A New Approach to Neoflavonoid Synthesis

Dervilla M. X. Donnelly,*[a] Jean-Pierre Finet,[b] Patrick J. Guiry,[a] and Rhona M. Hutchinson[a]
[a] *Department of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland.*
[b] *Laboratoire S.R.E.P., Faculté des Sciences St. Jérôme, Université de Provence–13397–Marseille Cedex 13, France*

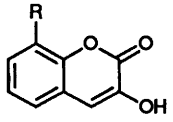
Neoflavonoids or 4-arylcoumarins are prepared by arylation of 3-hydroxycoumarins with aryl-lead triacetates followed by palladium-catalysed reduction of the derived 3-trifluoromethylsulphonyloxyarylcoumarins.

The 4-arylcoumarins or neoflavonoids are of limited distribution and are found in the *Leguminosae, Guttiferae, Rubiaceae* and *Passifloraceae*. Many studies have been devoted to their isolation,[1] and synthesis.[2–7] However, the synthetic methods employed were primarily *via* Perkin or von Pechmann condensations involving low-yielding synthesis of the appropriate precursors of the cyclisation step.

Direct arylation at C-4 of the preformed coumarin ring would be a more efficient route to these compounds. Direct arylation with aryl-lead triacetates,[8] a class of organometallic reagents which behave as aryl cation equivalents, enabling the selective arylation of an activated carbon and of other nucleophiles under mild conditions,[9] is now proposed. The presence of a hydroxy function at position 3 activates carbon-4 towards direct selective arylation.

We now report our preliminary results on the preparation of a range of 4-arylcoumarins, *via* C-4 arylation of 3-hydroxycoumarin (**1**) and the 8-methoxy derivative (**2**) by aryl-lead triacetates. 3-Hydroxycoumarins (**1**) and (**2**) were prepared by condensation of salicylaldehyde with acetylglycine.[10]

They were treated with a series of aryl-lead reagents (**3**)–(**8**),[11,12] to yield the corresponding 4-aryl-3-hydroxycoumarins and in good to high yields (Table 2). These arylation reactions



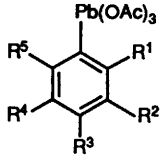
(**1**) R = H
(**2**) R = OMe

were best performed at 40 °C. However, in the reactions with 4-methoxyphenyl-lead triacetate (**4**), best yields were obtained at 60 °C. A similar trend was noted[12] using aryl-lead triacetates for the preparation of 3-aryl-4-hydroxycoumarins.[12]

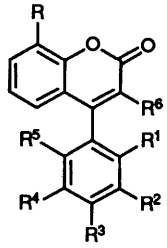
Triflation of the 4-aryl-3-hydroxycoumarins, followed by palladium-catalysed reduction with ammonium formate,[13] afforded good yields of a range of 4-arylcoumarins. This sequence affords a facile entry into neoflavanoids and their 3-hydroxy derivatives, which are suitable for further elaboration. During the course of these studies, a related approach towards the synthesis of neoflavonoids using palladium-catalysed coupling of arylstannanes with 4-trifluoromethyl sulphonyloxycoumarin was described by Wattanasin.[14]

Work is now under progress to apply our sequence to a variety of A-ring substituted 3-hydroxycoumarins.

Table 1. Lead reagents and arylcoumarins.



(**3**) – (**8**)



(**9**) – (**17**) $R^6 = OH$
(**18**) – (**23**) $R^6 = OSO_2CF_3$
(**24**) – (**29**) $R^6 = H$

Aryl substituents					Lead reagents	4-Arylcoumarin derivatives					
						R = H	R = OMe	R = H	R = OMe	R = H	R = OMe
R^1	R^2	R^3	R^4	R^5		R^6 = OH	R^6 = OH	R^6 = OTf	R^6 = OTf	R^6 = H	R^6 = H
H	H	H	H	H	(**3**)	(**9**)	(**14**)	(**18**)		(**24**)	
H	H	OMe	H	H	(**4**)	(**10**)	(**15**)		(**22**)		(**28**)
OMe	H	OMe	H	H	(**5**)	(**11**)	(**16**)	(**19**)		(**25**)	
H	OMe	H	H	H	(**6**)	(**12**)		(**20**)		(**26**)	
H		OCH_2O	H	H	(**7**)	(**13**)		(**21**)		(**27**)	
OMe	H	H	OMe	H	(**8**)		(**17**)		(**23**)		(**29**)

Table 2. Reaction conditions and yields of the arylation, triflation and reduction reactions.

Substrate	Lead reagent and reaction conditions (T/°C, t/h)[15]	Arylation product (%)	Triflation product (t/h, %)[16]	Reduction product (%)[17]
(1)	(3) (40, 9)	(9) (60)	(18) (8, 68)	(24) (60)
(1)	(4) (60, 10)	(10) (56)	—	—
(1)	(5) (40, 9)	(11) (92)	(19) (9, 85)	(25) (70)
(1)	(6) (40, 9)	(12) (72)	(20) (9, 80)	(26) (80)
(1)	(7) (40, 9)	(13) (62)	(21) (8, 72)	(27) (72)
(2)	(3) (40, 9)	(14) (59)	—	—
(2)	(4) (60, 10)	(15) (58)	(22) (10, 74)	(28) (75)
(2)	(5) (40, 9)	(16) (76)	—	—
(2)	(8) (40, 9)	(17) (69)	(23) (10, 76)	(29) (69)

Acknowledgements

R. H. and J. P. F. thank CNRS, EOLAS, and 'Ministère Français des Affaires Etrangères' for exchange fellowships. We also thank Prof. P. Tordo (University of Provence) for his interest in this work.

References

1 D. M. X. Donnelly, and M. H. Sheridan, in 'The Flavonoids, Advances in Research since 1980,' J. B. Harborne, ed., Chapman and Hall, London, 1988, p. 211 and references therein.
2 D. M. X. Donnelly, J. O'Reilly, and W. B. Whalley, *Phytochemistry*, 1975, **14**, 2287.
3 V. K. Ahluwalia, K. Kapur, and S. Manchanda, *Indian J. Chem., Sect. B*, 1982, **21**, 186.
4 A. Chatterjee, D. Ganguly, and R. Sen, *Tetrahedron*, 1976, **32**, 2407.
5 S. Abe, K. Sato, T. Asami, K. Amakasu, T. Itakura, N. Nishio, Japan Pat. 70 00 666 (*Chem. Abstr.*, 1970, **72**, 78881u).
6 A. K. Das Gupta, and M. S. Paul, *J. Indian Chem. Soc.*, 1970, **47**, 1017.
7 R. T. Taylor and R. A. Cassell, *Synthesis*, 1982, 672.
8 R. P. Kozyrod and J. T. Pinhey, *Aust. J. Chem.*, 1985, **38**, 1155 and references therein.
9 R. A. Abramovitch, D. H. R. Barton, and J.-P. Finet, *Tetrahedron*, 1988, **44**, 3039.
10 K. N. Trivedi and S. Sethna, *J. Org. Chem.*, 1960, **25**, 1817.
11 D. H. R. Barton, D. M. X. Donnelly, J.-P. Finet, and P. J. Guiry, unpublished work
12 D. H. R. Barton, D. M. X. Donnelly, J.-P. Finet, and P. J. Guiry, *Tetrahedron Lett.*, 1989, **30**, 1539.
13 G. A. Peterson, F. A. Kunng, S. J. McCallum, and W. D. Wulff, *Tetrahedron Lett.*, 1987, **28**, 1381.
14 S. Wattanasin, *Synth. Commun.*, 1988, **18**, 1919.
15 *A typical arylation reaction.* To a well stirred suspension of the substrate (**1**) (0.6 mmol) and the aryl-lead triacetate (**7**) (0.66 mmol) in dry chloroform (1 ml) was added dry pyridine (2 mmol, 0.19 ml). The reaction mixture was refluxed at 40 °C and the reaction monitored by TLC. On completion, the reaction mixture was diluted with $CHCl_3$ (50 ml) and washed with dilute sulphuric acid (3M, 2 × 25 ml). The organic layer was filtered through Celite, dried ($MgSO_4$), and evaporated. Purification of the residue by preparative TLC yielded 3-hydroxy-4-(3,4-methylenedioxyphenyl)-1-benzopyran-2-one (**13**), m.p. 214–217 °C; δ(DMSO) 6.10 (2 H, s, OCH_2O), 6.85 (1 H, dd, *J* 7.7, 1.5 Hz, 6'-H), 6.94 (1 H, d, *J* 1.46 Hz, 2'-H), 7.17 (1 H, d, *J* 7.7 Hz, 5'-H), and 7.1–7.4 (4 H, m, A-ring).
16 *A typical triflation reaction.* To a well stirred solution of the 4-aryl-3-hydroxy-1-benzopyran-2-one (**13**) (0.3 mmol) and triethylamine (36.4 mg, 0.36 mmol) in dry dichloromethane (15 ml) at 0 °C under nitrogen was added trifluoromethanesulphonic anhydride (107.3 mg, 0.36 mmol). The mixture was stirred at 0 °C and the reaction monitored by TLC. On completion, the reaction mixture was diluted with 50% ether–light petroleum (50 ml), filtered through a short pad of silica gel, and evaporated. Purification of the residue by preparative TLC yielded 3-trifluoromethylsulphonyloxy-4-(3,4-methylenedioxyphenyl)-1-benzopyran-2-one (**21**), m.p. 126–130 °C; $\delta_H(CDCl_3)$ 6.10 (2 H, s, OCH_2O); $\delta_C(CDCl_3)$ 115.8 (s, CF_3).
17 *A typical detriflation reaction.* A solution of the 4-aryl-3-trifluoromethylsulphonyloxy-1-benzopyran-2-one (**21**) (0.1 mmol) in DMF (5 ml) was treated with triphenylphosphine (1.31 mg, 0.005 mmol), palladium diacetate (2.2 mg, 0.01 mmol), triethylamine (30.8 mg, 0.3 mmol), and formic acid (9.2 mg, 0.2 mmol). The mixture was stirred at 65 °C for 12 h and monitored by TLC. On completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried, evaporated, and purified to yield 4-(3,4-methylenedioxyphenyl)-1-benzopyran-2-one (**27**), m.p. 182–185 °C; $\delta_C(CDCl_3)$ 6.07 (2 H, s, OCH_2O) and 6.35 (1 H, s, 3-H).

Paper 0/02248I
Received 21*st May* 1990
Accepted 21*st May* 1990