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Formation of a Novel Thiopyranoindole Ring System

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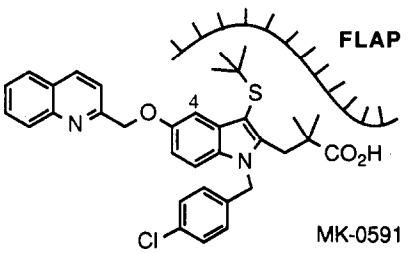
Abstract: The novel thiopyran[2,3,4-c,d]indole ring system (e.g. 3) has been prepared from a substituted indole by intramolecular cyclisation of a t-BuS group onto an allyl substituent. The reaction occurs in high yield under the influence of protic acids, Lewis acids or electrophiles (Br_2, I_2, $Hg(OAc)_2$)

The use of a t-butyl group as a labile protecting group for sulfur has recently been demonstrated in the preparation of cyclic disulfides[1] and benzo[c]thiophene derivatives[2]. In this Letter, we report the preparation of functionalised cyclic sulfides appended to an indole nucleus by the reaction between a t-butylsulfide and a proximate double bond. This finding occurred during work designed to delineate the structural features required in a series of novel 5-lipoxygenase biosynthesis inhibitors (exemplified by MK-0591[3]) where we had occasion to examine the effect of a lipophilic C-4 substituent on the indole ring system. The hypothesis being that the t-BuS group occupies a hydrophobic pocket on the 5-lipoxygenase activating protein (FLAP)[4] and that this binding site may also be accessible from a substituent at the C-4 position on the indole ring (Figure 1).

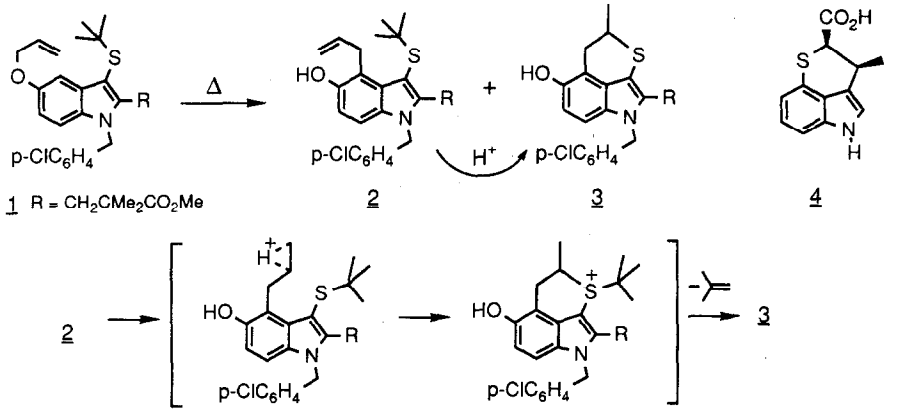
Figure 1



MK-0591

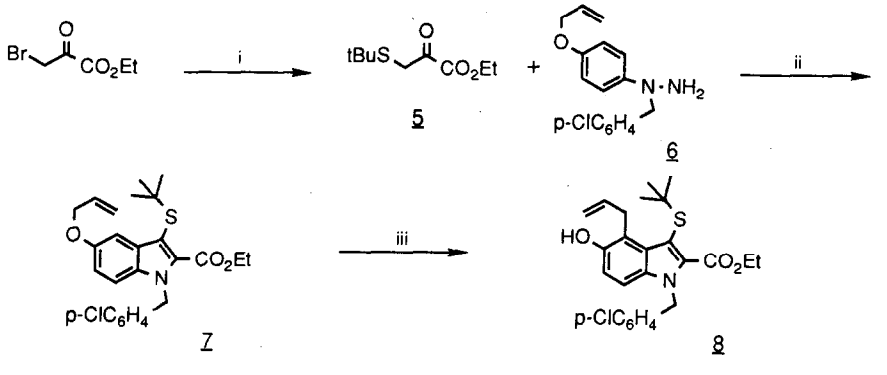
It is well known that the Claisen rearrangement of indolic C-5 allylethers results in the exclusive formation of a C-4 allyl substituted indole[5]. Thus the allyl ether 1[6] smoothly rearranges upon heating to 150°C in 1,2-dichlorobenzene to give the desired compound 2 in 60% yield (Scheme 1). In addition to this compound a minor, more polar, product was isolated which was not the C-6 allyl isomer. In fact, ^{1}H NMR analysis showed the loss of the t-butyl group as well as the vinyl protons of the allyl group. In their place were new peaks including signals corresponding to the protons for a -CH_2CH(Me)- system i.e. δ (d^6 acetone, 300 MHz): 1.43 (3H, d, J=6.7 Hz), 2.71 (1H, dd, J=15.9, 9.3 Hz), 3.28 (1H, m) and 3.35 (1H, dd, J=15.9, 3.1 Hz). Moreover, the mass spectrum showed a molecular ion at m/e 443 and these facts together indicate that the compound has the thiopyrano[2,3,4-c,d]indole structure 3. Presumably, the sulfur atom in 2 attacks the protonated vinyl group and cyclisation occurs to form a sulfonium ion intermediate[7] which then eliminates isobutylene[8]. Indeed, we found that the C-4 allylindole 2 could be efficiently converted into the tricyclic system 3 by treatment of 2 in hot 1,2-dichlorobenzene containing a catalytic amount of p-TSA. This particular ring system has not been previously described although a similar isomeric ring system has been identified in the antibiotic chuangxinmycin 4.[9]

Scheme 1



To examine the parameters governing this interesting reaction, we chose to investigate a structurally simpler system which is more readily accessible (Scheme 2). Ethyl bromopyruvate was condensed with t-butylthiol and Et_3N in THF and the crude product, 5, underwent a Fischer condensation with the hydrazine 6 to provide the indole 7 in 75% yield based on the hydrazine. Claisen rearrangement of 7, in refluxing 1,2-dichlorobenzene containing a trace of K_2CO_3 (to inhibit *in situ* cyclisation to 9), gave only the allylindole 8 in 70% yield after recrystallisation, m.p. 137-139°C. The conversion of 8 to 9(X=H) (Scheme 3) occurs in the presence of p-TSA in 1,2-dichlorobenzene, toluene or CH_2Cl_2 but not in acetic acid. In all cases minor amounts of the ether 10(X=H) were also isolated. Of these solvents the most efficient appeared to be CH_2Cl_2 and so this solvent was used for further studies comparing the effect of different acid catalysts (see Table). Cyclisations were also studied using various electrophiles.

Scheme 2



Reagents: (i) tBuSH/Et_3N/THF; (ii) HOAc/toluene/NaOAc,80°C; (iii)1,2-$Cl_2C_6H_4$/K_2CO_3,150°C.

Scheme 3

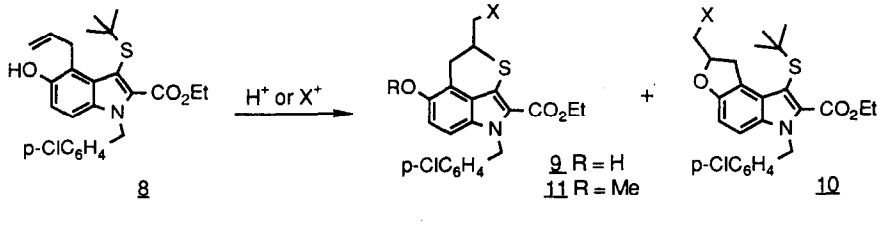


Table Cyclisation of 8 → 9 in CH_2Cl_2

Entry	Acid	no.equiv.	Temp.	Time	Yield (of 9)
1	p-TSA	1	RT	24 hr	74%
2	p-TSA	14	RT	1 hr	71%
3	(+)-CSA	10	50°C	30 hr	85%
4	TFA	30	RT	24 hr	96%
5	conc.HCl	3 drops	RT	3 days	93%
6	$TiCl_4$	1	RT	30 hr	~5%
7	$TiCl_4$	5	RT	5 min	71%
8	$Ti(iPrO)_2Cl_2$	10	RT	2 days	52%
9	$Ti(iPrO)_4$	10	40°C	2 days	no rxn
10	$BF_3.OEt_2$	10	RT	1.5 hr	64%
11	$AlCl_3$	0.1	RT	15 min	decompn.

(a) Cyclisations using protic acids

At room temperature (RT) using p-TSA the reaction is slow and ≥1 equivalent is required for the reaction to go to completion. Using (+)-CSA did not appear to be as effective; reactions did not occur at RT but required heating to 50°C but the reaction did appear to give less by-product 10(X=H). With TFA (30 equivalents) the reaction proceeded smoothly over a 24-hour period to give the tricyclic indole in 96% yield. Lastly, the use of conc. HCl also proved effective, giving the desired compound in 93% yield although the reaction is considerably slower.

(b) Cyclisations using Lewis acids

The cyclisation 8 → 9 in CH_2Cl_2 at RT using a catalytic amount of $TiCl_4$ (0.1 equivalent) gave no reaction while 1 equivalent gave a sluggish reaction and a low yield of product. But in the presence of 5 equivalents of $TiCl_4$, a 71% yield of product was obtained after 5 minutes. As shown in the Table, $Ti(iPrO)_2Cl_2$ is less effective than $TiCl_4$ while $Ti(iPrO)_4$ fails altogether. This indicates that the effectiveness of the Lewis acid increases with its Lewis acidity. The use of $BF_3.OEt_2$ requires a considerably longer time for complete reaction than $TiCl_4$ while $AlCl_3$, even in catalytic amounts, causes complete destruction of the starting material.

(c) Cyclisation with other electrophiles

The reaction of the allylindole 8 with Br_2, I_2 and pyridinium bromide perbromide are quite vigorous; they proceed in a matter of minutes at -60°C in $CHCl_3$ to give the functionalised products 9(X=Br or I) in 82-87% yield. In contrast, the reaction with $Hg(OAc)_2$ in THF gave the cyclic ether 10(X=HgCl) as the sole product in 80% isolated yield. Blocking of the phenol group of 8 by formation of the methyl ether and repeating the reaction with $Hg(OAc)_2$ did allow the desired cyclisation to 11(X=HgCl; 80%) to take place.

In conclusion, the intramolecular S-alkylation/dealkylation of 3-t-butylthio-4-allylindoles provides a facile route to the novel thiopyrano[2,3,4-c,d]indole nucleus. We are currently investigating extensions of this methodology to the preparation of other cyclic sulfides as well as the use of thiopyrano[2,3,4-c,d]indoles in our leukotriene biosynthesis inhibitor program.

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References and Notes

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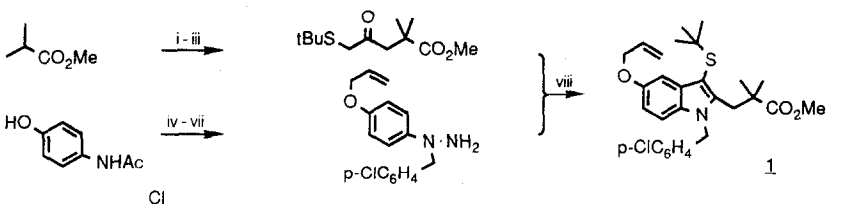
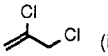
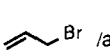
6. Preparation of 1.



Reagents: (i)LDA/THF/  (ii) Br_2/MeOH/H_2O (iii) tBuSH/Et_3N/THF (iv) K_2CO_3/  /acetone (v) KOH/EtOH then HCl (vi) HCl/$NaNO_2$/H_2O then $Na_2S_2O_4$/H_2O/Et_2O/NaOH (vii) 4-$ClC_6H_4CH_2Cl$/Et_3N/ toluene (viii) toluene/HOAc/NaOAc

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