A Novel Kinetic Deprotonation at a Vinylic Carbon in a Pyrone Ring

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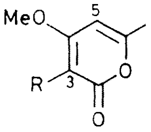
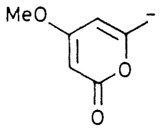
Summary Treatment of 4-methoxy-α-pyrones with butyllithium or lithium di-isopropylamide causes rapid deprotonation at C(3) of the pyrone ring to give moderately stable vinylic carbanions.

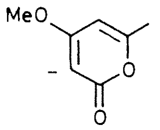
The methyl ether (**1**) of triacetic lactone is a versatile polyketide synthon because of its ability to react regiospecifically, both as an electrophile at C(2)[1] or C(4)[2] and as a nucleophile at C(7), in a condensation reaction with aldehydes catalysed by base (methoxide).[3] The latter reaction is presumably initiated by deprotonation of C(7) to give the carbanion (**4**) in which the negative charge is conjugated with the carbonyl group through the π-system of the pyrone ring. With the aim of achieving greater control over these various reactions we have studied the behaviour of (**1**) towards strong bases, with surprising results. Thus, we found that the kinetically favoured site of deprotonation is not the C-methyl group but C(3), one of the sp² carbons of the pyrone ring. Furthermore, the deprotonation is extraordinarily rapid and competes with nucleophilic attack even when the reagent is a carbanion (BuLi).



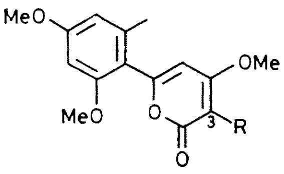
(1) R = H
(2) R = D
(3) R = $SiMe_3$



(4)



(5)



(6) R = H
(7) R = D

Reaction of (**1**) with lithium di-isopropylamide in tetrahydrofuran (THF) at −78 °C followed by quenching with D_2O yields a monodeuterio-derivative (72%; 95% deuterium by ^1H n.m.r.). This retained the H(5) resonance, δ 5·7 (br m), of (**1**) but not the H(3) resonance, δ 5·35(d), and was therefore assigned structure (**2**). No deuterium was detected at C(7) and the non-involvement of this centre in the proton transfer was confirmed by repeating the sequence on (**2**) but with an H_2O work-up; the recovered triacetic lactone methyl ether was devoid of deuterium within the limits of detection by ^1H n.m.r. spectroscopy. The carbanion (**5**) is therefore presumed to be formed as an intermediate by direct reaction of the base at the C(3) proton. Surprisingly, this deprotonation is also effected by BuLi at −78 °C in THF; quenching the solution after as little as 1 min with D_2O results in the formation of (**2**) (40% unoptimised; 95% deuterium) and again no deuterium was detected at C(7).

Another example of this unexpected type of carbanion formation was found when the 6-arylpyrone (**6**) was allowed to react with lithium di-isopropylamide at −78 °C in THF followed by work-up with D_2O. Again C(3) of the pyrone ring was deuteriated (95%) to give (**7**) in preference to deuteriation either in the 1,3-dimethoxybenzene ring or at the aryl-substituted methyl group. We have also observed exchange of the C(3) hydrogen in 4-methoxy-6-phenylpyran-2-one.

The reason for the facility of deprotonation at C(3) in these pyrones is not clear. The flanking carbonyl and methoxy-groups could have a favourable influence over both the position of lithiation and the stability of the resulting anion. The pyrone ring system itself may play a vital role.† The carbanion (**5**) is moderately stable at −78 °C but no initial pyrone or characterisable reaction product is recovered if it is allowed to warm to 0 °C prior to work-up.

The anion (**5**) generated with either BuLi or lithium di-isopropylamide reacts readily with Me_3SiCl at −78 °C to give (**3**) (35—45% unoptimised yield); the resonance for H(5) appears at δ 5·8 (br m) and ν_{max} (CO) is at 1695 cm⁻¹. The reaction is necessarily regiospecific and therefore there is synthetic potential in this method of generating nucleophilic reactivity at C(3) which merits further investigation. The alternative strategy of using the ambident anion derived from triacetic lactone itself suffers the disadvantage that reaction at oxygen can compete with reaction at C(3).[3]

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† Dr. F. M. Dean and coworkers at Liverpool have discovered similar novel lithiations at sp² sites in other oxygen heterocyclic systems. We thank Dr. Dean for exchange of information prior to publication.

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