REGIO- AND STEREOSELECTIVE REACTIONS OF FLAVONES WITH BUTYLLITHIUM-TMEDA: SYNTHESIS OF (*E*)-4-BUTYLIDENEFLAVONES

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Abstract: The regio- and stereoselective reactions of flavones with a mixture of butyllithium and N,N,N',N'-tetramethylethylenediamine are reported. The obtained (*E*)-4-butylideneflavones were characterised by NMR and mass spectrometry and the stereochemistry established by NOE experiments.

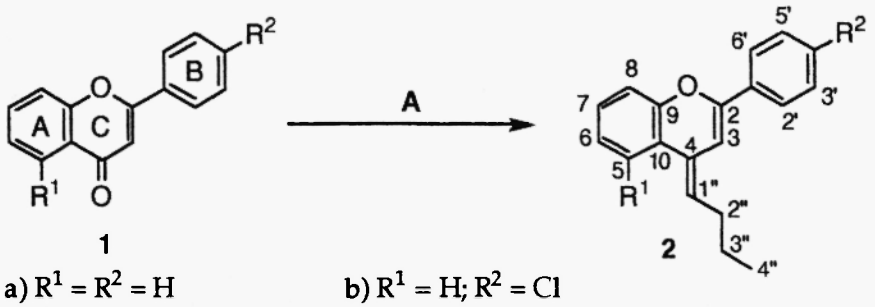
Natural and synthetic flavones are known by their potential applications as agrochemicals,[1] antioxidants[2] and pharmaceutical drugs.[3] In particular flavone-8-acetic acid (FAA) has received considerable attention since the discovery of its exceptional and selective activity on several tumours which are resistant to most chemotherapeutic drugs.[4] Unfortunately these results have not yet been confirmed in Man, and these disappointing results have pointed to the search of new derivatives of flavone-8-acetic acid or other related heterocycles.[5]

In the present work the synthesis of new ring B flavone derivatives related with FAA type compounds was considered. In such way it was considered that lithiation of ring B methoxylated flavones, followed by alkylation, could be a possible route to the required 3'(5') derivatives, if the α,β-unsaturated keto moiety would not react under such conditions. However, treatment of 4'-methoxyflavone **1c** with two equivalents of both BuLi and TMEDA[6] (N,N,N',N'-tetramethylethylenediamine), in anhydrous THF, followed by addition of deuterium oxide, did not gave the required 3'(5')-deuteriated flavone. Instead the new (*E*)-4-butylideneflavone **2c** derivative was obtained in 26% yield (Scheme 1); its formation can be explained by a nucleophilic addition to the flavone carbonyl group followed by HDO elimination.

Treatment of **1c**, in toluene, with two equivalents of both BuLi and TMEDA, followed by addition of water, gave the (*E*)-4-butylidene-4-methoxyflavone **2c** in a better yield (67%)[7] (Scheme 1). This situation is comparable to that reported by Tamaru and Saito for certain

lithiation reactions in which, due to different solubilities of the lithium salt, the product yields are dependent upon the solvent employed.[8]

Flavones 1a,b,d, under similar conditions, gave the corresponding (*E*)-4-butylidene-flavones 2a,b,d[7] (Scheme 1). These results indicate that regioselective reactions occur between flavones and BuLi-TMEDA mixtures.



1 2

a) $R^1 = R^2 = H$ b) $R^1 = H$; $R^2 = Cl$

c) $R^1 = H$; $R^2 = OCH_3$ d) $R^1 = R^2 = OCH_3$

A - i) *n*-BuLi-TMEDA; toluene

ii) H_2O

Scheme 1

Structures of the (*E*)-4-butylideneflavones 2a-c were determined using several NMR techniques [^1H, ^{13}C, COSY ($^1H/^1H$), HETCOR ($^1H/^{13}C$) and one-dimensional selective INEPT] and mass spectrometry.[9]

The most noticeable features in the ^1H NMR spectra of 4-butylideneflavones 2a-c include the resonances due to the aliphatic protons and the signals corresponding to the H-1" and H-3 proton resonances, which appear, respectively, at δ 5.66-5.71 and 6.37-6.48 ppm. The H-3 resonance appears as a doublet with a small coupling constant (J 0.7-0.8 Hz), due to the long-range coupling with H-1"; the one due to H-1" is a triplet due to the coupling with the two H-2" protons (J 7.4 Hz) which is broadened by that small coupling with H-3. In the case of 4-butylideneflavone 2d the resonances due to H-1" and H-3 appear, respectively, at δ 6.49 and 6.38 ppm; this shift to the higher frequency values of the H-1" resonance is due to the deshielding effect of the 5-methoxy oxygen atom.

The stereochemistry of 4-butylideneflavones 2a-d was established using NOE experiments. For compounds 2a-c these have indicated close proximity between H-3 and H-2',6' and H-2", and between H-1" and H-5; for 2d close proximity between H-2" and H-3 was also observed (Table 1). The (*E*) stereochemistry is then assigned for those compounds, as shown in Scheme 1. These

results led us to conclude that a reaction between a flavone and BuLi-TMEDA mixture is a stereoselective process.

Table 1: Results Obtained From The NOE Experiments

Compound	Irradiation	NOE Effect
2a	H-3	H-2" (12%) and H-2',6' (18%)
	H-1"	H-5 (22%)
2b	H-3	H-2" (11%) and H-2',6' (22%)
	H-1"	H-5 (19%)
2c	H-3	H-2" (10%) and H-2',6' (15%)
	H-1"	H-5 (18%)
2d	H-2"	H-3 (10%)

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7. **Experimental procedures:**

   To an anhydrous toluene solution (50 ml) of flavones 1 (0.6 mmol), under nitrogen, at - 78°C, were slowly added N,N,N',N'-tetramethylethylenediamine (0.2 ml, 1.2 mmol) and a 2M cyclohexane solution of butyllithium (0.6 ml, 1.2 mmol). After stirring during 20 minutes, the reaction mixture was allowed to reach - 10°C, and then water (0.2 ml) was added. The reaction mixture was stirred at room temperature, during 3 hours, and then the solvent evaporated to dryness. The residue was dissolved in dichloromethane (15 ml) and purified by column chromatography, using dichloromethane as eluent, giving the (*E*)-4-butylideneflavones 2 (2a, 72%; 2b, 83%; 2c, 75%; 2d, 56%). Structural characterisation of the (*E*)-4-butylideneflavones 2 must be carried out immediately after purification, because they are light sensitive compounds.
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9. We present the spectroscopic characterization of 2a as an example of this set of compounds: 2a: ^{1}H NMR ($CDCl_3$; δ, ppm from TMS; J Hz) 0.99 (3H, H-4'', t, J 7.4), 1.52 (2H, H-3'', sxt, J 7.4), 2.26 (2H, H-2'', q, J 7.4), 5.69 (1H, H-1'', t broad, J 7.4), 6.48 (H-3, d, J 0.7), 7.06 (H-6, ddd, J 7.9, 7.2 and 1.3), 7.09 (H-8, dd, J 8.0 and 1.3), 7.21 (H-7, ddd, J 8.0, 7.2 and 1.5), 7.31-7.43 (H-3',4',5', m), 7.58 H-5, dd, J 7.9 and 1.5), 7.76 (H-2',6', m); ^{13}C NMR ($CDCl_3$; δ, ppm from TMS) 14.0 (C-4''), 23.1 (C-3''), 29.4 (C-2''), 100.2 (C-3), 115.1 (C-1''), 117.5 (C-8), 122.1 (C-5), 122.2 (C-10), 123.8 (C-6), 124.7 (C-2',6'), 125.1 (C-4), 128.4 (C-7), 128.4 (C-3',5'), 128.7 (C-4'), 133.9 (C-1'), 148.9 (C-2), 151.1 (C-9); IEMS (int. rel) 263 [$(M+H)^+$, 63], 262 [$M^{+\cdot}$, 73], 261 (40), 234 (20), 233 (100), 207 (17), 105 (25).

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