Synthesis and reactivity of 3-(1-hydroxy-3-buten-1-yl)chromone

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Zn-induced allylation of chromone-3-carbaldehyde **1** produces 3-(1-hydroxy-3-butene-1-yl)chromone **2**, which gives back **1** on treatment with formalin under acidic conditions, and reacts differently towards nitrogenous nucleophiles.

Keywords: allylation, oxonia-Cope rearrangement, 3-formylchromone, Schiff bases, 1-benzopyrans

Prins reaction on homoallyl alcohol has drawn much attention in recent years as it provides an easy route for the synthesis of tetrahydropyran rings, which are widely distributed in many complex natural products.[1] 4-Substituted tetrahydropyran moieties have been synthesied from the reaction of homoallylic alcohol and aldehyde in the presence of Brønsted or Lewis acid, HCl or HBr,[2-4] $InCl_3$[5,6] and $In(OTf)_3$.[7,8] Acetals involving the homoallyl alcohol in place of a mixture of aldehyde and homoallyl alcohol can produce tetrahydropyran in the presence of $TiCl_4$ or $SnBr_4$.[9] Recently, one-pot Prins-Ritter reaction on homoallyl alcohol has been carried out in the presence of $CeCl_3$ catalyst.[10] Alkenes react with formaldehyde in presence of H_2SO_4 in AcOH to produce 1,3-diacetoxy compounds.[11] In an attempt to synthesise a tetrahydropyran ring linked at the 3-position of a chromone ring, Barbier allylation and then the Prins reaction were employed on chromone-3-carbaldehyde **1**.[12] The synthesis of 3-(1-hydroxy-3-buten-1-yl)chromone **2** and some of its reactions are reported in this paper.

Results and discussion

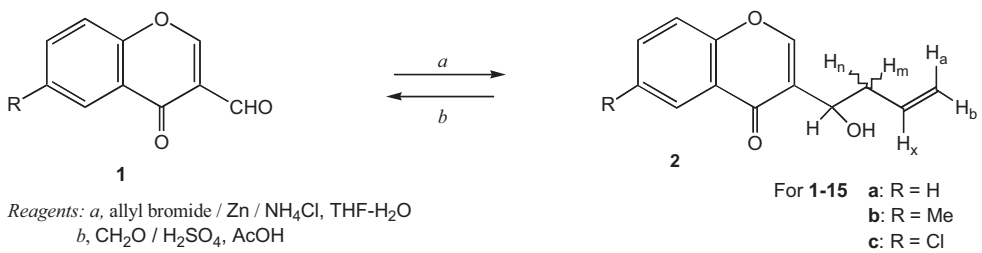
A mixture of aldehyde **1** (1 equiv.), allyl bromide (1.5 equiv.) and Zn dust (4 equiv.) in THF containing saturated aqueous NH_4Cl was stirred for 12 h. After the usual work-up and chromatographic separation compound **2** was isolated in moderate yields (Scheme 1). In order to synthesise the dihydropyran, homoallylic alcohol **2** was heated with formalin under reflux in acetic acid containing a trace of H_2SO_4. Surprisingly, and somewhat disappointingly, the compound isolated after work up was found to be **1** (Scheme 1).

A few cases of allyl transfer reaction have been reported.[13-19] Pyrolysis of a β–hydroxyolefin produces the carbonyl compound and alkene.[20] To verify the possibility of thermal rearrangement, compound **2** was heated neat at 150°C for 4 h, but no change was observed. Again, no aldehyde **1** was detected from the reaction mixture obtained by heating **2** under reflux for 6 h in AcOH containing a trace of concentrated H_2SO_4. Considering the involvement of formaldehyde, a plausible mechanism is considered based on 2-oxonia Cope rearrangement. In this, a [3,3]-sigmatropic shift on **3** produces **4**, which on hydrolysis gives **1** (Scheme 2).

Considering the overall process to be a case of allylation and deallylation on the formyl function of **1**, we tried to utilise this chemistry as a protection and deprotection of aldehyde function in **1**. It has been reported that acetalation of **1** is not adequate protection for the aldehyde function towards nitrogenous nucleophiles.[21]

Treatment of **2** with NH_2OH in ethanol produces **5**, which appeared from ^1H NMR as a mixture of the *syn* and *anti* dioximes. It resembles the product obtained from the reaction of hydroxylamine with chromone **6** (Scheme 3),[22] but compound **5a** could not be isolated in pure form from the reaction mixture of **2a** and NH_2OH.

The reaction may proceed by initial attack of NH_2OH at the C-2 position of the chromone moiety of **2** to produce **7**, which tautomerises to the monooxime **8** (Scheme 3). Base-induced retro-aldol type C–C bond cleavage followed by oxymation or oximation followed by base-induced C–C bond cleavage leads to **5** as a mixture of *syn* and *anti* dioximes. Formation of **5**

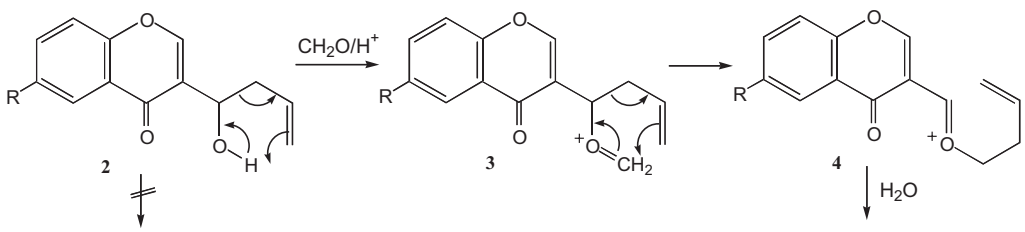


1 **2**

Reagents: a, allyl bromide / Zn / NH_4Cl, THF-H_2O
b, CH_2O / H_2SO_4, AcOH

For **1-15** **a**: R = H
b: R = Me
c: R = Cl

Scheme 1



2 **3** **4**

1 + $CH_3CH{=}CH_2$ **1** + $HOCH_2CH_2CH{=}CH_2$

Scheme 2

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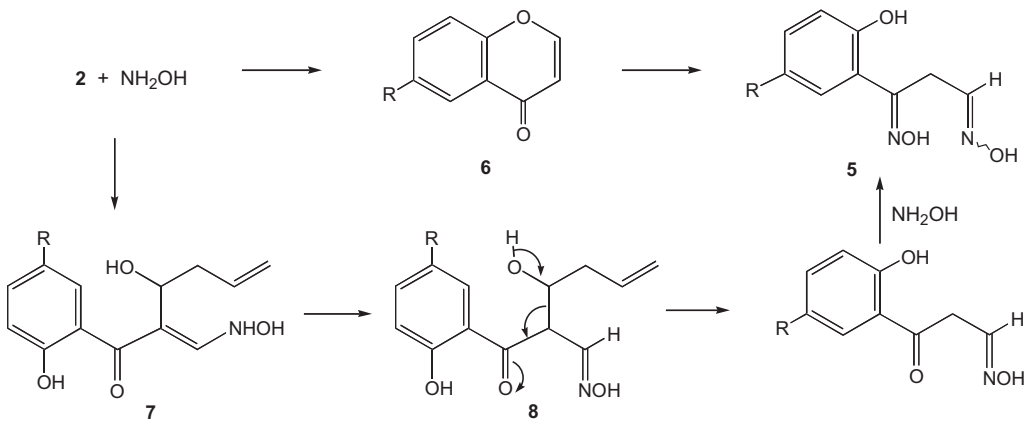
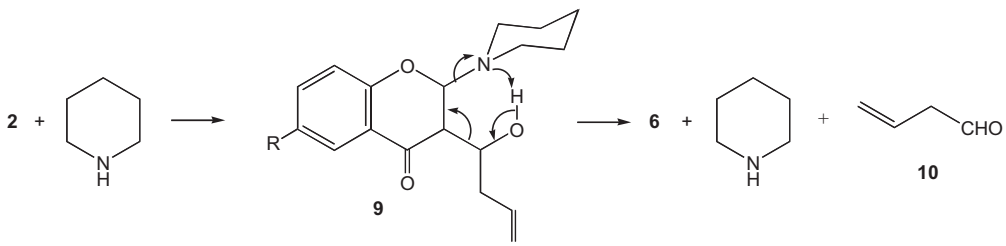


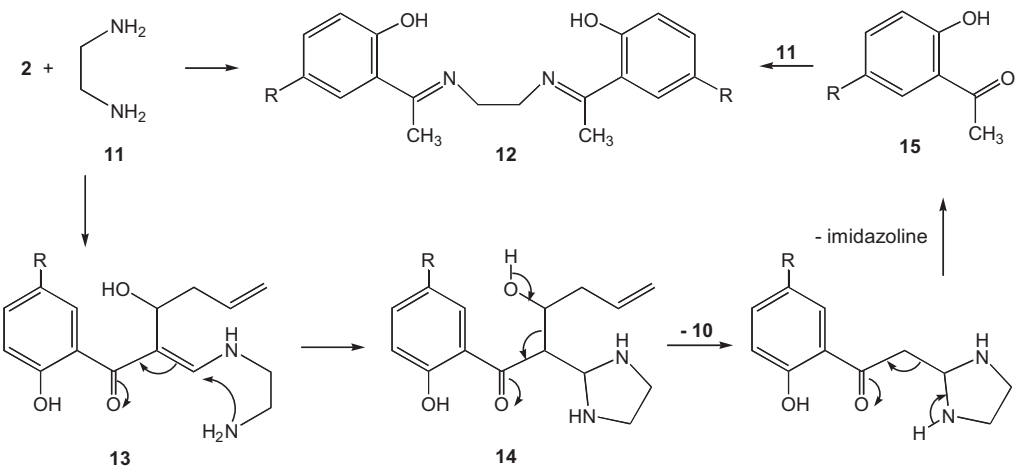
Scheme 3

from **2** may also be considered to proceed *via* the intermediate formation of chromone **6**. To confirm the feasibility of the formation of **6** from **2**, it was heated in EtOH containing 2 equiv. of pyridine for 6 h, but no change was observed. However, when the same experiment was performed using piperidine (2 equiv.) in place of pyridine, chromone **6** was produced as the only isolable product (Scheme 4). Formation of chromone **6** from **2** may be rationalised by considering a Michael-type addition of piperidine to the C_2-C_3 bond of the chromone ring of **2** to form **9**. Intramolecular proton transfer followed by the expulsion of 3-butenal (**10**) and piperidine from **9** lead to the formation of **6**. Regarding the function of piperidine as a catalyst here, it was found that a lesser amount of piperidine (0.5 equiv.) failed to complete the reaction even after 10 h of heating. This may be due to interaction of the piperidine with 3-butenal. Compound **2** failed to react with *o*-phenylenediamine or *p*-toluidine when heated in ethanol for 20 h or 12 h, respectively.

Reaction of **2** with ethylenediamine (**11**) produces the Schiff base **12**, rather than a diazepine derivative bearing the homoallylic alcohol moiety. It has been reported[23] that the chromone **6** reacts with ethylenediamine to form 2,3-dihydro-5-(2-hydroxyphenyl)-1,4-diazepine. Hence the possibility of formation of **6** as an intermediate en route to **12** can be ruled out. Formation of **12** may be rationalised by considering the initial attack of an amino function of ethylenediamine at the C-2 position of the pyran ring of **2** followed by the pyran ring opening to form **13** (Scheme 5). The second amino function of ethylenediamine attacks the β–position of the αβ–unsaturated ketone moiety of **13** resulting in the imidazolidine **14**. Subsequent expulsions of butenal and imidazoline lead to the formation of *o*-hydroxyacetophenone **15**, which reacts with ethylenediamine to form the diimine **12**. Indeed, *o*-hydroxyacetophenone reacts with ethylenediamine in EtOH readily to form **12** (R = H) in excellent yield. The sequence of elimination of the butenal and imidazoline moieties in **14** could not be ascertained.



Scheme 4



Scheme 5

In conclusion, we have studied an allylation-deallylation reaction of the chromone aldehydes **1** and also the retro-aldol reaction of the homoallyl alcohols **2** induced by some nitrogenous nucleophiles.

Experimental

IR spectra were recorded in KBr on a Beckmann IR 20A instrument, ^{1}H NMR spectra in $CDCl_3$ on a Bruker 300 MHz spectrometer, mass spectra on an Qtof Micro YA 263 instrument and elemental analyses on a Perkin Elmer 240C elemental analyser. Light petroleum refers to the fraction with distillation range 60-80°C.

Allylation of chromone-3-carbaldehyde (**1**): *general procedure*
The aldehyde **1** (10 mmol), Zn dust (2.5 g, 40 mmol), allyl bromide (1.8 g, 15 mmol) was stirred in THF (100 ml) containing saturated aqueous NH_4Cl (2 ml) for 12 h at room temperature. The reaction mixture was then filtered, the solvent was removed from the filtrate under reduced pressure, and ice-water (50 g) was added to the concentrate. An oily mass separated and was extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4 and chromatographed on silica gel (100–200). Compound **2** was obtained from the column using benzene as eluent.

3-(1-Hydroxybut-3-en-1-yl)chromone (**2a**):[24] Faintly yellow oil (1.20 g, 56%). IR: ν_{max} 3320, 2900, 1650, 1605, 1470 cm^{-1}. NMR: δ_H 2.50-2.60 (1 H, m, Hm), 2.69–2.77 (1 H, m, Hn), 3.38 (1 H, brs, exchangeable, OH), 4.77 (1 H, t, *J* = 6.4 Hz, C*H*OH), 5.13–5.18 (2 H, m, Ha + Hb), 5.80–5.91 (1 H, m, Hx), 7.39–7.48 (2 H, m, 6-H, 8-H), 7.66–7.71 (1 H, m, 7-H), 7.94 (1H, s, 2-H) and 8.21 (1 H, dd, *J* = 7.9, 1.5 Hz, 5-H).

3-(1-Hydroxybut-3-en-1-yl)-6-methylchromone (**2b**): Light yellow crystalline solid (1.40 g, 61%); m.p. 68–70°C. IR: ν_{max} 3399, 2917, 1638, 1605, 1484 cm^{-1}; δ_H 2.45 (3 H, s, CH_3), 2.50–2.60 (1 H, m, Hm), 2.67–2.75 (1 H, m, Hn), 3.40 (1 H, br, s, exchangeable, OH), 4.72 (1 H, t, *J* = 5.5 Hz, C*H*OH), 5.12–5.17 (2 H, m, Ha + Hb), 5.79–5.92 (1 H, m, Hx), 7.36 (1 H, d, *J* = 8.6 Hz, 8-H), 7.48 (1 H, dd, *J* = 8.6, 2.2 Hz, 7-H), 7.90 (1 H, s, 2-H) and 8.00 (1 H, d, *J* = 2.2 Hz, 5-H). Anal. calcd. for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 72.84; H, 5.90%.

6-Chloro-3-(1-hydroxybut-3-en-1-yl)chromone (**2c**): Light yellow crystalline solid (1.50 g, 60%); m.p. 84–86°C. IR: ν_{max}/cm^{-1} 3319, 2918, 1641, 1604, 1464; δ_H 2.46–2.55 (1 H, m, Hm), 2.68–2.76 (1 H, m, Hn), 3.22 (1 H, brs, exchangeable, OH), 4.79 (1 H, t, *J* = 5.8 Hz, C*H*OH), 5.13–5.17 (2 H, m, Ha + Hb), 5.79–5.92 (1 H, m, Hx), 7.43 (1 H, d, *J* = 8.8 Hz, 8-H), 7.61 (1 H, dd, *J* = 8.8, 2.3 Hz, 7-H), 7.96 (1 H, s, 2-H) and 8.15 (1 H, d, *J* = 2.3 Hz, 5-H); Anal. calcd. for $C_{13}H_{11}ClO_3$: C, 62.29; H, 4.42. Found: C, 61.72; H, 4.25%.

Reaction of the hydroxybutenyl chromone **2** *with formaldehyde*
The chromone **2** (2 mmol), 37% aqueous formaldehyde (1 ml) and concentrated H_2SO_4 (three drops) in AcOH (10 ml) were heated under reflux for 2 h. The reaction mixture was concentrated under reduced pressure. Ice-water (15 g) was then added to the concentrate to afford a solid mass. This was filtered off, washed with water, dried in air and crystallised from benzene-light petroleum to afford **1** as a white crystalline solid. Compounds **1a** (210 mg, 60%), **1b** (300 mg, 80%) and **1c** (340 mg, 81%) were identical in all respects with authentic samples.

Reaction of chromone **2** *with hydroxylamine; formation of dioximes* **5**
Compound **2** (0.5 mmol), hydroxylamine hydrochloride (140 mg, 2 mmol) and sodium acetate (330 mg, 4 mmol) in EtOH (25 ml) were heated under reflux for 4 h. Solvent was then removed under reduced pressure to leave a white solid. Ice-water (10 g) was added, stirred for 10 min and filtered. The residue was washed with water, dried in air and recrystallised from $CHCl_3$/MeOH to give the dioxime **5** as white fine crystalline solid.

1-(2-Hydroxy-5-methylphenyl)propane-1,3-dione 1,3-dioxime (**5b**): White finely crystalline compound (80 mg, 77%); m.p. 156–158°C. IR: ν_{max} 3250, 2868, 1650, 1570, 1480 cm^{-1}. NMR: δ_H (DMSO-d_6) (*syn: anti* 9: 7) 2.20 (6 H, s, ArCH_3 *s* + *a*), 3.66 (2 H, d, *J* = 5.2 Hz, CH_2 *a*), 3.75 (2 H, d, *J* = 4.9 Hz, CH_2 *s*), 6.61 (1 H, t, *J* = 4.9 Hz, C*H*=*N s*), 6.75 (1 H, d, *J* = 8.2 Hz, 3'-H *a*), 6.76 (1 H, d, *J* = 8.2 Hz, 3'-H *s*), 7.01-7.04 (2 H, m, 4'-H *s* + *a*), 7.19 (1 H, d, *J* = 1.0 Hz, 6'-H *s*), 7.22 (1 H, d, *J* = 1.0 Hz, 6'-H *a*), 7.35 (1 H, t, *J* = 5.2 Hz, C*H*=*N a*), 10.64 (1 H, s, exchangeable, C3-OH *a*), 10.89 (1 H, brs, exchangeable, C3-OH *s*), 11.00 (1 H, s, exchangeable, C1-OH *a*), 11.16 (1 H, s, exchangeable, C1-OH *s*) and 11.66 (2 H, s, exchangeable, C2'-OH *s* + *a*). Anal. calcd. for $C_{10}H_{12}N_2O_3$: C, 57.69; H, 5.81; N, 13.45. Found: C, 57.20; H, 5.65; N, 13.35.

1-(5-Chloro-2-hydroxyphenyl)propane-1,3-dione 1,3-dioxime (**5c**): White fine crystalline compound (105 mg, 92%); m.p. 168–170°C. IR: ν_{max} 3279, 2888, 1640, 1595, 1485 cm^{-1}. NMR: δ_H (DMSO-d_6) (*syn: anti* 5: 3) 3.68 (2 H, d, *J* = 4.9 Hz, CH_2 *a*), 3.74 (2 H, d, *J* = 4.9 Hz, CH_2 *s*), 6.66 (1 H, t, *J* = 4.9 Hz, C*H*=*N s*), 6.90 (2 H, d, *J* = 8.6 Hz, 3'-H *s* + *a*), 7.27 (2 H, dd, *J* = 8.6, 2.1 Hz, 4'-H s + a), 7.39 (1 H, d, *J* = 2.1 Hz, 6'-H *s*), 7.42 (1 H, d, *J* = 2.1 Hz, 6'-H *a*), 7.49 (1 H, t, *J* = 4.9 Hz, C*H*=*N a*), 10.69 (1 H, s, exchangeable, C3-OH *a*), 11.10 (1 H, s, exchangeable, C3-OH *s*), 11.18 (1 H, s, exchangeable, C1-OH *s*), 11.28 (1 H, s, exchangeable, C1-OH *a*), 11.85 (1 H, s, exchangeable, C2'-OH *s*) and 11.87 (1 H, s, exchangeable, C2′-OH *a*). Anal. calcd. for $C_9H_9ClN_2O_3$: C, 47.28; H, 3.97; N, 12.25. Found: C, 47.05; H, 3.85; N, 12.01.

Treatment of **2** *with piperidine: formation of chromones* **6**
The chromone **2** (1 mmol) and piperidine (170 mg, 2 mmol) were heated under reflux in ethanol (15 ml) for 6 h. The reaction mixture was concentrated under reduced pressure. Ice-water (25 g) was added to the concentrate. The oily mass separated was extracted with $CHCl_3$, washed with water, dried over Na_2SO_4 and chromatographed over silica gel (100–200). Compound **6** was isolated using benzene as eluent. The compounds were identical in all respects with authentic samples.

6-Methylchromone (**6b**): Yield 90 mg (56%), m.p. 92–94°C; (lit.[25] m.p. 93°C).

6-Chlorochromone (**6c**): Yield 100 mg (55%), m.p. 138–140°C; (lit.[25] m.p. 140°C).

Action of ethylenediamine with **2**: *formation of bisimines* **12**
A mixture of homoallylic alcohol **2** (1 mmol), ethylenediamine (180 mg, 3 mmol) in EtOH (15 ml) was heated under reflux for 5 h. Solvent was removed from the reaction mixture under reduced pressure and cold water (15 ml) was added to the concentrate. The resultant semisolid mass was extracted with benzene, washed with water and dried over Na_2SO_4. On concentration it afforded **12** as a yellow crystalline solid.

N,N′-bis[1-(2-hydroxyphenyl)ethylidene]ethylenediamine (**12a**): Yield (80 mg, 54%); m.p. 188–190°C. IR: ν_{max} 3450, 2960, 1615, 1500 cm^{-1}. δ_H 2.39 (6 H, s, 2 × CH_3), 3.98 (4 H, s, 2 × CH_2), 6.76–6.82 (2 H, m, 2 × 5-H), 6.92 (2 H, dd, *J* = 8.3, 0.9 Hz, 2 × 3-H), 7.25–7.30 (2 H, m, 2 × 4-H), 7.52 (2 H, dd, *J* = 8.0, 1.2 Hz, 2 × 6-H) and 15.84 (2 H, brs, exchangeable, 2 × OH); MS: m/z 297 ($M + H^+$).

N,N′-bis[1-(5-Chloro-2-hydroxyphenyl)ethylidene]ethylenediamine (**12c**): Yield (120 mg, 66%); m.p. 236–238°C. IR: ν_{max} 3447, 2910, 1615, 1492 cm^{-1}. δ_H 2.38 (6 H, s, 2 × CH_3), 4.00 (4 H, s, 2 × CH_2), 6.88 (2 H, d, *J* = 9.0 Hz, 2 × 3-H), 7.23 (2 H, dd, *J* = 9.0, 0.9 Hz, 2 × 4-H), 7.50 (2 H, d, *J* = 0.9 Hz, 2 × 6-H) and 15.76 (2 H, brs, exchangeable, 2 × OH).

Compounds **12a, c** are identical in all respect (m.p, m.m.p and superimposable IR) with the samples prepared from appropriate hydroxyacetophenones **15** and ethylenediamine.

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