THE FIRST DIRECT SYNTHESIS OF ISOFLAVANS VIA α-ALKYLATION OF PHENYLACETATES

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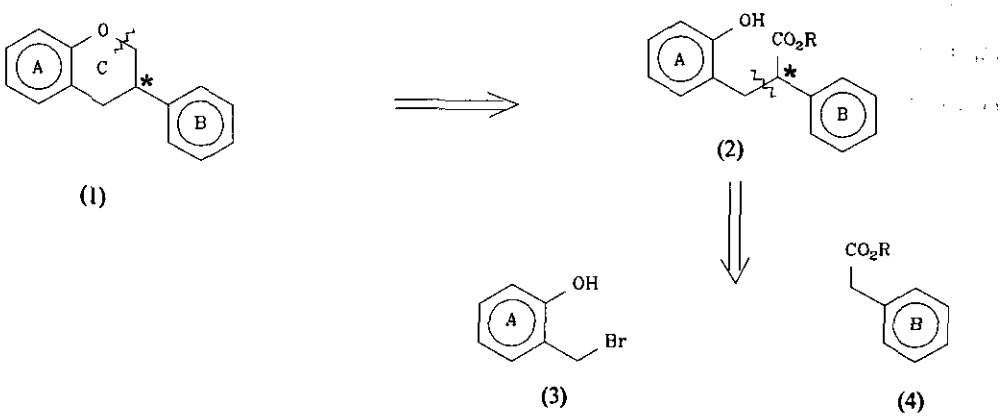
Abstract – Deprotonation of phenylacetates and quenching of the enolates with benzylic electrophiles, afford 2,3-diarylpropanoates which serve as precursors to isoflavans following consecutive reduction and cyclization steps.

Despite the structural simplicity of the isoflavans, the only synthetic access to this class of phenolic metabolites[1] involves the cumbersome process of hydrogenation of isoflavones[2] or pterocarpans.[3] The utility of such an approach is, however, limited by its inability to address the issue of the C-3 stereogenic center, the integrity of which is invariably being conserved in the naturally occurring compounds. We have therefore opted for a more direct synthetic approach that is based on the α-alkylation of phenylacetates and which possesses the potential of introducing stereoselectivity during establishment of the single stereocenter.

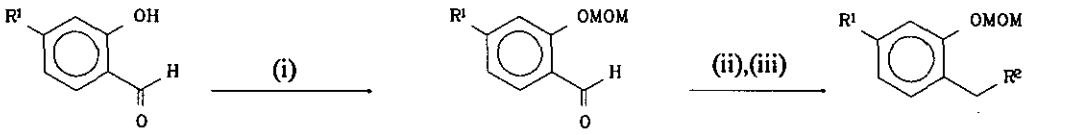
Consideration of the simple retro-synthetic sequence, (1) ⇒ (2) ⇒ (3) + (4), indicates that our protocol for constructing the $C_6.C_3.C_6$ framework involves the synthesis of oxygenated benzylic electrophiles of type (3)



(1) (2) (3) (4)

($C_6.C_1$ fragment involving ring A), α-benzylation of phenylacetates (4) ($C_6.C_2$ fragment involving the B-ring) to give 2,3-diarylpropanoates of type (2), and subsequent reduction and cyclization of the latter compounds to give the isoflavans, e.g. (1).

The protected phenolic benzyl bromides were prepared according to the sequence in Scheme 1. Methoxymethylation of the o-hydroxybenzaldehydes (5) and (6) gave the O-methoxymethyl ethers (7) and (8) which were subsequently reduced with sodium borohydride to the benzyl alcohols (9) and (11). Treatment of these alcohols with methanesulfonyl anhydride and 2,6-lutidine gave the labile intermediate sulfonates which were trapped in reasonable yields as the benzyl bromides (10) and (12) using lithium bromide in anhydrous THF.[4] The bromide (10) could be preserved for up to five months, analogue (12), however, was unstable and had to be used immediately.



(5) R^1=H
(6) R^1=OMe

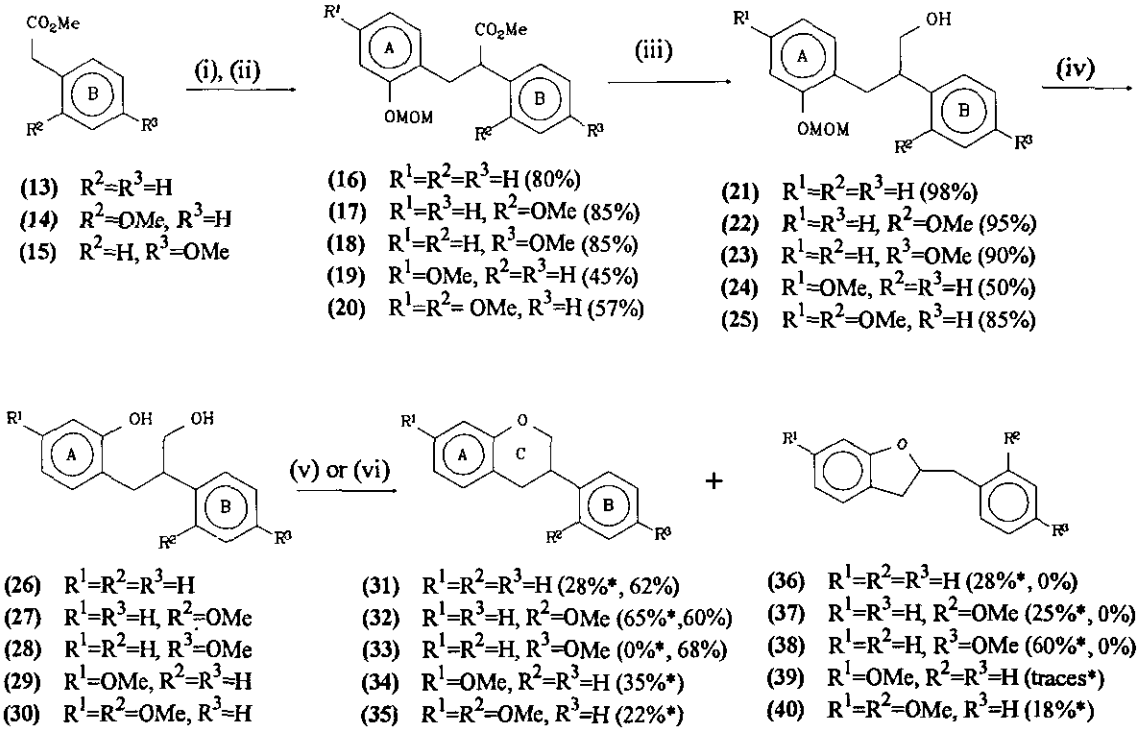
(7) R^1=H (66%)
(8) R^1=OMe (89%)

(9) R^1=H, R^2=OH (60%)
(10) R^1=H, R^2=Br (75%)
(11) R^1=OMe, R^2=OH (96%)
(12) R^1=OMe, R^2=Br (70%)

Scheme 1. Reagents and conditions : (i) NaH/DMF, $ClCH_2OMe$; (ii) $NaBH_4$,EtOH/THF; (iii)Ms_2O/2,6-Lutidine, LiBr/THF. Yields are indicated in brackets.

The consecutive steps of α-alkylation of the phenylacetates and the reduction and cyclization of the 2,3-diarylpropanoates were performed according to the sequence in Scheme 2. Owing to the excellent results reported[5,6] for the α-alkylation of esters with lithium isopropylcyclohexylamide (LICA) in the presence of hexamethylphosphoric triamide (HMPA),[7] this hindered base was selected for the deprotonation of esters (13) - (15). The efficiency of this system to produce the ester enolates within 15 min at -78°C was demonstrated via quenching of the reaction with D_2O. At elevated temperatures rapid decomposition of the enolates occurred which adversely affected yields. The ester enolates were subsequently alkylated by trapping with the benzylic electrophiles (10) and (12) hence affording the 2,3-diarylpropanoates (16) - (20) in moderate to good yields. These were smoothly converted into the 2,3-diarylpropan-1-ols (21) - (25) by reduction with lithium aluminiumhydride.

Quantitative deprotection with 3M HCl in methanol afforded the phenolic propan-1-ols (26) - (30) which were subsequently subjected to cyclization using p-toluenesulfonic acid (PTSA) in refluxing benzene.[8] The target racemic isoflavans (31) - (35)[9,10] were, however, accompanied by various proportions of isomeric



(13) R^2=R^3=H
(14) R^2=OMe, R^3=H
(15) R^2=H, R^3=OMe

(16) R^1=R^2=R^3=H (80%)
(17) R^1=R^3=H, R^2=OMe (85%)
(18) R^1=R^2=H, R^3=OMe (85%)
(19) R^1=OMe, R^2=R^3=H (45%)
(20) R^1=R^2= OMe, R^3=H (57%)

(21) R^1=R^2=R^3=H (98%)
(22) R^1=R^3=H, R^2=OMe (95%)
(23) R^1=R^2=H, R^3=OMe (90%)
(24) R^1=OMe, R^2=R^3=H (50%)
(25) R^1=R^2=OMe, R^3=H (85%)

(26) R^1=R^2=R^3=H
(27) R^1=R^3=H, R^2=OMe
(28) R^1=R^2=H, R^3=OMe
(29) R^1=OMe, R^2=R^3=H
(30) R^1=R^2=OMe, R^3=H

(31) R^1=R^2=R^3=H (28%*, 62%)
(32) R^1=R^3=H, R^2=OMe (65%*,60%)
(33) R^1=R^2=H, R^3=OMe (0%*, 68%)
(34) R^1=OMe, R^2=R^3=H (35%*)
(35) R^1=R^2=OMe, R^3=H (22%*)

(36) R^1=R^2=R^3=H (28%*, 0%)
(37) R^1=R^3=H, R^2=OMe (25%*, 0%)
(38) R^1=R^2=H, R^3=OMe (60%*, 0%)
(39) R^1=OMe, R^2=R^3=H (traces*)
(40) R^1=R^2=OMe, R^3=H (18%*)

Scheme 2 Reagents and conditions: (i) LICA/THF/-78°C; (ii) HMPA, benzyl bromides(10),(12); (iii) $LiAlH_4/Et_2O$ under N_2 at room temperature; (iv) 3M HCl/MeOH-reflux; (v) PTSA/benzene-reflux; (vi) Pyridine(1.2 eq.)/Brosyl Chloride(1.1 eq.)/DCM followed by NaH(excess); * Indicates yields for procedure (v).

2-benzyldihydrobenzo[*b*]furans (36) - (40).[9,10] Formation of these artefacts is explicable in terms of the generation of an incipient primary carbocation via protonation of the alcohol functionality. The instability of such a species then induces a concerted 1,2-migration of the C-2 aryl group and cyclization of the transient C-2 carbocation. Confirmation for such a conjecture stems from the observation that the rate of formation of the dihydrobenzofurans is enhanced by increased hydroxylation of the B-ring in the 1,2-diarylpropan-1-ols of type (26) hence increasing the migratory aptitude of this phenolic moiety. This is most evident from comparison of the yields of cyclization products of the 2,3-diarylpropan-1-ols (26) and (28). A notable exception to this phenomenon is prevalent in the 2,3-diarylpropanol (27) where the o-methoxy group presumably causes steric

compression in the transient benzenonium ion hence favouring the 6-Exo-Tet process[11] with formation of the isoflavan series of compounds.

However, the selective transformation of the 2,3-diarylpropan-1-ols (26) - (28) to the isoflavans (31) - (33) in good yield was eventually effected by formation of the brosyl esters of the propanols using 4-bromobenzenesulfonyl chloride in dichloromethane / pyridine and subsequent cyclization of the brosylates by the addition of sodium hydride at room temperature.

We have thus amply demonstrated the applicability of this novel approach towards the first direct synthesis of isoflavans.

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REFERENCES AND NOTES

1. P.M. Dewick, 'The Flavonoids-Advances in Research since 1980', ed. by J.B. Harborne, Chapman and Hall, London, 1988, 171.
2. J.A. Lamberton, H. Suares, and K.G. Watson, *Austr. J. Chem.*, 1978, 31, 455.
3. T.B.H. McMurry, E. Martin, D.M.X. Donnelly, and J.C. Thompson, *Phytochemistry*, 1972, 11, 3283.
4. E.W. Collington and A.I. Meyers, *J. Org. Chem.*, 1971, 36, 3044.
5. R.E. Ireland, R.H. Mueller, and A.K. Willard, *J. Am. Chem. Soc.*, 1976, 98, 2868.
6. M.W. Rathke and A. Lindert, *J. Am. Chem. Soc.*, 1971, 93, 2318.
7. S. Lavielle, S. Bory, B. Moreau, M.J. Luche, and A. Marquet, *J. Am. Chem. Soc*, 1978, 100, 1558.
8. Efforts to combine the deprotection and cyclization steps with PTSA in benzene failed. This demonstrated the necessity of an aqueous medium for the hydrolysis of the acetal moiety.
9. All new compounds gave satisfactory micro-analyses or accurate mass values.
10. The remaining material is composed of an intractable gum-like substance.
11. J.E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734.

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