The Use of Pyrylium Tetrafluoroborate for the Stereoselective Synthesis of 2*Z*,4*E*-Dienals

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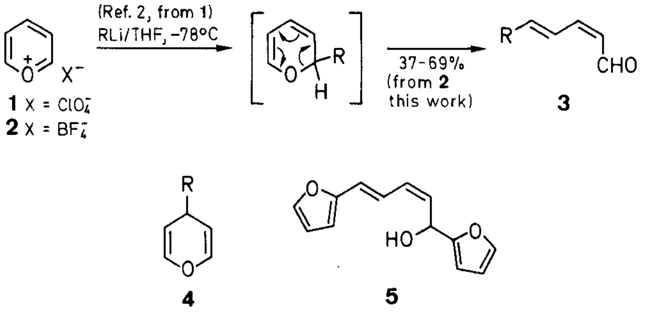
The addition of organolithium reagents to pyrylium tetrafluoroborate followed by in situ electrocyclic ring opening of the intermediate 2*H*-pyrans gives the title *Z*,*E*-dienals with high stereoselectivity.

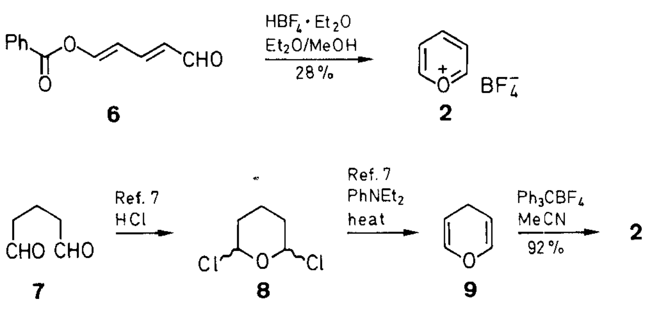
The continued interst in biologically active conjugated polyenes, including arachidonic acid metabolites and pheromones, has encouraged research into the development of new methods for the stereoselective synthesis of this class of compounds.[2] We recently reported[2] that 2*Z*,4*E*-dienals could be formed in a stereoselective manner by the addition of organolithium reagents to pyrylium perchlorate **1** followed by in situ electrocyclic ring opening of the intermediate 2*H*-pyrans as shown in Scheme **1**. This procedure has great potential for natural product synthesis,[3] but to a certain extent this is offset by the hazards associated with the use of perchlorate salts. We now report that pyrylium tetrafluoroborate **2** can be employed successfully in these reactions and give detailed procedures for its preparation.



3	R	3	R
a	Ph	d	(*E*)-PhCH=CH
b	$C_5H_{11}C{\equiv}C$	e	(*E*)-PhC(Me)=CH
c	(*E*)-$Bu_3SnCH{=}CH$	f	2-furyl

Scheme 1

Treatment of sodium glutaconaldehyde dihydrate with ethereal tetrafluoroboric acid, following the literature procedure[4] for the preparation of perchlorate salt **1**, gives pyrylium tetrafluoroborate (**2**) in an impure state which is unsuitable for the organometallic reactions outlined in Scheme **1**.[2] We have now found that treatment of the readily available glutaconaldehyde benzoate (**6**)[5] with ethereal tetrafluoroboric acid gives tetrafluoroborate salt **2** in 28% recrystallised yield as an analytically pure crystalline solid (Scheme **2**). Although low-yielding, this procedure is extremely straightforward and convenient. Alternatively, the procedure of Sandor and Radics[6] which proceeds via 4*H*-pyran (**9**)[7] (Scheme **2**) can be followed. The preparation of pyran **9** from glutaric dialdehyde (**7**) via dichloride **8** is rather involved,[7] and the intermediates are prone to polymerisation but tetrafluoroborate salt **2** can be obtained in 20 g batches via this route.[8]



Scheme 2

Treatment of tetrafluoroborate salt **2** with a range of organolithium reagents in THF gave 2*Z*,4*E*-dienals **3a–f** in reasonable yield (Scheme **1**, Table). In all cases, the dienals were formed with high 2*Z*,4*E*-stereoselectivity, the corresponding 2*E*,4*E*-isomers being present in < 5% according to ^{1}H-NMR analysis.[2] With the exception of the reaction of **2** with 1-heptynyllithium, the 4*H*-pyrans **4** were formed as minor byproducts in all cases according to ^{1}H-NMR spectroscopy although they were readily removed by chromatography and not normally isolated. Of particular note are the trienes **3c** and **3e**. The use of (*E*)-2-tributylstannylvinyllithium[9] gives the stannyl triene **3c** which should be of value in palladium catalysed coupling reactions, whereas the formation of **3e** illustrates that trisubstituted vinyl organometallic reagents are compatible with the pyrylium methodology. Finally, it is of interest to note that under

Table. Dienals 3 Prepared

RLi	Product	Yield[a] (%)	mp (°C)	Molecular Formula[b] or Lit. Data	IR (Nujol/film) $\nu_{C=O}$ (cm^{-1})	^{1}H-NMR (CDCl$_3$/TMS)[c] δ, *J* (Hz)
PhLi	**3a**	61[d]	oil	oil[2]	1665	[e]
$C_5H_{11}C{\equiv}CLi$	**3b**	69	oil	$C_{12}H_{16}O$ (176.3)	1685	see experimental section
(*E*)-$Bu_3SnCH{=}CHLi$	**3c**	37[d, f]	oil	$C_{19}H_{34}OSn$ (397.2)	1676	0.92 (br t, 9H), 1.10–2.26 (m, 18H), 5.76–7.60 (m, 6H), 10.15 (d, 1H, *J* = 7.2)
(E)-PhCH=CHAl(*i*-Bu)$_2$BuLi	**3d**	58[d]	72–73	$C_{13}H_{12}O$ (184.2)	1681	5.88 (dd, 1H, *J* = 7.2, 9.5), 5.62–7.60 (m, 10H), 10.22 (d, 1H, *J* = 7.2)
(E)-PhC(Me)=CAlMe$_2$BuLi	**3e**	54[d, g]	35–36	$C_{14}H_{14}O$ (198.3)	1663	2.28 (s, 3H), 5.88 (dd, 1H, *J* = 7.9, 10.7), 6.48–7.14 (m, 9H), 10.23 (d, 1H, *J* = 7.3)
2-furyllithium	**3f**	62[d, h]	oil	$C_9H_8O_2$ (148.2)	1676	5.88 (dd, 1H, *J* = 7.5, 10.7), 6.51 (m, 2H), 6.80–7.28 (m, 2H), 7.48 (m, 1H), 7.66 (dd, 1H, *J* = 12.0, 14.2), 10.30 (d, 1H, *J* = 7.5)

[a] Yield of isolated, analytically pure product, not optimised. Unless otherwise stated, ca. 1.5 mol equiv of organometallic reagents were employed the reaction was carried out in THF for 4 h at −78 °C, and quenched at the same temperature.

[b] Satisfactory microanalyses obtained: C ±0.3, H ±0.4.

[c] Measured at 60 MHz unless otherwise stated.

[d] The corresponding pyran **4** was also formed (in 15–25% yield according to ^{1}H-NMR spectroscopy) but was removed by chromatography.

[e] ^{1}H-NMR and IR data consistent with published[2] values. Use of Et_2O or DME as solvent gave similar yields.

[f] This reaction is extremely slow, 20 h at −78 °C was required to bring the yield up to 37%.

[g] Reaction carried out with 4 mol equiv of organometallic reagent;[10] the use of 4 equiv of vinyl aluminium reagent[10] in place of aluminate also gave **3e** (41%).

[h] Slow addition (ca. 10 min) of furyllithium required; addition over 1 min gave **3f** (49%), **4f** (16%) and **5** (19%). When the reaction was left for 18 h at −78 °C, only alcohol **5** was observed.

certain reaction conditions (Table, footnote h) 2-furyllithium gave the difuryl alcohol **5** in addition to the expected dienal **3f**; it would appear that the electrocylic ring opening of the 2*H*-pyran precursor to **3f** occurs at an unusually low temperature.[2]

THF was distilled from sodium/benzophenone and MeCN from CaH_2. Chromatography refers to preparative centrifugal chromatography, carried out on silica gel plates (Merck 7749) using a Chromatotron™ model 7924T. Melting points are uncorrected. Mass spectra were obtained on a Kratos MS25 spectrometer, IR spectra on a Perkin-Elmer 1720X FT-IR spectrophotometer. ^{1}H-NMR spectra were obtained on a Jeol PMX-60, ^{13}C-NMR spectra on a Jeol FX-400 spectrometer.

Pyrylium Tetrafluoroborate (2):

Method A: *from Glutaconaldehyde Benzoate* (**6**): A solution of $HBF_4 \cdot Et_2O$ complex (85%, 13.3 mL) in Et_2O (200 mL) is added to solution of glutaconaldehyde benzoate (**6**)[5] (5.2 g, 12.4 mmol) in Et_2O (100 mL) at 0 °C. The mixture is left for 20 h at 0 °C. Precipitated crystals are then filtered under N_2, washed with Et_2O (200 mL), dissolved in anhydrous MeCN (80 mL), precipitated with Et_2O (100 mL), filtered and washed with Et_2O (200 mL), and dried at 0.133 mbar for 2 h. This procedure affords pyrylium tetrafluoroborate (**2**) as analytically pure, off-white crystals; yield: 1.2 g (28%); mp > 210 °C (dec).

$C_5H_5BF_4O$	calc.	C 35.77	H 3.00
(167.9)	found	35.79	2.88

IR (Nujol): ν = 3130, 1620 cm^{-1}.

^{1}H-NMR (TFA/TMS): δ = 8.64 (2H, m), 9.48 (1H, m), 9.81 (2H, m).

Method B: *from 4H-Pyran* (**9**) (*based on published reactions*[6,7]): A solution of freshly prepared and distilled 4*H*-pyran (**9**)[7] (12.8 g, 0.16 mol) in MeCN (30 mL) is cooled to −40 °C. A solution of trityl tetrafluoroborate[11] (46.7 g, 0.14 mol) in MeCN (230 mL) is added to the mixture which is kept at 0 °C for 30 min. Et_2O (500 mL) is then added to the mixture to precipitate the pyrylium salt which is removed by filtration, washed with Et_2O (200 mL), and dried at 0.133 mbar for 2 h. The product is purified by precipitation from MeCN/Et_2O, washed and dried as above giving pyrylium tetrafluoroborate (**2**) as analytically pure, off-white crystals with spectral properties identical to the material produced by method A; yield: 21.7 g (91%).

(2*Z*,4*E*)-Dodeca-2,4-dien-6-ynal (3b); Typical Procedure:

A solution of 1-heptynyllithium, prepared by treatment of 1-heptyne (236 mg, 2.46 mmol) with BuLi (2.5 M, 0.8 mL, 2.0 mmol) in THF (3 mL) at −78 °C followed by warming to 0 °C for 15 min, is added to a stirred suspension of pyrylium tetrafluoroborate (**2**); 0.275 g, 1.64 mmol) in THF (10 mL) under a N_2 atmosphere at −78 °C. The mixture is stirred for 4 h at −78 °C and then sat. aq NH_4Cl (10 mL) is added. The aqueous mixture is extracted with Et_2O (2 × 15 mL), the combined extracts are dried ($MgSO_4$), and the solvent removed under reduced pressure. The resulting oil is purified by preparative centrifugal chromatography on silica gel eluting with EtOAc/petroleum ether (bp 40–60 °C) (1 : 13) to give **3b** as a pale yellow oil; yield: 0.198 g (69%).

$C_{12}H_{16}O$	calc.	C 81.77	H 9.15
(176.3)	found	82.10	9.15

IR (neat): ν = 2933, 2861, 2208, 1685, 1608 cm^{-1}.

^{1}H-NMR (CDCl$_3$/TMS): δ = 0.91 (br t, 3H, *J* = 7.0 Hz), 1.12–1.76 (m, 6H), 2.38 (m, 2H), 5.85 (dd, 1H, *J* = 7.8, 10.1 Hz), 6.00 (dt, 1H, *J* = 14.4, 2.4 Hz), 6.91 (dd, 1H, *J* = 10.1, 12.0 Hz), 7.43 (dd, 1H, *J* = 12.0, 14.4 Hz), 10.15 (d, 1H, *J* = 7.3 Hz).

^{13}C-NMR (CDCl$_3$/TMS): δ = 13.7, 19.6, 22.0, 28.0, 30.9, 79.3, 99.7, 122.4, 127.5, 133.1, 145.6, 189.6.

MS: *m/z* = 176 (M^{+}, 21%), 147 (10.5), 133 (18.7), 119 (41.8), 105 (75.1), 91 (100).

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We obtained 56% overall, distilled yield of pyran **4** starting from dialdehyde **7** (87 g).

(8) Pyrylium hexafluorophosphate was made in a similar manner (77%), but we were unable to obtain it in analytically pure form. Reaction of this impure salt with phenyllithium gave (2*Z*,4*E*)-5-phenylpenta-2,4-dienal (**3a**) in 56% yield.

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