A New Approach to Retinoids *via* Organometallic Addition to Pyrylium Salts

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A new, concise approach to retinoid synthesis is described based on organometallic addition to pyrylium salts; the use of 4-methylpyrylium tetrafluoroborate giving 13*Z*-retinal which is readily isomerised to retinal itself; the corresponding unsubstituted and 4-cyclohexyl pyrylium salts are transformed into 13-H and 13-cyclohexyl retinal analogues.

We have recently described the stereocontrolled preparation of 2*Z*,4*E*-dienals by organometallic addition to pyrylium salts[1] and the use of this procedure in natural product synthesis.[2] In an extension to this work (Scheme 1), we envisaged the use of a 4-methylpyrylium salt (*e.g.* **1**) to provide a six-carbon homologation procedure leading to methyl substituted dienals **2** with potential in isoprenoid natural product synthesis. A major attraction of this approach is that it would be expected[1] initially to produce *Z*,*E*-dienals **2**, which should be easily isomerised to their all *trans*-isomers **3**, thereby making both systems readily accessible in a stereocontrolled manner.

Such an approach seemed ideally suited to the synthesis of retinoids[3] which are of interest in studies of visual processes,[4] as devices[5] and as anti-cancer agents[6] in both 13*E*- and 13*Z*-forms.[7] In addition retinoic acid analogues, which are of use in cell growth studies,[8] would be readily available by such a route. In this communication we describe the successful implementation of this strategy as illustrated in Schemes 2 and 3.[9] The viability of the process was first tested using pyrylium tetrafluoroborate[10] producing 13-unsubstituted 13*Z*-retinal **7**[7a] as shown in Scheme 2. β-Ionone **4** was first converted into alkyne **5** and then into vinylalane **6a** using the methodology devised by Negishi's group.[11,12] Addition of excess of **6a** to pyrylium tetrafluoroborate gave retinal analogue **7** in 31% yield. The use of the corresponding alanate **6b** raised the yield of **7** to 43%.

With this success in hand we turned our attention to the use of 4-methylpyrylium salts. 4-Methylpyrylium tetrafluoroborate **8a** was obtained by modification[10] of the procedure employed by Degani and Vicenzi[13] for the preparation of the corresponding perchlorate salt. We were aware that **8a** might undergo deprotonation to the corresponding anhydro base[14] on treatment with organometallic reagents but this process was not detected (Scheme 3). Thus 13*Z*-retinal **9**[7b] was obtained using alanate **6b** in 48% yield and was readily and efficiently isomerised to retinal **10** itself.[15]†

This route enables a range of retinal analogues to be prepared extremely easily. Thus, the organometallic component can be varied with, for example, the use of metallated **5** giving **11**[7c] in 57% yield (Scheme 3). In addition, the pyrylium component can be varied with 4-cyclohexylpyrylium tetrafluoroborate **8b**‡ reacting with metallated **5** to give the novel retinal analogue **12** in 52% unoptimised yield.

Although the yields in these reactions still require optimisation, we feel that these examples illustrate the potential of this new route to retinoids.

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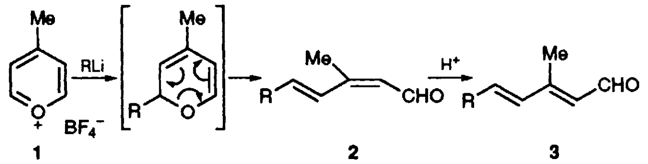
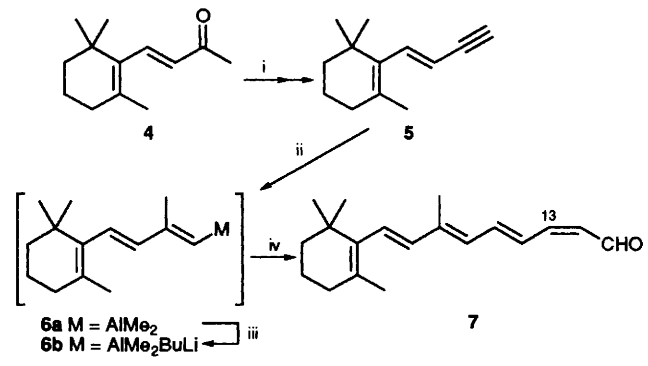
Footnotes

† Characteristic NMR peaks (the Me substituent on C-13 is particularly diagnostic) which are in accord with literature values.[7b] **9**: ^{1}H δ 10.21 (*J* 8 Hz, CHO), 2.14 (*J* 1.2 Hz, C-13 Me); ^{13}C δ 20.1 (C-13 Me), 191.1 (CHO). **10**: ^{1}H δ 10.10 (*J* 8 Hz, CHO), 2.26 (*J* 1.2 Hz, C-13 Me); ^{13}C δ 13.1 (C-13 Me), 189.9 (CHO).

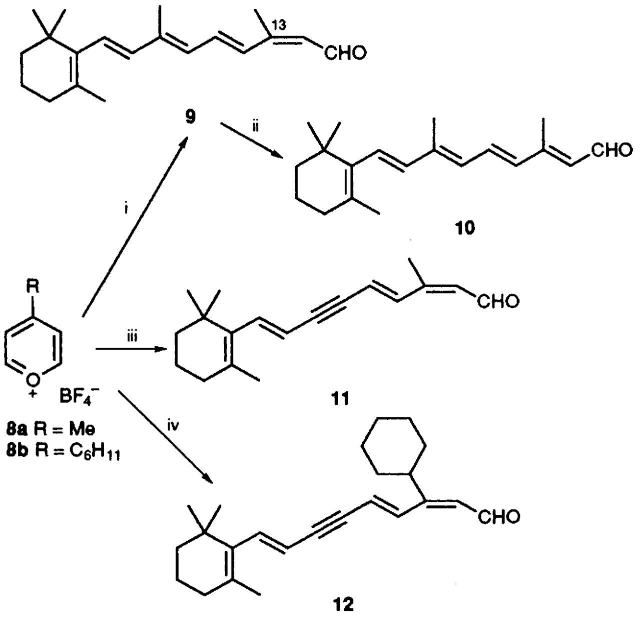
‡ The preparation of **8b** (and other 4-substituted pyrylium salts) from pyrylium tetrafluoroborate will be described in a forthcoming paper.



Scheme 1



Scheme 2 *Reagents and conditions*: i, see ref. 11; ii, Me_3Al, $ZrCl_2(\eta\text{-}C_5H_5)_2$, $(CH_2Cl)_2$, 0 °C to room temp.[12] (then replace solvent with THF); iii, BuLi, THF, −78 to 0 °C; iv, pyrylium tetrafluoroborate, THF, −78 °C (see text)



Scheme 3 *Reagents and conditions*: i, for **8a**: 4 equiv. **6b**, THF, −78 °C, 48%; ii, I_2, Et_2O, PhH, room temp. 48 h, 91%; iii, for **8a**: **5** + BuLi, THF, −78 °C, 57%; iv, for **8b**: **5** + BuLi, THF, −78 °C, 52%

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