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A NEW SYNTHESIS OF 2-SUBSTITUTED BENZOFURANS AND BENZOTHIOPHENS: NOVEL FRAGMENTATION REACTIONS OF SIMPLE ALKYL GROUPS

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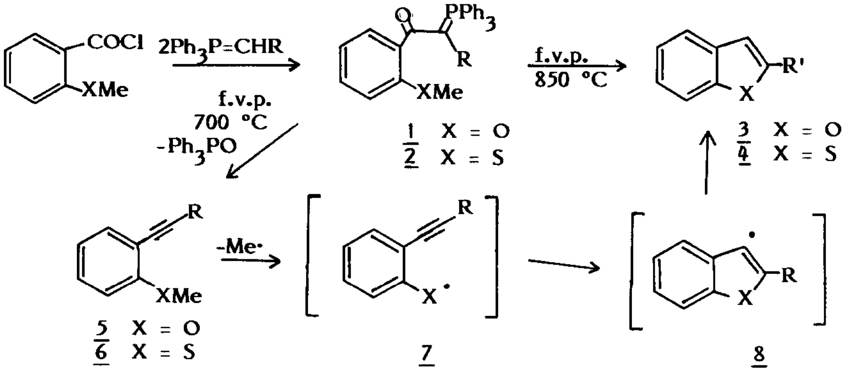
Summary: Flash vacuum pyrolysis of (2-methoxy- and (2-methylthiobenzoyl)alkylidenetriphenylphosphoranes results in loss of Ph_3PO and methyl radical; cyclisation of the resulting radical intermediates leads to benzofurans and benzothiophens in which the 2-substituents have undergone novel fragmentation processes.

A large number of substituted benzofurans possess useful biological activity[1] and their synthesis is of considerable interest[2]. It was recently reported[3] that attempted demethylation of (2-methoxyphenyl)alkynes 5 with lithium iodide in 2,4,6-trimethylpyridine led to cyclisation to produce 2--substituted benzofurans. Our recent work on the pyrolysis of β-oxoalkylidenetriphenylphosphoranes[4] suggested not only that this method could provide convenient access to 5, but that, in view of the known thermal lability of aromatic methoxy groups[5], it might be possible to obtain the benzofuran directly upon pyrolysis of an appropriate β-oxoylide. We now report the success of this strategy which represents a new synthesis of 2-substituted benzofurans and benzothiophens.

The required β-oxoylides 1 and 2[6] were readily obtained as stable solids by reaction of 2-methoxy- or 2-methylthio-benzoyl chloride with two equivalents[7] of Wittig reagent. When these were subjected to flash vacuum pyrolysis (f.v.p.) at 700 °C, triphenylphosphine oxide was cleanly eliminated to give the expected alkynes 5 and 6 in good yield. For both X = O and S, simply raising the furnace temperature to 850 °C led to complete loss of methyl radical to give the desired heterocycles.



For R = Ph this was straightforward and gave (3, R' = Ph) in 80% and (4, R' = Ph) in 53% yield.

For aliphatic groups R, f.v.p. of 1 and 2 at 850 °C again gave 3 and 4 but the cyclisation was now accompanied by a series of remarkable fragmentation processes. In all the cases examined the original R group had been transformed to give products with R' = Me, Et or vinyl (Table).

FLASH VACUUM PYROLYSIS OF YLIDES 1 TO GIVE 3 AND 2 TO GIVE 4

		Yield of 3 (%)				Yield of 4 (%)		
R	R' =	Me	Et	vinyl	R' =	Me	Et	vinyl
Me		8	20	-		14	17	-
Et		-	-	83		-	-	49
Pr^{i}		-	-	60		-	-	24
Pr^{n}		9	52	10		6	45	9
Bu^{n}		4	30	25		10	31	23
Pent^{n}		3	14	21		10	28	14

The formation of 5 and 6 with R unchanged at 700 °C, together with the production of 3 and 4 with R' = Me, Et as stable products at 850 °C, implies that the transformation of the R group occurs at the stage of the radical intermediates 7 and 8. Previous studies on the pyrolysis of related systems have revealed that migration of R in 5 to give a vinylidene carbene is a possibility, leading in the case of 2-alkynylphenols, for example, to 3-substituted benzofurans.[8,9] However this mechanism does not operate here since all the products obtained had a 3-H substituent and the radical reaction appears to be preferred.

The result for (1, R = Me) is in good agreement with the work of Barton[9] who obtained (R = Me and Et) in yields of 29% and 15% respectively by pyrolysis of (5, R = Me) at 700 °C and proposed a radical mechanism to account for incorporation of the methoxy carbon atom to form the ethyl group.

The exclusive formation of vinyl compounds in good yield from 1 and 2 with R = Et, Pr^{i} is readily explained by intramolecular abstraction of a β-hydrogen atom in 8 *via* a five-membered transition state with expulsion of H• or Me•. Increasing the length of the carbon chain in R gave more complex product mixtures but the total yields of products 3 and 4 were still reasonable. For R = Pr^{n} these were the only volatile products and for R = Bu^{n} and Pent^{n} no other benzofurans or benzothiophens were detected. The mechanisms for these interesting and novel transformations of simple alkyl groups are currently under investigation.

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