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CYCLOOXYGENASE AND 5-LIPOXYGENASE INHIBITORY ACTIVITY OF 2,6 DI-*t*-BUTYLPHENOLS LINKED BY A SULFUR ATOM TO 1,3,4-THIADIAZOLES AND 1,3,4-OXADIAZOLES

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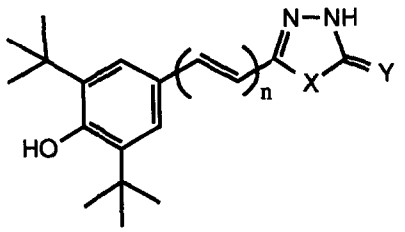
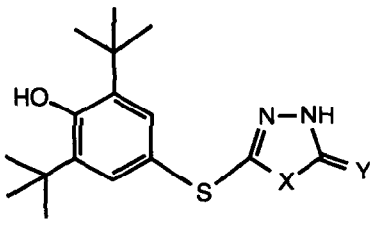
Abstract: The preparation of a series of 1,3,4-thiadiazoles and 1,3,4-oxadiazoles linked by a thioether to 2,6-di-t-butylphenol and the inhibition of cyclooxygenase (CO) and 5-lipoxygenase (5-LO) by these compounds is discussed.

Non-steroidal anti-inflammatory drugs (NSAIDs)[1] reduce the pain and swelling associated with arthritis by blocking the metabolism of arachidonic acid by the enzyme cyclooxygenase (CO) and thereby the production of prostaglandins. An undesirable side effect of the chronic use of NSAIDs is the formation of gastric ulcers[2]. This adverse event may be attenuated in the presence of an inhibitor of 5-lipoxygenase (5-LO). Dual inhibitors of CO and 5-LO are currently under investigation for the treatment of arthritis[3].

We recently reported the preparation of a series of 5-(3,5-di-*t*-butyl-4-hydroxyphenyl)-1,3,4-thiadiazoles and 1,3,4-oxadiazoles[4]. The two rings were either directly attached or linked by a double bond. Several of these compounds, exemplified by **Ia** and **Ib**, inhibit both CO and 5-LO. We describe here the preparation of a series of related compounds **II**, where a sulfur atom now links the two rings.



Ia : n = 0
Ib : n = 1
X = Y = S

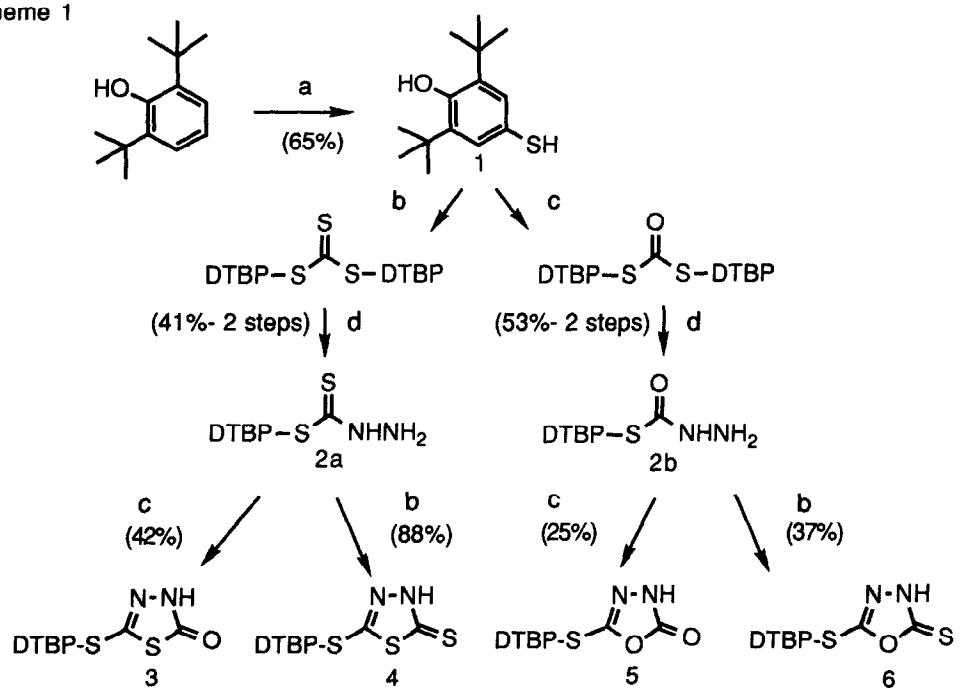


II
X= O, S
Y= O, S, NCN, NH

Two key intermediates to the desired compounds are thiohydrazide 2a and hydrazide 2b. Both are obtained from the known thiophenol 1[5] as depicted in scheme 1. Treatment of

thiohydrazide 2a with phosgene in the presence of Hunig's base provided the 1,3,4-thiadiazol-2-one 3 while thiophosgene provided the corresponding 2-thione analog 4. The same conditions when applied to hydrazide 2b yielded the 1,3,4-oxadiazoles 5 and 6[6].

Scheme 1



DTBP = 3,5-di-*tert*-butyl-4-hydroxyphenyl

a) 1) NH_4SCN / Cl_2 / NH_3 2) Et_3P; b) $CSCl_2$ / i-Pr_2NEt; c)$COCl_2$ / i-Pr_2NEt; d) NH_2NH_2-H_2O

The values obtained for 3, 4, 5 and 6 in an intact RBL-1 cell line assay for the inhibition of 5-LO and CO activity are presented in Table 1[7]. The activity of KME-4, a di-*t*-butyl phenol analog currently under clinical investigation, is provided for reference[8]. The 1,3,4-thiadiazole-2-thione 4 and the 1,3,4-oxadiazole-2-thione 6 were dual inhibitors. Since the corresponding 2-one analogs 3 and 5 were much weaker inhibitors of CO, the acidity of the 2-thione compounds appears to be of major importance. The pKa values for 4 and 6 are 5.8 and 5.2 while the values for 3 and 5 are 8.1 and 7.8.

From our previous work we believed that the exocyclic sulfur atom of 4 could be undesirable due to metabolism at this site[9]. Since the cyanoimino group has been shown to be a bioisosteric replacement for a thione [10] we next targeted analog 9. We envisioned that 9 could be prepared by cyanamide displacement of a leaving group such as a sulfoxide. While the

prerequisite thiomethyl ether analog 7 could be prepared by treating 3 with iodomethane in the presence of base, the alternate route shown in scheme 2, was used. Reaction of 4-bromo-2,6-di-*t*-butylphenol with 5-methylthio-1,3,4-thiadiazole-2-thiol with 1 equivalent of 1,8-diazabicyclo-[5.4.0]undecen-7-ene in DMF gave 7 in good yield. Treatment of 7 with sodium perborate in acetic acid selectively oxidized the methylsulfide group providing 8. Addition of cyanamide to a mixture of 8 and KO-*t*-Bu in *t*-butanol furnished 9. As shown in Table 1, 9 was a dual inhibitor.

To further establish that activity is related to the acidity of the compounds, 10 , which contains a basic heterocycle, was prepared (scheme 2). This 1,3,4-thiadiazol-2-amino analog has a pKa of 11.5 and was inactive against both 5-LO and CO.

This work is being extended to include linkers such as ethers and alkyl groups between the 1,3,4-oxadiazole or 1,3,4-thiadiazole and the di-*t*-butyl phenol. We are also investigating the influence of other heterocyclic rings.

Scheme 2

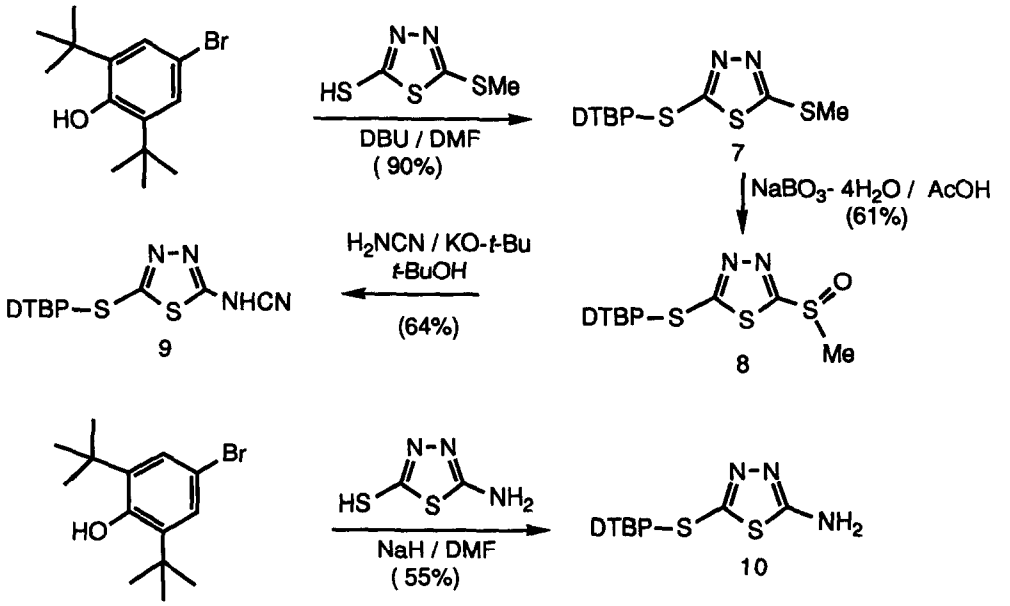
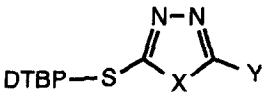


TABLE 1 : INHIBITION of 5-LO and CO



Compound	X	Y	5-LO[a]	CO[a]
Ia	S	SH	2.8	0.8[4]
Ib	S	SH	1.8	5.2[4]
3	S	OH	75% @1.0	N @16[b]
4	S	SH	1.1	3.6
5	O	OH	1.1	N @16[b]
6	O	SH	2.0	1.5
9	S	NHCN	3.1	6.0
10	S	NH_2	N @10[b]	N @10[b]
KME-4			2.5[8]	0.2[8]

a) Data reported as IC_{50} (μM) or the percent inhibition at the stated concentration- 1.0, 10 or 16 μM. IC_{50} calculated as the concentration of test compound causing 50% inhibition of LTB_4 (5-LO) or $PGF_{2\alpha}$ (CO) formation. Standard errors for replicate determinations in these assays average 16% and 11% of the values determined for 5-LO and CO inhibition, respectively. b) N-less than 40% inhibition at the screening dose.

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References and Notes

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