Tetrahedron Letters,Vol.29,No.11,pp 1311-1314,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

EFFICIENT, HIGHLY REGIOSELECTIVE FRIES REARRANGEMENTS OF METHYL 3-(2-ACYLOXY-4-METHOXYPHENYL)PROPANOATES: THE FIRST TOTAL SYNTHESES OF THE LINEAR ACYLATED COUMARINS GEIJERIN AND DEHYDROGEIJERIN.

Nicholas Cairns,[a] Laurence M. Harwood,*[a] and David P. Astles.[b]

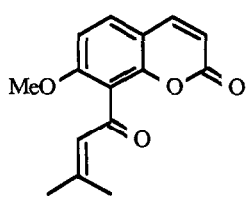
[a]*Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford OX1 3QY.*

[b]*Shell, Sittingbourne Research Centre, Sittingbourne ME9 8AG, U.K.*

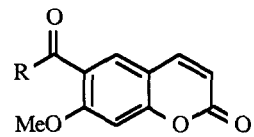
Aluminium chloride catalysed *para*-Fries rearrangement of methyl 3-(2-acyloxy-4-methoxyphenyl)propanoates (**5**) in nitromethane furnishes the corresponding 5-acylated products (**6**) cleanly and in high yield. The rearrangement products may be converted into 6-acyl-7-methoxycoumarins (**2**) including the naturally occurring geijerin (**2a**) and dehydrogeijerin (**2b**).

We have recently reported two complementary approaches towards the syntheses of 6-prenylated coumarins which utilise either a regioselective Lewis acid catalysed *ortho*-Claisen rearrangement[1] or a sterically driven thermal *para*-Claisen.[2] In this communication we wish to report our recent studies which have shown that the Fries rearrangement can be used to effect the first total syntheses of the naturally occurring 6-acylated coumarins, geijerin (**2a**) and dehydrogeijerin (**2b**).

Within the large class of coumarins possessing isoprene derived substituents, there is a small group of compounds in which the aromatic side chain has been modified into an acyl substituent.[3] Examples of this group include the angular coumarin (**1**), isolated from *Ligusticum hultennii*,[4] which has been synthesised *via* the coupling of an 8-iodocoumarin with a copper (I) acetylide,[5] and its linear counterparts geijerin (**2a**) and dehydrogeijerin (**2b**) isolated from *Geijera salcifolia*[6] and *Geijera parviflora*[7] respectively.



1



2

a R = $(CH_3)_2CHCH_2$ -

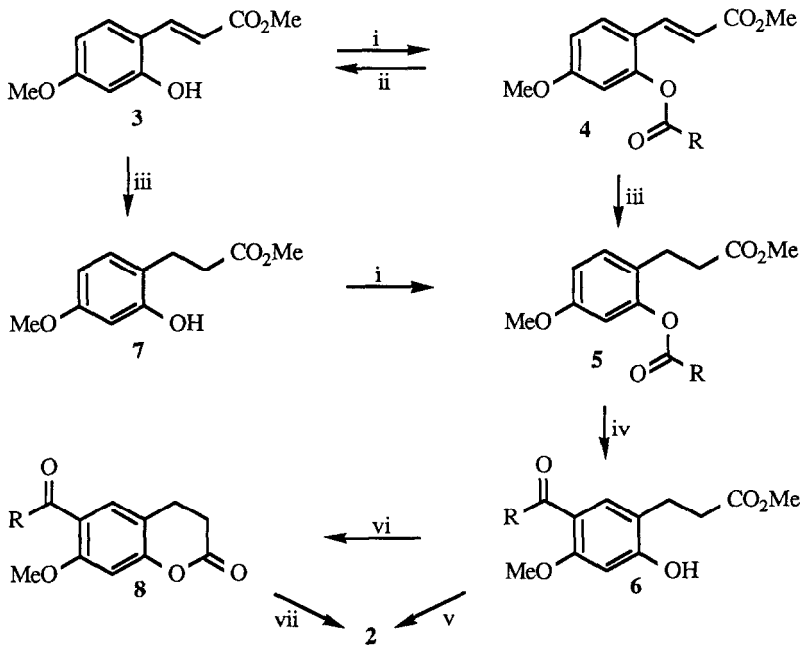
b R = $(CH_3)_2C{=}CH$ -

Whilst a Friedel -Crafts or Fries approach to structures (**2a, b**) appears attractive at first sight, umbelliferone derivatives have been shown not to undergo such reactions in a synthetically useful manner,[5, 8] although 7-hydroxy-3, 4-dihydrocoumarin has been reported to undergo Friedel-Crafts acylation in 28% yield

to give 6-acetyl-7-hydroxycoumarin.[8] *In situ* base cleavage of the coumarin ring followed by reclosure has been used to perform intramolecular aldol condensations leading to linear furanocoumarins.[9]

We have previously demonstrated successful Lewis acid catalysed *ortho*-Claisen rearrangements with substrates in which the coumarin ring has been cleaved,[1] when the migrating allyl group can be considered to possess some cationic nature,[10] and provide an analogy with the Fries rearrangement. Therefore, we decided to investigate Fries rearrangements of related substrates (**4**) and (**5**) in order to ascertain if such rearrangements were possible in a regioselective manner.

7-methoxycoumarin was cleaved to 2'-hydroxy-4'-methoxycinnamate (**3**) and the product acetylated (Ac_2O, pyridine, quant.).† Unfortunately, all attempts at rearrangement of the product (**4c**) led to deacylation of the starting material, presumably due to the electron withdrawing nature of the conjugated ester moiety. In order to increase the electron density of the aromatic ring, methyl 2'-acetoxy-4'-methoxycinnamate (**4c**) was reduced to methyl 3-(2-acetoxy-4-methoxyphenyl)propanoate (**5c**) (Pd-C, H_2, quant.). Subsequent rearrangement of (**5c**) using 5 equivalents of aluminium chloride in nitromethane[11] enabled the desired product, methyl 3-(5-acetyl-2-hydroxy-4-methoxyphenyl)propanoate (**6c**) to be isolated in 70% yield with no isomeric products being detected (Scheme). The substitution pattern of the aromatic ring was clearly indicated by the appearance of two 1H singlets at δ 6.51 and 7.45, indicating their *para*-relationship.



(**a**) R = $(CH_3)_2CHCH_2$
(**b**) R = $(CH_3)_2C{=}CH$-
(**c**) R = CH_3 -
(**d**) R = CH_3CH_2 -
(**e**) R = $(CH_3)_2CH$-
(**f**) R = $(CH_3)_3C$-
(**g**) R = Ph-

Reagents and conditions: (i) RCOCl or $(RCO)_2O$, pyridine, r.t.; (ii) Lewis acid, (iii) Pd-C, H_2; (iv) $AlCl_3$ (5 equiv.), $MeNO_2$, r.t.; (v) Ph_2O, Pd-C, reflux; (vi) Ph_2O, reflux; (vii) Ph_2O, 1-dodecene (5 equiv.), Pd-C, reflux.

Scheme

Similar results were obtained for a range of precursors prepared by the same procedure (Table), with the exception of the senecioyl ester (**5b**), the preparation of which necessitated initial quantitative reduction of (**3**) to (**7**) before acylation of the phenol to furnish (**5b**). Increasing α-substitution of the acyl groups, as in (**5e, g**) resulted in rearrangement occurring in reduced yields, with the pivalate ester (**5f**) giving no substitution products.[§] In all cases deacylation was the competing reaction, probably due to the increased steric bulk of the acyl groups (also making the acyl group less electrophilic) and the relative ease of decomposition of the acylium species.

Product	Isolated Yield (%)			
	5	6	8	2
a	96	65	90	66
b	95	73	84	10
c	quant	71	b	70
d	quant	62	83	61
e	95	35	b	54
f	19	a	-	-
g	quant	17	b	64

a - No product obtained
b - Intermediate not isolated

Table

Concomitant lactone formation and dehydrogenation of the rearranged products to form the 6-acyl-7-methoxycoumarins (**2**) was conveniently carried out in most cases by refluxing in diphenyl ether in the presence of Pd-C. However, in the case of (**6b**), the senecioyl side chain acted as an intramolecular hydrogen acceptor furnishing geijerin (**2a**) in 40% yield [mp. 122-122.5°C, lit.[6] 121°C; δ 6.85 (1H, s), 7.83 (1H, s)]. Geijerin was more conveniently synthesised from 7-methoxycoumarin in 40% overall yield in 5 steps *via* rearrangement of the 3-methylbutanoyl aryl ester (**5a**), followed by the usual oxidative ring closure with Pd-C in diphenyl ether at reflux. Dehydrogeijerin [**2b**, mp. 125-128°C, lit.[7] 130°C; δ 6.62 (1H, m), 6.84 (1H, s), 7.67 (1H, s)] was obtained from (**6b**), in 10% yield (6% overall yield from 7-methoxycoumarin), by first isolating the dihydrocoumarin intermediate (**8b**) and then treating this with Pd-C in the presence of 1-dodecene (hydrogen acceptor).[12]

In summary, 6-acylated umbelliferone derivatives have been prepared in good overall yield and with very high regioselectivity from 3-(2-acyloxy-4-methoxyphenyl)propanoic acid derivatives by using a *para*-Fries rearrangement strategy. This has been applied to the first total syntheses of the naturally occurring linear acylated coumarins, geijerin (**2a**) and dehydrogeijerin (**2b**) in 40% and 6% overall yields respectively from 7-methoxycoumarin.

We thank the S.E.R.C. and Shell Research, Sittingbourne for financial support (to N.C.).

References

1. N. Cairns, L. M. Harwood, D. P. Astles and A. Orr, *J. Chem. Soc. Chem. Commun.*, 1986, 182; also, N. Cairns, L. M. Harwood and D. P. Astles, *J. Chem. Soc. Chem. Commun.*, 1986, 750.
2. N. Cairns, L. M. Harwood and D. P. Astles, *J. Chem. Soc. Chem. Commun.*, 1986, 1264; also, N. Cairns, L. M. Harwood and D. P. Astles, *J. Chem. Soc. Chem. Commun.*, 1987, 400.
3. For a complete survey of naturally occurring coumarins see, R. D. H. Murray, J. Méndez and S. A. Brown, "*The Natural Coumarins, Occurrence, Chemistry and Biochemistry*" Wiley-Interscience, New York, 1982.
4. K. Hata, M. Kozawa, K. Baba and M. Mitsui, *J. Pharm. Soc. Japan*, 1973, **93**, 248.
5. R. D. H. Murray and I. T. Forbes, *Tetrahedron Lett.*, 1977, 3077.
6. F. N. Lahey and D. J. Wluka, *Aust. J. Chem.*, 1955, **8**, 125.
7. F. N. Lahey and J. K. MacLeod, *Aust. J. Chem.*, 1967, **20**, 1943.
8. D. K. Chatterjee and K. Sen, *J. Ind. Chem. Soc.*, 1969, **46**, 275.
9. J. K. MacLeod and R. B. Worth, *Tetrahedron Lett.*, 1972, 237.
10. T. Borgulya, R. Madela, P. gahrni, H. J. Hanson, H. Schmid and R. Barner, *Helv. Chim. Acta*, 1973, **56**, 14.
11. S. H. Pines and A. W. Douglas, *J. Org. Chem.*, 1978, **43**, 3126.
12. G. Kneen and P. J. Maddox, *Synth. Commun.*, 1986, **16**, 1635.

† All novel compounds isolated gave spectroscopic and analytical data in keeping with their assigned structures.

‡ ***General procedure***: a solution of aluminium chloride (5 mol. equiv.) in nitromethane was added, with stirring at 0°C under nitrogen to the aryl ester (**5**) dissolved in nitromethane. After addition, the reaction was allowed to warm up to room temperature and stirred until no starting material remained by tlc (ether; *ca.* 30 minutes). After quenching (5M HCl) and work up, the crude product was purified by flash column chromatography (20-40% ether/pentane).

§ Attempts to introduce acyl groups by direct Friedel-Crafts acylation of (**7**) also led to the desired products (**6**) but in inferior yields to those obtained under the above Fries rearrangement conditions.

(Received in UK 21 January 1988)