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Conjugate Addition to Thiin-4-ones; A Novel Route to Thiathromboxane Analogues

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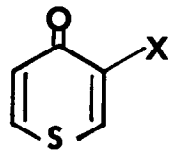
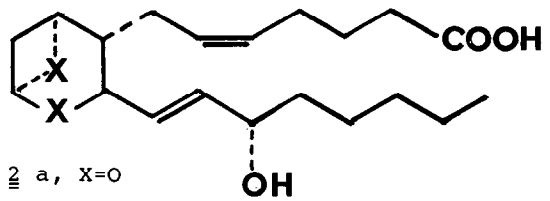
Summary: In contrast to thiin-4-one, its 3-carbomethoxy-derivative undergoes efficient conjugate addition with organocuprate reagents; this procedure has been utilised as the key step in the synthesis of novel thiathromboxane analogues and in an extremely short formal synthesis of dithiathromboxane A_2.

A wide range of α,β-unsaturated substrates undergo efficient organocuprate conjugate addition reactions[1] but, to our knowledge, such reactions have not been reported with thiin-4-one (4H-thiopyran-4-one) 1a or its derivatives.[2,3] We decided to investigate these reactions because, if successful, they could be employed to prepare a range of synthetically-valuable substituted dihydrothiin-4-ones[4] and, by subsequent dehydrogenation, the corresponding substituted thiin-4-ones.[5] In addition, this procedure also seemed well-suited[6] to the synthesis of sulphur-containing analogues of Thromboxane A_2 (2a), e.g. dithiathromboxane A_2 (2b).[7] Such compounds are of current interest in biological and pharmaceutical studies.[8]



1 a, X=H
b, X=CO_2Me



2 a, X=O
b, X=S

Unfortunately, thiin-4-one (1a)[3] failed to react with a variety of organocopper and organocuprate reagents. However, we found that conjugate

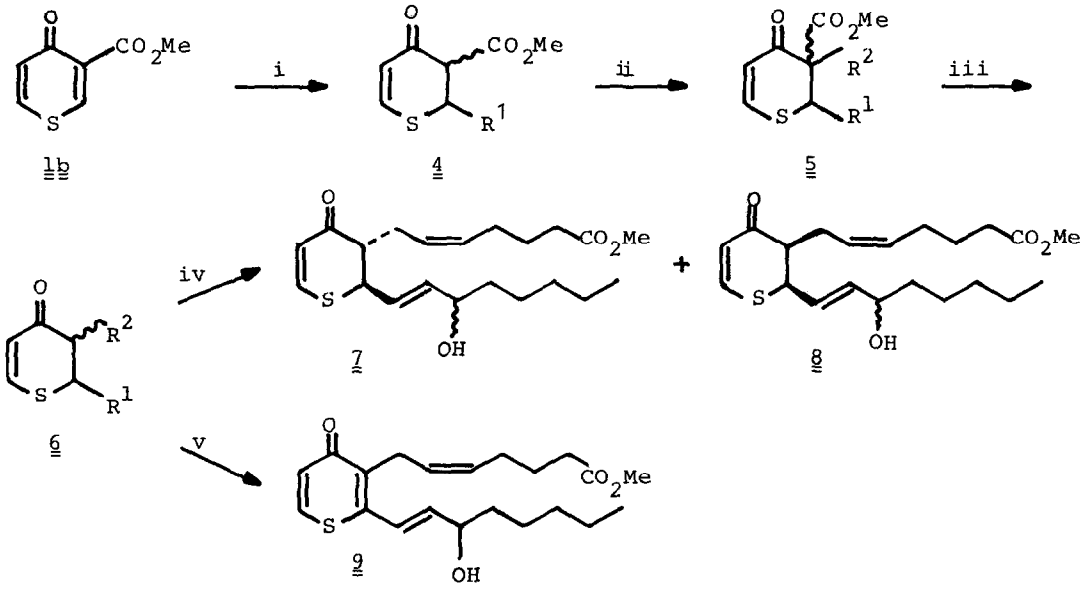
addition reactions could be carried out if the corresponding 3-carbomethoxy-derivative (1b)[9] was treated with lithium organocuprates in ether. Details of the scope and limitations of this reaction will be presented in a full paper; this letter illustrates the application of the methodology (i) to the synthesis of the novel thiathromboxane analogues 7, 8 and 9 and (ii) to an extremely short, formal synthesis of dithiathromboxane A_2 (2b), a compound with potent biological properties.[7]

The studies leading to the novel thiathromboxane analogues 7-9 are shown in Scheme 1. Treatment of thiopyran-4-one 1b with cuprate 3 gave β-keto ester 4[10] (82%) which was alkylated using NaH/THF followed by methyl 7-bromohept-5Z-enoate to give compound 5 in 62% yield. Demethoxycarbonylation of ester 5 proved somewhat troublesome but it was found that the transformation could be effected efficiently using magnesium chloride in aqueous dimethylformamide.[11] The required ketone 6 was obtained as a cis-trans mixture (ca. 40:60) in 69% yield along with a mixture of the corresponding alcohols 7 and 8 (16%). Desilylation (HF/CH_3CN) of 6 produced alcohols 7 and 8 in 92% yield and the two isomeric thiathromboxane analogues were separated using preparative centrifugal chromatography. The 15-diastereomers of both 7 and 8 were chromatographically identical in a number of solvent systems.

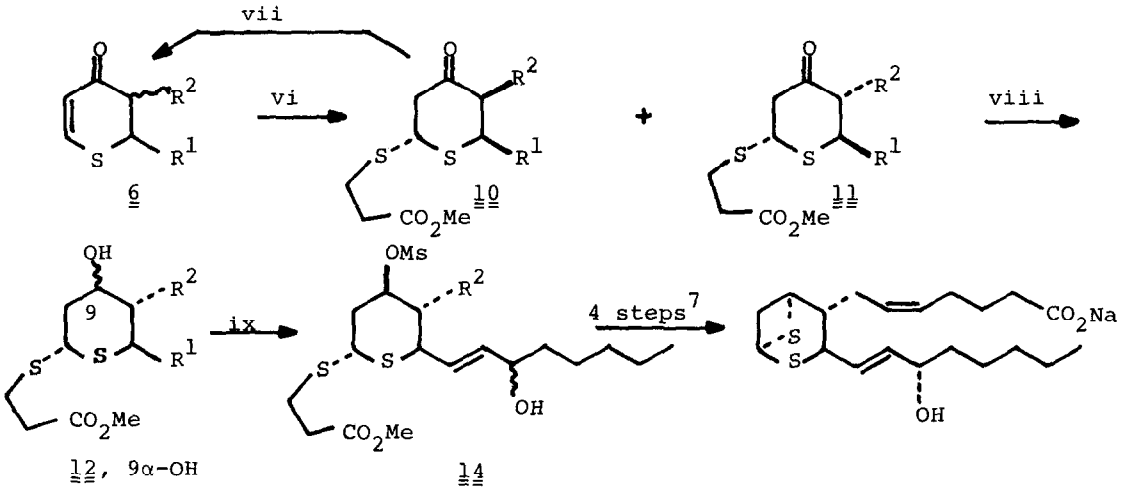
The thiopyranone thromboxane analogue 9 was also obtained from ketone 6 in 74% overall yield by dehydrogenation using o-chloranil followed by hydrofluoric acid desilylation.

The unsaturated thianone 6 was also employed to prepare a key precursor of dithiathromboxane A_2 (Scheme 2). Michael addition of methyl 3-mercaptopropanoate gave a chromatographically-separable mixture of sulphide 11 and its 8,12-cis-epimer 10. Compound 10 was converted back to the mixture of enones 6 using sodium methoxide and the whole cycle repeated twice more to give a combined yield of 78% of the required epimer 11, the stereochemical assignments being supported by 400 MHz ^{1}H-n.m.r. We did not observe any of the corresponding 11β-adduct although this may have been present as a minor, co-chromatographing component. The stereoselective formation of the 11α-adduct 11 during thiol addition is to be expected from a consideration of the anomeric effect.[7,12] Reduction of ketone 11 with sodium borohydride gave the required 9β-alcohol 13 (31%) along with the 9α-epimer 12 (63%) which could be recycled by oxidation back to ketone 11 using pyridinium dichromate. Treatment of alcohol 13 with methanesulphonyl chloride and triethylamine produced mesylate 14 in 76% yield. It should be noted that desilylation took place during the work-up of the mesylation reaction. The ^{1}H-n.m.r. and i.r. spectra of mesylate 14 were essentially identical to those of an authentic sample.[7] Mesylate 14 can be converted

SCHEME 1 R^1=E-CH=CH.CH(OSiMe$_2$Bu^t)C$_5$H$_{11}$ R^2=Z-CH$_2$CH=CH(CH$_2$)$_3$CO$_2$Me



SCHEME 2



REAGENTS (i) $R^1{}_2CuLi$ (3) (ii) NaH,THF,R^2I (iii) $MgCl_2$,DMF-H_2O (iv) HF,CH_3CN (v) o-chloranil then HF,CH_3CN (vi) $HSCH_2CH_2CO_2Me$, $^iPr_2NEt$ (vii) NaOMe (viii) $NaBH_4$ (ix) CH_3SO_2Cl

into the sodium salt of dithiathromboxane A_2 (2b) in 4 steps using literature procedures.[7] Overall, this methodology enables dithiathromboxane A_2 to be prepared in 10 steps from readily-available starting materials, under half the number used by the Ono group in their pioneering first synthesis.[7]

The biological properties of thiathromboxane analogues 7, 8 and 9 are currently being evaluated.

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