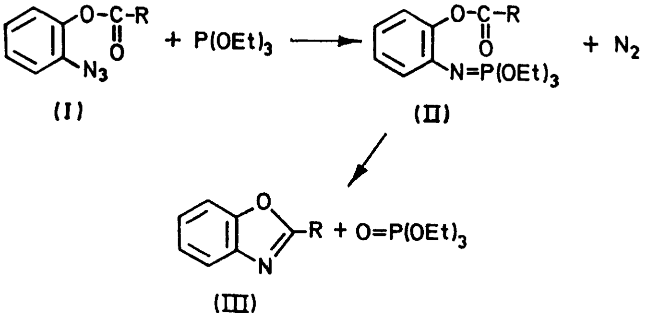
Summary Triethyl phosphite reacts with *o*-azidophenyl esters to give 2-substituted benzoxazoles *via* phosphorimidate intermediates, but a comparison with the corresponding reaction of *o*-nitrophenyl esters suggests different mechanisms for these two reactions.

RECENTLY one of us reported the production of 2-phenylbenzoxazole in good yield by the action of triethyl phosphite on *o*-nitrophenyl benzoate.[1] Subsequent work has shown that a similar reaction occurs with *o*-nitrophenyl acetate to give 2-methylbenzoxazole, but in low yield (6·5%). We have now found that the same products can be obtained by the reaction of triethyl phosphite with the corresponding 2-azidophenyl esters. To *o*-azidophenyl benzoate (0·002 moles) was added a solution of triethyl phosphite (5 ml, 0·40 molar) in cyclohexane. An exothermic reaction ensued (occasional cooling in ice was necessary) and a gas was evolved as the azide dissolved. Subsequent heating of the reaction mixture under reflux (25 h) produced 2-phenylbenzoxazole (71% yield). Similarly, *o*-azidophenyl acetate gave 2-methylbenzoxazole (69% yield). Trialkyl phosphites are known to produce phosphorimidates with azides,[2] and we believe that the reaction sequence shown takes place (Scheme). Evidence for the postulated scheme is presented below.



SCHEME

(i) The existence of the intermediate was shown by u.v. absorption spectroscopy. The Figure shows the spectral changes following addition (in the dark) of a large excess of triethyl phosphite to a solution of *o*-azidophenyl benzoate. The initial change is very rapid, but the new spectrum decays as the 2-phenylbenzoxazole spectrum slowly develops. Similar changes accompany the conversion of *o*-azidophenyl acetate into 2-methylbenzoxazole.

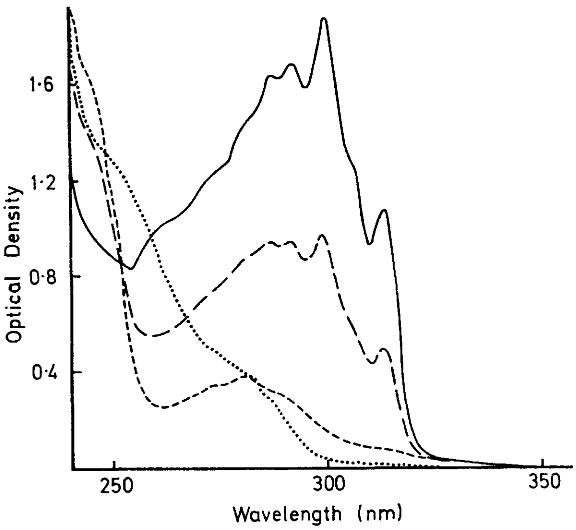


FIGURE. *Changes in u.v. absorption spectrum following addition of triethyl phosphite* (10^4 *fold excess*) *to* o-*azidophenyl benzoate* (1·21 × 10^{-4}M) *in hexane at room temperature.*
······ o-*azidophenyl benzoate alone*; ----- 2 *min after addition of triethyl phosphite—spectrum of phosphorimidate intermediate* (II; R = Ph); – – – 19 *h after mixing*; ——— 72 *h after mixing.*

(ii) The intermediate is formed with the evolution of nitrogen (1 equiv) and disappears by a unimolecular reaction [k_{21}(R=Ph) = 0·11 × 10^{-5} s^{-1}, k_{21}(R=Me) = 9·59 × 10^{-5} s^{-1}].

(iii) The n.m.r. spectrum of the intermediate showed a characteristic quintet around τ6·1, similar to those observed for triethyl phosphite at τ6·23 and for triethyl phosphate at τ6·0. A phosphorimidate signal would be expected to lie between these values.† As the intermediate reacted its signal slowly decayed and was replaced by one corresponding to triethyl phosphate.

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† *E.g.* A typical value is τ 6·15 for triethyl-*N*-[2-(2,6-dimethylphenylthio)phenyl]phosphorimidate.[3]

(iv) The intermediate (II; R = Ph) was isolated as a yellow oil, from a reaction of the azide (I; R = Ph) with an excess of triethyl phosphite in hexane at 0°, and was stored at $-80°$. The i.r. spectrum of the material showed no azido-group band at 2100 cm^{-1} but the expected features for a compound of structure (II; R = Ph) were present, *i.e.* an ester carbonyl frequency at 1740 cm^{-1} and aliphatic hydrogen peaks at 2900—3000 cm^{-1}.

Finally, the molecular formula for the above oil was confirmed by high-resolution mass spectrometry. The molecular ion peak was found to lie at *m/e* 377·139515. The formula for structure (II; R = Ph), $C_{19}H_{24}NO_5P$, requires *m/e* 377·139211. The agreement is excellent.

The evidence is thus overwhelmingly in favour of the participation of the phosphorimidate intermediate in reactions of triethyl phosphite with *o*-azidophenyl esters. The same intermediate seems unlikely in the reactions of nitro-esters in view of the difference in yield of 2-methylbenzoxazole from *o*-nitrophenyl acetate and *o*-azidophenyl acetate.‡ Neither is it reasonable to invoke a nitrene intermediate, because we have been able to show that thermal or photolytic generation of the nitrene from *o*-azidophenyl benzoate in the absence of triethyl phosphite failed to produce significant yields of 2-phenylbenzoxazole.

Cadogan[4,5] has suggested an alternative intermediate of the type $R-\overset{-}{N}-O-\overset{+}{P}(OEt)_3$ in the reaction of triethyl phosphite with nitro- and nitroso-compounds. We believe that the mechanism of the reaction of triethyl phosphite with *o*-nitrophenyl esters may well involve such an intermediate.

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‡ The low yield from the nitro-ester is not attributable to instability of the product under the more vigorous experimental conditions necessary in this case, because 2-methylbenzoxazole is not decomposed when heated under reflux with a mixture of triethyl phosphite and triethyl phosphate in t-butylbenzene.

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