A Novel Bromo Lactonization of Acylated Phosphoranes. A New Route to Bromo Enol Lactones.

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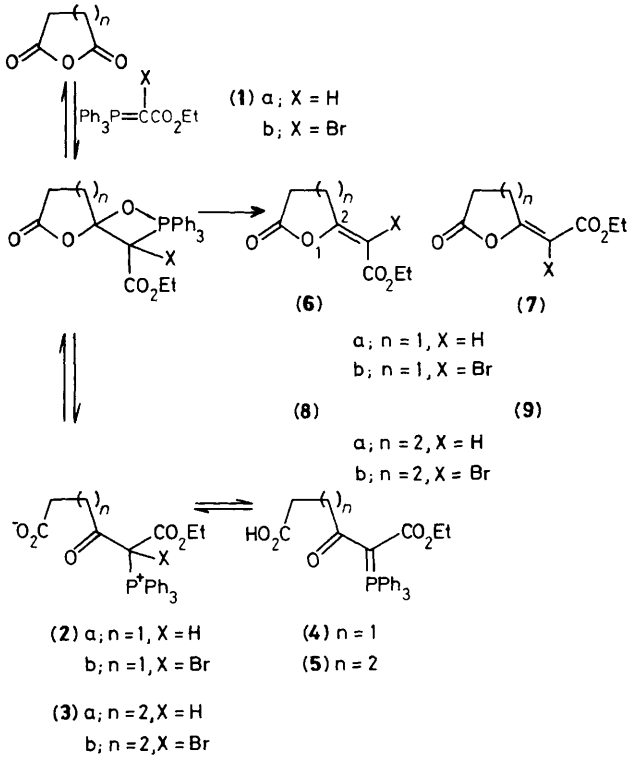
A simple and general method for the preparation of bromo enol lactones from acylated phosphoranes is described.

Halo enol lactones are an important class of compounds. Recently, examples of these compounds have gained considerable attention as mechanism based inhibitors of serine proteases.[1,2] A number of naturally occurring halo enol lactones, for example the fimbrolides, have also been reported.[3] To date the most widely used route to halo enol lactones is based on the halo lactonization of acetylenic acids.[2] Here we report a novel and simple one pot synthesis of halo enol lactones *via* a bromination mediated lactonization of acylated phosphoranes.



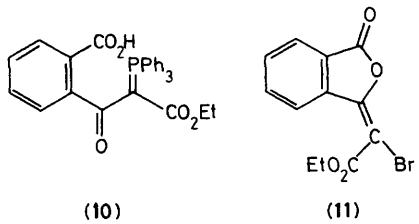
Scheme 1

It is known that the Wittig reaction between the stabilized ylide (**1a**) and cyclic anhydrides from the succinic, glutaric, maleic and phthalic series yields enol lactones, *e.g.* (**7a**) and (**9a**), *via* an acylated phosphorane, *e.g.* (**4**) and (**5**) respectively, Scheme 1.[4,5] The equivalent reaction using the bromo ylide[6] (**1b**) gave only starting material. We reasoned that an independent synthesis of the proposed intermediate phosphonium salt (**2b**) (Scheme 1) may permit the bromo enol lactone synthesis by avoiding the initial, and presumably slow step of ylide attack on the anhydride. Indeed, treatment of the phosphorane (**4**) with an equivalent of bromine and triethylamine in dichloromethane at 0 °C gave immediate decolourization of the bromine. Isolation gave the *E* and *Z* enol lactones (**6b**) and (**7b**) respectively, in a ratio of 7 : 3 and in a combined yield of 77%. The assignment of configuration was based on the chemical shift of the $(H\text{-}3)_2$ resonance.† The $(H\text{-}3)_2$ resonance occurs some 0.2—0.4 p.p.m. downfield in enol lactone isomers with the ester group *trans* to the lactone oxygen.[7]

The equivalent bromination reaction of the glutaric anhydride derived phosphorane (**5**) gave a mixture of the *E* enol lactone (**8b**), the *Z* enol lactone (**9b**) and the corresponding endocyclic isomer in a ratio of 41 : 5 : 4 and in a combined isolated yield of 81%. Again the stereochemistry was tentatively assigned on the basis of the chemical shift of the $(H\text{-}3)_2$ protons.‡

† N.m.r. ($CDCl_3$, 300 MHz); for (**6b**) δ 1.34 (3H, t, J = 7.1 Hz, CH_3), 2.79 [2H, m, $(H\text{-}4)_2$], 3.10 [2H, m, $(H\text{-}3)_2$], 4.30 (2H, q, J = 7.1 Hz, OCH_2); for (**7b**) δ 1.35 (3H, t, J = 7.1 Hz, CH_3), 2.85 [2H, m, $(H\text{-}4)_2$], 3.42 [2H, m $(H\text{-}3)_2$], 4.28 (2H, q, J = 1 Hz, OCH_2).

‡ N.m.r. ($CDCl_3$, 300 MHz); for (**8b**) δ 1.34 (3H, t, J = 7.2 Hz, CH_3), 1.98 [2H, m, $(H\text{-}4)_2$], 2.65 [2H, t, J = 6.6 Hz, $(H\text{-}5)_2$], 2.82 [2H, t, J = 6.6 Hz, $(H\text{-}3)_2$], 4.30 [2H, q, J = 7.2 Hz, OCH_2]; for (**9b**) as above except δ 2.72 [2H, t, J = 6.5 Hz, $(H\text{-}5)_2$], 3.17 [2H, t, J = 6.5 Hz, $(H\text{-}3)_2$].



These phosphorane lactonization reactions are presumed to occur *via* the initially formed brominated phosphonium salts, *e.g.* (**2b**) and (**3b**), which by analogy with the H-ylide series can then enter the normal Wittig sequence. Interestingly, the brominating reagent pyridinium bromide perbromide worked just as efficiently in the preparation of the bromo enol lactones (**6b**) and (**7b**). The formation of the succinic and glutaric bromo enol lactones from the bromination of the corresponding acyl phosphoranes is extremely rapid at 0 °C while the alternative formation of enol lactones (**7a**) and (**9a**) requires refluxing in chloroform for 4 h (82% yield of enol lactone)[4] and 168 h (40% yield of enol lactone),[5] respectively. Therefore, it would appear unlikely that the bromo enol lactone formation occurs *via* incipient formation of (**7a**) or (**9a**) followed by bromination. Indeed the attempted bromination of (**7a**) under conditions identical to those described previously failed to yield the bromo enol lactone (**6b**) or (**7b**).

The reaction is not limited to glutaric and succinic anhydrides. The phosphorane (**10**), which can be generated at low temperature (65% at 0 °C)[4] from the ylide (**1a**) and phthalic anhydride, undergoes a similar lactonization reaction with bromine and triethylamine. The corresponding *E* and *Z* enol lactones are produced in a ratio of 7 : 13 and in a combined yield of 74%.§ The major isomer, (**11**), was assigned the *Z* configuration on the basis of a single crystal *X*-ray analysis.

Interestingly the bromo ylide (**1b**) reacted directly with phthalic anhydride to yield the *E* and *Z* enol lactones in the same ratio of 7 : 13 and in a combined yield of 85%, a result that would support a common mechanism. Aspects of the mechanism of the halogenation mediated lactonization reaction and the biological properties of the product halo enol lactones are under investigation.

Received, 23rd September 1988; Com. 8/03731K

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§ The yield is based on the acylated phosphorane.