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KETO-ALKYNE CYCLISATION REACTIONS: HETEROCYCLIC PROSTACYCLIN ANALOGUES

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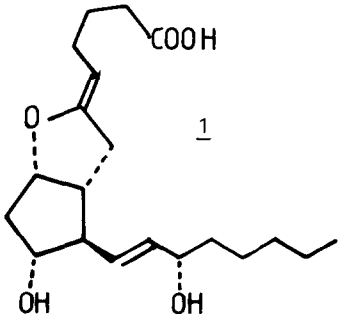
Summary: Simple furan, thiophene and pyrrole analogues of prostacyclin have been prepared from readily-available 4-alkynyl ketones; the cyclohexa[b]-furano-prostacyclin analogue 3 has also been synthesised using the keto-alkyne cyclisation procedure.

There has been a considerable amount of recent interest in the synthesis of stable, biologically-active analogues of prostacyclin 1.[1] Hydrolytic stability has been conferred in a number of ways, one of the most attractive from the chemical point of view being the transformation of the labile methylenetetrahydrofuran moiety into an aromatic heterocycle.[2,3] We decided to synthesise a range of heterocyclic prostacyclin analogues for biological testing and here describe the development of cyclisation procedures for the preparation of the simple cyclopenta- and cyclohexa-annelated heterocyclic systems 2 and the application of this methodology to the synthesis of the cyclohexa[b]furano-prostacyclin analogue 3. A cyclopenta[b]furano-prostacyclin analogue has recently been prepared using an entirely different synthetic strategy.[2d]



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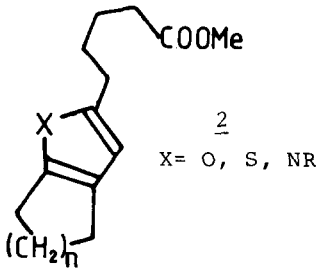
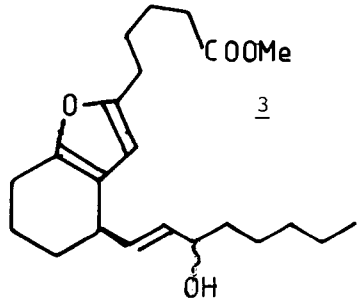


2

X= O, S, NR



3

Our aim was to prepare heterocycles 2 from common precursors and we decided to investigate the suitability of the 4-alkynyl ketone cyclisation reactions, first described by Schulte and Reisch[4,5,6] and subsequently applied to the synthesis of monocyclic furan-based prostaglandin analogues.[7]

The 4-alkynyl ketones 4a and 4b were chosen for the initial studies (Scheme 1) and readily obtained by literature procedures.[8] Furan formation was studied first.[4,7] Treatment of ketone 4a with a catalytic amount of p-toluenesulphonic acid (pTSA) and acetic anhydride (0.1 equivalents of each) in refluxing toluene for 24 hours gave the required furan 5a in 45% yield.[9] Unfortunately, this methodology could not be employed for the preparation of the corresponding cyclopenta[b]furan 5b. Treatment of ketone 4b with pTSA/acetic anhydride, or with mercury(II),[10] palladium(0), palladium(II) or rhodium(I) catalysts failed to produce furan 5b. The difficulties associated with the synthesis of the 4,5-dihydro-4H-cyclopenta[b]furan system are well recognised.[2d,11]

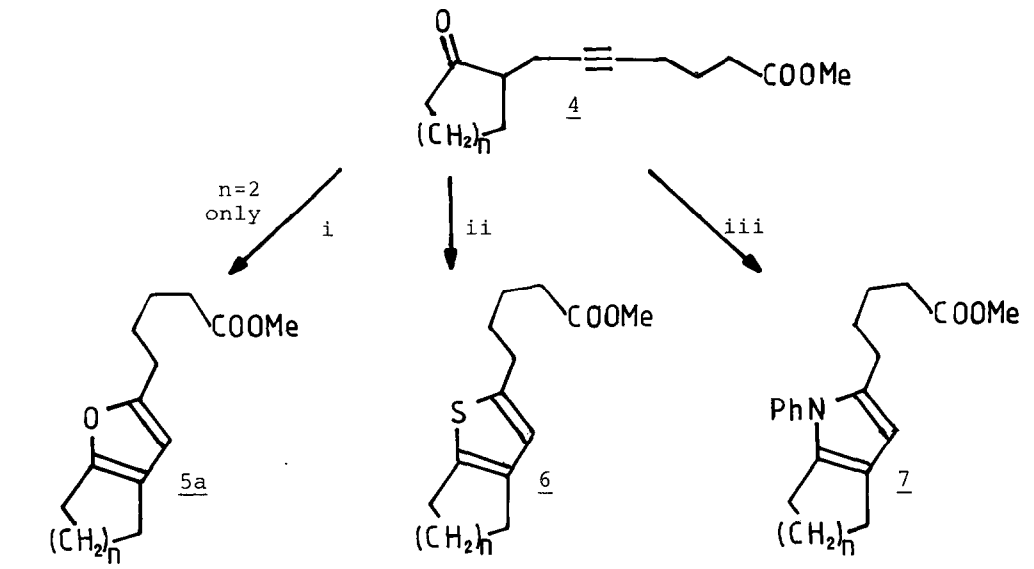
The conversion of ketones 4 into thiophenes 6 with H_2S/HCl[5] proved to be relatively straightforward. The cyclisation to produce the cyclohexa-compound 6a proceeded efficiently at room temperature but elevated temperatures were required to obtain 6b. The latter reaction could be carried out at room temperature, however, if mercury(II) trifluoroacetate was added to activate the alkyne to nucleophilic attack. This is the first time that a cyclopenta[b]thiophene has been prepared in synthetically useful quantities by keto-alkyne cyclisation.[5]

The preparation of N-phenyl pyrroles 7 was of interest in view of the leukotriene antagonist properties shown by related compounds.[2c] Annelated pyrroles have not previously been prepared from keto-alkynes but we found that treatment of compounds 4 with aniline, pyridine hydrochloride and mercury(II) trifluoroacetate produced the required heterocycles 7. In contrast to related literature procedures,[6] the cyclisation conditions were extremely mild although the yields of these reactions were rather disappointing.

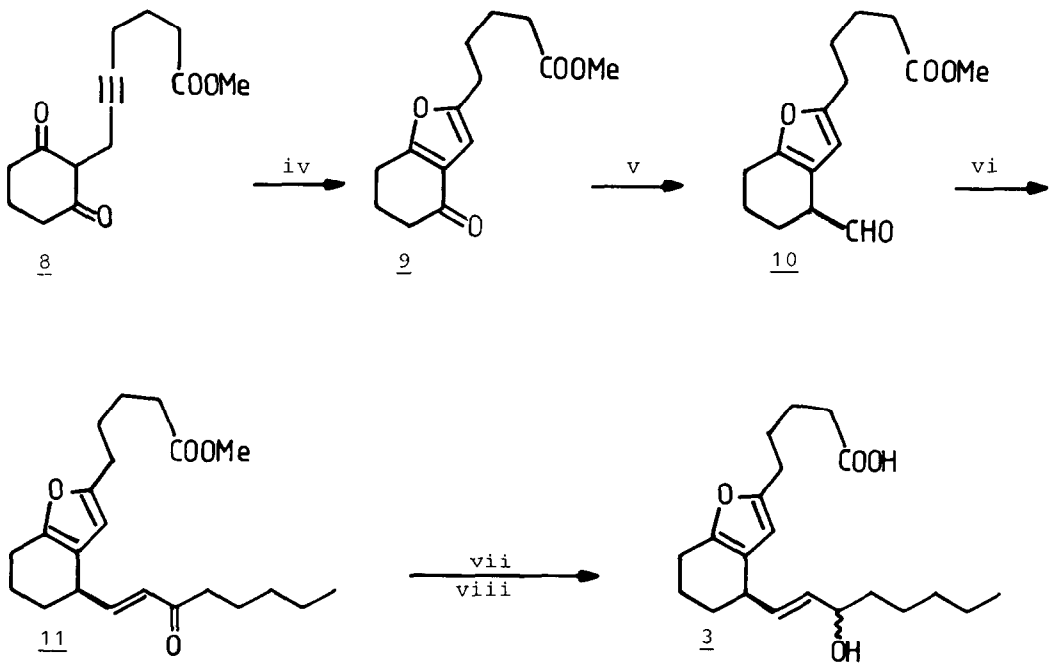
The keto-alkyne cyclisation procedure was then applied to the synthesis of the more elaborate cyclohexa[b]furano-prostacyclin analogue 3 (Scheme 2). The known 2-alkylated cyclohexanedione 8[12] readily cyclised[4,13] to give the 4-keto-cyclohexa[b]furan 9, the reaction being complete in two hours and giving an 80% yield. Ketone 9 was converted into aldehyde 10 using methoxymethylene-triphenylphosphorane followed by unmasking of the resulting enol ether.[14] The second stage proved troublesome although it was eventually found that trimethylsilyl iodide[15] gave the required transformation, aldehyde 10 being obtained in 28% overall yield. The synthesis was completed by Wittig condensation to give enone 11 (83%) followed by reduction (83%) and saponification (72%). The C-15 diastereomers of 3 (and of the corresponding methyl ester) were chromatographically identical in a range of solvents. This sequence is extremely short, only five/six steps from the known and readily-available alkylated dione 8.

The biological screening of compounds 3, 5a, 6 and 7 is currently being carried out.[16]

SCHEME 1 (a, n=2; b, n=1)



SCHEME 2



Reagents: (i) pTSA, Ac_2O, Δ (5a, 45%). (ii) H_2S, HCl (6a, 80%; 6b, 72%). (iii) $PhNH_2$, Py.HCl, $Hg(OCOCF_3)_2$ (7a, 56%; 7b, 23%). (iv) pTSA, Ac_2O, toluene (80%). (v) $Ph_3P{=}CHOMe$ then Me_3SiI (28%). (vi) $(EtO)_2P(O)CH(Na)-COC_5H_{11}$ (83%). (vii) $NaBH_4$ (83%). (viii) NaOH (72%).

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