An Investigation into the Regioselectivity of the Acid Catalysed Claisen Rearrangement of Methyl 4- and 5-Allyloxy-2-hydroxybenzoate and Derivatives

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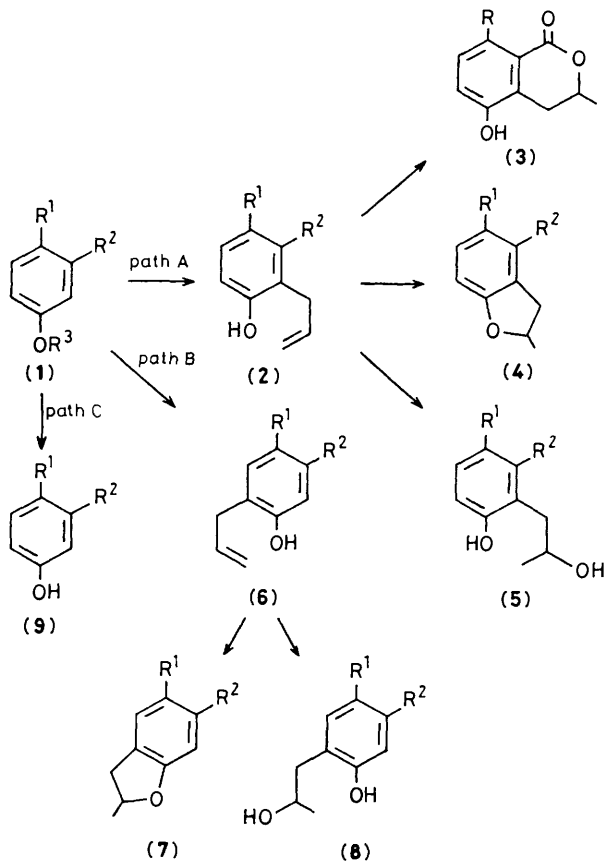
The observed products from the acid catalysed Claisen rearrangement of the methyl esters (**1c—g**) indicate that, unlike the thermal reaction, regiochemical control is independent of internal hydrogen bonding.

Thermal Claisen rearrangements of compounds having the general structure (**1a**) occur with high selectivity for the sterically disfavoured *ortho*-position.[1–4] This selectivity has been explained by transition state stabilisation through biased Kekulé forms due to internal hydrogen bonding.[2–4] Structure (**1b**) in which the hydroxy and carbonyl substituents are inter-



Scheme 1

a; R^1 = OH, R^2 = COR, R^3 = $-CH_2CH{=}CH_2$
b; R^1 = COMe, R^2 = OH, R^3 = $-CH_2C{\equiv}CH$
c; R^1 = OH, R^2 = CO_2Me, R^3 = $-CH_2CH{=}CH_2$
d; R^1 = OAc, R^2 = CO_2Me, R^3 = $-CH_2CH{=}CH_2$
e; R^1 = H, R^2 = CO_2Me, R^3 = $-CH_2CH{=}CH_2$
f; R^1 = OMe, R^2 = CO_2Me, R^3 = $-CH_2CH{=}CH_2$
g; R^1 = CO_2Me, R^2 = OH, R^3 = $-CH_2CH{=}CH_2$

changed but in which a similar hydrogen bonding arrangement in relation to the migrating group still exists likewise shows selectivity for the sterically disfavoured position in thermal rearrangements.[5] Acetylation of the hydroxy group in this system causes randomisation of rearrangement.

Trifluoroacetic acid (TFA) catalysed[6] rearrangements of such substrates show a departure from the results observed in the uncatalysed reaction. Although methyl 5-allyloxy-2-hydroxybenzoate (**1c**) in refluxing TFA follows the expected regiochemical course of rearrangement[7] (Scheme 1, path A) giving (**3c**) and (**4c**)† *via* the intermediate (**2c**), the acetylated derivative (**1d**) does not show any loss in regiospecificity yielding (**3c**) and (**4c**) after work up.‡ The ester (**1e**) lacking the 2-hydroxy substituent, under the same conditions, gives a complex mixture of products from which an initial path A : path B ratio of 2.5 : 1.0 can be deduced. Similarly ester (**1f**) possessing a 2-methoxy group gives a product mixture resulting from a path A : path B ratio of 1.3 : 1.0 which is still significant in view of the opposing steric effects. The results are summarised in Table 1.

In contrast methyl 4-allyloxy-2-hydroxybenzoate (**1g**) under identical acid catalysed conditions gives two isomeric Claisen rearrangement products (Scheme 1, Table 1) in ratio 1.0 : 2.9.

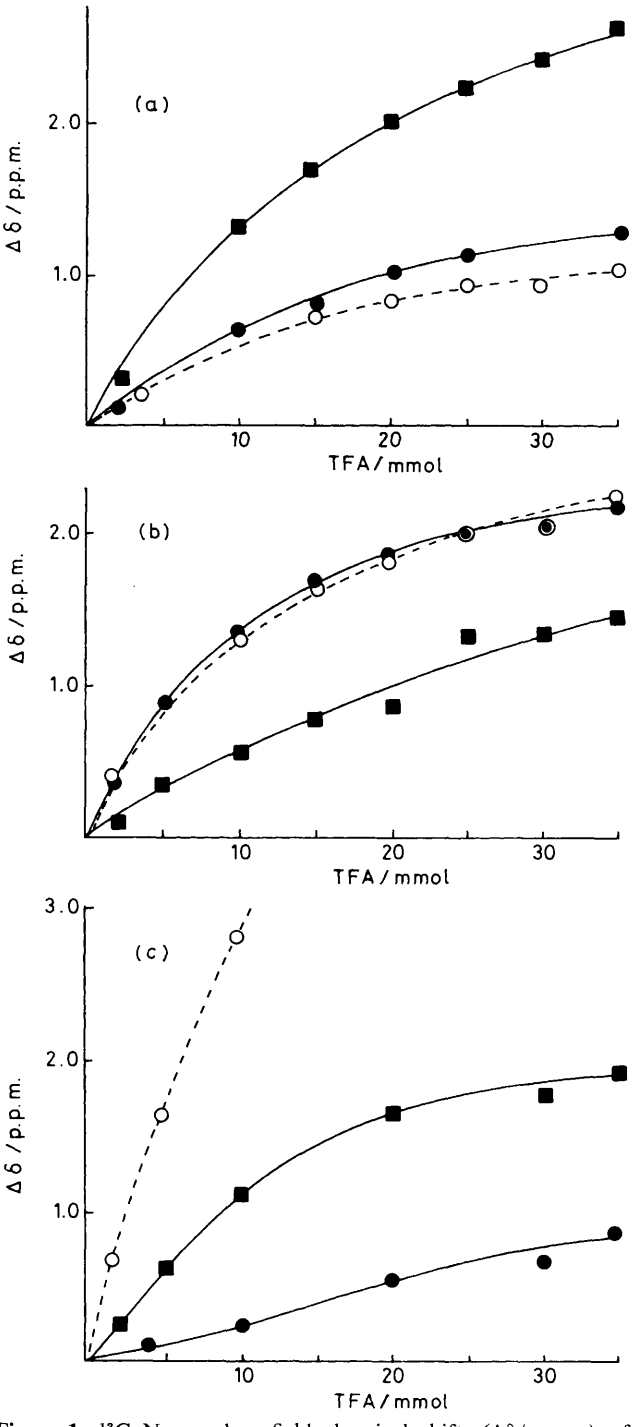


Figure 1. ^{13}C N.m.r. downfield chemical shifts (Δδ/p.p.m.) of resonances due to *ortho*-carbons (■) and (●), and ester carbonyl carbon (○) on addition of TFA, (a) for (**1c**), (b) for (**1g**), and (c) for (**1e**) (5.0 mmol substrate in 2.0 ml $CDCl_3$ in each case).

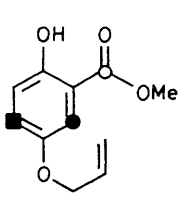
† All reactions were analysed by isolation and capillary g.c. analysis[7] of the crude product obtained by removal of TFA at reduced pressure followed by sequential washing of a diethyl ether solution of the residue with 5% aqueous KOH, reacidification, re-extraction [to hydrolyse any trifluoroacetates or acetates in the case of (**1f**)], and brief treatment with diazomethane to remethylate any aromatic acids produced during the procedure. All new compounds isolated in >1% yield have analytical and spectral data in accord with their assigned structures.

‡ The crude product mixture obtained before saponification exhibits an i.r. absorption at 1760 cm^{-1} (ArOCOMe) but none due to a hydrogen bonded aromatic ester indicating that hydrolysis does not occur under the reaction conditions.

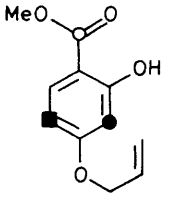
Table 1. TFA catalysed Claisen rearrangement of esters (**1c—g**).

Substrate	Path A derived products isolated yield, %			Path B derived products isolated yield, %			Path C isolated yield, %	Ratio path A : path B
	(3)	(4)	(5)	(6)	(7)	(8)	(9)	
(**1c**)	32.0	21.0	—	—	—	—	—	[a]
(**1d**)[b]	50.0	10.5	—	—	—	—	4.0	[a]
(**1e**)	36.0	7.5	—	—	13.5	4.0	4.0	2.5 : 1.0
(**1f**)[c]	12.5	7.5	—	1.0	4.5	10.0	6.0	1.3 : 1.0
(**1g**)	—	—	3.5	—	—	10.0	17.0	1.0 : 2.9

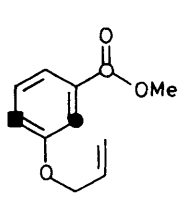
[a] No products from path B detected. [b] Products isolated as (**3c**) and (**4c**). [c] 3% Starting material recovered.



(**1c**)



(**1g**)



(**1e**)

The major product (**8g**) possesses a 2-hydroxypropyl substituent at C-5 of the aromatic ring [^{1}H n.m.r. ($CDCl_3$, 220 MHz) δ 7.53 (s, 1H) and 6.48 (s, 1H)] and the minor product (**5g**) at C-3 [^{1}H n.m.r. ($CDCl_3$, 220 MHz) δ 7.68 (d, J 8.5 Hz, 1H) and 6.48 (d, J 8.5 Hz, 1H)]. Obtaining the sterically favoured isomer (Scheme 1, path B) as the major rearrangement product contrasts with the results obtained from uncatalysed rearrangements.

A study of the behaviour of the ^{13}C n.m.r. spectra of the isomeric hydroxybenzoates (**1c**) and (**1g**) provides a possible explanation for the experimental results. In both (**1c**) and (**1g**) the resonances for the carbons at the two possible sites for rearrangement show downfield shifts on addition of TFA§ [Figure 1(a), (b)], but in each case the major product is that formed by rearrangement to the *ortho*-carbon which is shifted downfield the least. Substrates having the same 1,3-relationship of allyloxy and ester groups as (**1c**) similarly show downfield shifts for C-4 and C-6 resonances, in which C-6 moves the least. For example (**1e**) although lacking the 2-hydroxy substitutent shows the same spectroscopic behaviour as (**1c**) [Figure 1(c)] in keeping with the observed regioselectivity in the acid catalysed rearrangement. In each case the downfield shift of the carbonyl carbon indicates that the ester group is a favoured site for protonation.[8] It appears that the response to TFA addition of the ^{13}C n.m.r. resonances due to the *ortho*-carbons provides an empirical technique for predicting the regioselectivity of acid catalysed Claisen rearrangements in systems (**1c—g**). There is however no correlation between preferred site for rearrangement and the relative chemical shifts of the *ortho*-carbons in neutral solution.

These observations suggest that the regioselectivity of the acid catalysed rearrangement of (**1c—f**) is dependent upon a 1,3-relationship between the allyloxy substituent and the ester functionality and is not due to internal hydrogen bonding. The observation that TFA catalysed double rearrangement of 1,4-diallyloxybenzene gives only the sterically favoured 2,5-diallyl-1,4-dihydroxybenzene[6] lends support to the conclusion that protonation of the ester group in (**1c—f**) is responsible for rearrangement being directed to the sterically disfavoured position.

This difference in regiochemical control between the thermal and acid catalysed rearrangement of such systems calls for caution when analysing results of high temperature reactions as it is possible that such reactions may benefit to some extent from acid catalysis. The formation of cyclised material (**4c**) together with (**2c**) on heating (**1c**) to 220 °C supports this possibility.[4]

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§ All absorptions in the ^{13}C n.m.r. spectra, except for those due to the two oxygen substituted aromatic carbons can be unambiguously assigned by selective proton decoupling experiments.

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