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A Hetero Diels-Alder Approach To Novel Thiopyran Analogues Of Aprikalim, A Potassium Channel Activator

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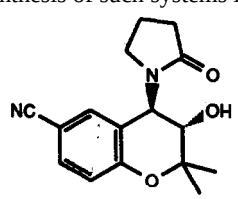
Key Words: Aprikalim; Hetero Diels-Alder; Potassium Channel Activator. Thiocarbonyl; Dihydrothiopyran.

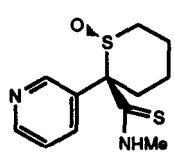
Abstract: a *-Thioketo-ester* (6) *derived from Bunte salt (5) has been shown to undergo a hetero Diels-Alder reaction with a variety of dienes to form the basis of a concise synthesis of dihydrothiopyran analogues of the potassium channel* activator *aprikalim.*

Potassium channel activators represent a new class of drug which appear to exert their smooth muscle relaxant activity through the opening of ATP-sensitive potassium channels and consequent **hyperpolarisation.**[1] Drugs **operating** by this **mec**hanism have potential in the treatment of a number of disorders including asthma, hypertension and angina pectoris. The **identification** of **cromakalim (1),** in particular, has **provided** an immense impetus to delineate the structural **features** required for **activity.**[2] While the majority of synthetic effort has **centred** on cromakalim and its **analogues**[2] relatively little work has appeared on **aprikalim (2),** a structurally distinct but **pharmacologically** similar potassium channel activator.3 A versatile synthesis of such systems is described.



(+-)

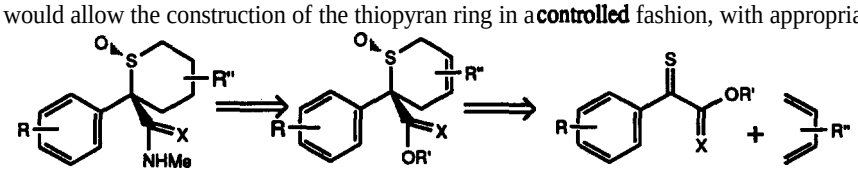
(1)



(1 R, 2R)

(2)

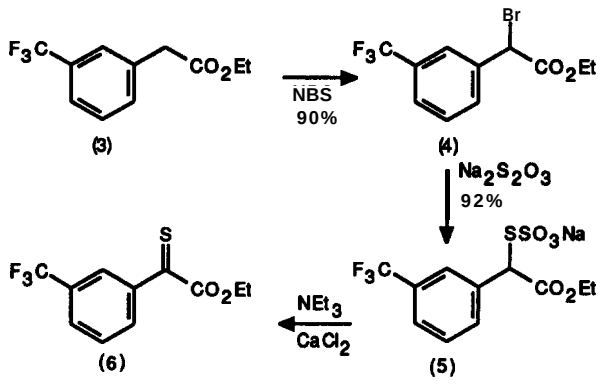
In order to investigate the structural requirements for activity in aprikahm a flexible route for the synthesis of **analogues** was required and in particular one which addressed the problem of generating the **quaternary** centre adjacent to the sulphoxide. **Retrosynthetic** analysis (Scheme 1) suggested a possible approach via hetero Diels-Alder reactions of **α-thioketo-esters** with suitably substituted dienes. Such an approach would allow the construction of the thiopyran ring in a **controlled** fashion, with appropriate



SCHEME 1

substituents derived from the diene component.

While thioketones of various types am readily available and are well documented as effective dienophiles,[4] α-thioketo-esters constitute a little investigated class. This is possibly due to the difficulty of selectively generating *the thioketone in the* presence of the ester. Adapting the thioaldehyde synthesis developed by Kirby5 has allowed the preparation of the key intermediate (6) (Scheme 2) required to investigate the hetero Diels-Alder approach. The 3-(trifluoromethyl)phenyl substituent in (6) was chosen for ease of synthesis and has been shown to be an effective replacement for the 3-pyridyl group in aprikalim.[6]



SCHEME2

Thus, benxylic bromination of the 3-(trifluoromethyl)phenyl acetate (3) followed by displacement of the bromide with sodium thiosulphate in aqueous ethanol yielded the Bunte salt(5)[7] in 83% overall yield5. Initial attempts at isolating the key a-thioketoester (6) by treating this salt, (5), with potassium t-butoxide or triethylamine in the presence of calcium chloride led only to complex mixtures. suggesting that if (6) was formed it was prone to rapid decomposition under the conditions employed. The feasibility of trapping (6) *in situ with* a suitable diene in the hope that cycloaddition would compete favourably with the decomposition pathway was therefore investigated In this manner successful cycloaddition was shown to proceed for a series of dienes (Table 1).

The conditions adopted in the first instance utiliscd potassium t-butoxide as the base and DMF as solvent. Under this regimen a modest yield of the dihydrothiopyran (7)[8] was isolated on trapping with 2,3-dimethylbuta-1.3-d (Entry 1, Table 1). However, upon similar treatment cyclopentadiene failed to provide any cycloaddition product, possibly due to the formation of the cyclopentadienyl anion. When the base was altered to triethylamine in ethanol and calcium chloride was added to precipitate the sulphite by-product5 a good yield of the [4 + 2] adduct (9) was observed (Entry 3, Table 1). These conditions were generally the most favourable and both 1,3-butadiene and the 1,3-cyclohexadiene adducts could be isolated in good yields (Entries 2 and 4, Table 1). The Diels-Alder reactions of cyclopentadiene and 1,3-cyclohexadiene with (6) proceeded without any preference for the endo over the exo isomer.

The only unsymmetrically substituted diene reacted with (6) was 2-(trimethylsilyloxy)buta-1,3-diene. Under the usual protic conditions employed substantial cleavage of the silyl group was observed, however, the Bunte salt (5) was, found to be soluble in most organic solvents and ether was a suitable alternative to ethanol in this instance. In contrast to the regiochemistry observed with 2-(silyloxy)buta-1,3-dienes and carbonyl dienophiles,[9] the reverse ngioisomer (11) was the exclusive cycloaddition product isolated (Entry 5, Table 1). This observation is in accord with those reported by Vedejs for a series of Diels-Alder reactions with thioaldehydes, ZCH=S, in which it was found that the regiochemistry of cycloaddition with electron-rich dienes was reversed for Z = ester, acyl, CN (electron withdrawing) compared with Z =

alkyl (electron donating).[10] Molecular orbital calculations confirmed that when Z is strongly electron withdrawing the sulphur of the thiocarbonyl is more electrophilic than the carbon terminus, due to an enlargement of the LUMO coefficient, while electron donors enhance the greater electrophilicity of the thiocarbonyl carbon atom.[10]

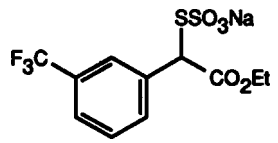
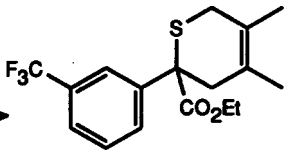
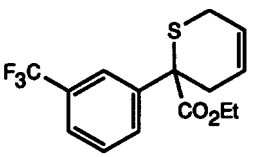
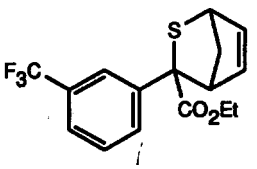
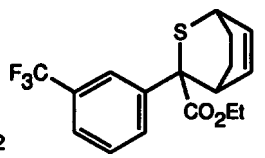
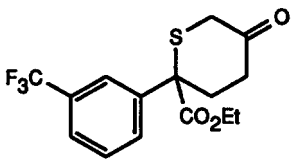
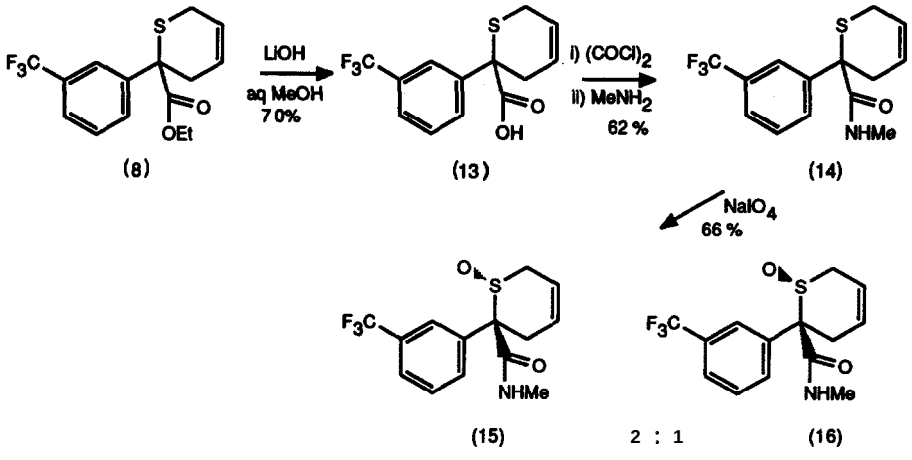
ENTRY	SUBSTRATE	PRODUCT	
1	 (5)	 35%	(7)
2		 65%	(8)
		 75%, 1 : 1 ENDO/EXO	(9)
		 74% 1 : 1 ENDO/EXO	(10)
		 39 %	(11)

TABLE 1

The Diels-Alder adducts described in Table 1 contain the framework of aprikalim, requiring only minimal manipulation to convert the ester function into an amide. This is exemplified with the butadiene derived tetrahydrothiopyran (8), (Scheme 3) where hydrolysis of the ester (8) followed by conversion into the N-methyl amide (14) via the acid chloride was achieved in good yield Finally, oxidation with sodium periodate proceeded to yield predominantly one isomer (15), assigned the *trans* stereochemistry on the basis of similar oxidations leading to aprikalim.[3]



SCHEME 3

A novel strategy for the synthesis of aprikalim analogues has been developed which should allow rapid access to compounds having functionalised tetrahydrothiopyran rings. The aromatic ring substituents can also be varied by chosing appropriate arylacetates in place of (3), so allowing a detailed structure-activity relationship profile to be built up.

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8. All compounds with chiral centers are racemates of which one isomer is depicted.
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