Unusual Regioselectivity in the Reduction of α,β-Unsaturated Carbonyl Compounds with Diisobutylaluminium Hydride (DIBAH): Direct Conversion of Isoflavones to Isoflavan-4-ones

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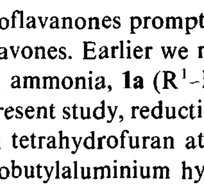
Our interest in the synthesis of natural isoflavanones[1] and the lack of a selective method for the conversion of isoflavones to isoflavanones prompted us to investigate the reduction of isoflavones. Earlier we reported[2], that on reduction with lithium in ammonia, **1a** (R^1-R^5 = H) yielded the ketone **2** and, in the present study, reduction of **1a** with lithium aluminium hydride in tetrahydrofuran at room temperature[3], or with lithium diisobutylaluminium hydride also gave **2**. Formation of **2** was rationalized by base catalyzed retro-Michael type ring opening[4] of the intermediate isoflavan-4-one to the vinyl-ketone **3** which was further reduced to **2**. In fact, when **4a** (R^1-R^6 = H) was treated with sodium hydride in benzene, **3** was obtained as an oil.



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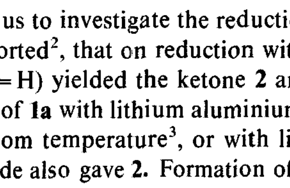

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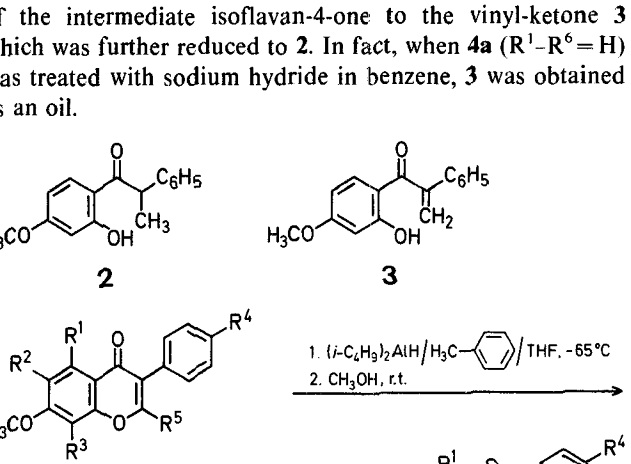


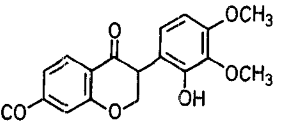
4a-f

These results suggested that, for the selective conversion of an isoflavone to an isoflavanone, a neutral reducing agent should be selected which would not induce the formation of a carbanion from the product. Despite an adverse prognosis of the literature (see below), diisobutylaluminium hydride (DIBAH) proved to be ideal for this purpose and converted the isoflavones **1a-e** to the isoflavan-4-ones **4a-f** in high yield (Table).

Reduction of the chromone **5**, of the exocyclic six-membered enones **6a, b**, and of the open-chain enones **7a, b** all followed the same pattern and gave rise to the corresponding saturated ketones **8, 9a, b**, and **11a, b**, respectively (Table). These results were unexpected in view of the literature reports in which only examples for the reduction of enones to allylic alcohols had been reported[5]. This discrepancy is not a result of the lower temperature (−65 °C) applied since reduction of cyclohexenone with DIBAH yielded cyclohexenol both at 0-5 °C[6] and at −65 °C.

Reduction with DIBAH seems to be very susceptible to minor structural changes as shown by the fact that the five-membered exocyclic enones **6c, d** provided the allylic alcohols **10a, b**. This may be ascribed to the strict coplanarity of the enone function in these compounds, while in the models giving saturated ketones, the carbonyl group and the double bond are either slightly twisted or freely rotating. With benzylidenetetralones this twisting was experimentally demonstrated[7].

The utility of the new method was demonstrated by the synthesis of (±)-2′-hydroxy-3′,4′,7-trimethoxyisoflavan-4-one (**12**), a constituent of *Myroxylon peruiferum*[8].



12

The ^{1}H-N.M.R. spectra were determined with TMS as internal standard using a Perkin-Elmer R12 instrument.

Isoflavan-4-ones; General Procedure:

To a solution of the isoflavone (1 mmol) in dry toluene (15 ml) and dry tetrahydrofuran (7 ml), a solution of DIBAH in toluene (2.5 mmol) is added at −65 °C under argon. After 1 h, the mixture is quenched with methanol (20 ml) and allowed to warm to room temperature. After the addition of 2.5% aqueous hydrochloric acid (10 ml) and benzene (30 ml), the organic phase is separated, dried, and evaporated to give the crude product which is purified by crystallization or chromatography (Table).

2′-Hydroxy-3′,4′,7-trimethoxyisoflavan-4-one (12):

Condensation of 2-hydroxy-4-methoxyacetophenone and 2-benzyloxy-3,4-dimethoxybenzaldehyde[9] as described earlier[10] gives *2-benzyloxy-2′-hydroxy-3,4,4′-trimethoxychalcone;* yield: 28%; m.p. 142-144 °C (methanol).

$C_{25}H_{24}O_6$	calc.	C 71.41	H 5.75
(420.5)	found	71.21	5.65

I.R. (KBr): ν = 1630, 1560 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 3.84 (s, 3 H); 3.94 (s, 6 H); 5.12 (s, 2 H); 6.30 (q, 1 H, J = 9 Hz, 2.5 Hz); 6.43 (d, 1 H, J = 2.5 Hz); 6.76 (d, 1 H, J = 9 Hz); 7.3-7.6 (m, 1 H); 7.65 (d, 1 H, J = 15.5 Hz); 7.94 (d, 1 H, J = 15.5 Hz); 13.62 ppm (s, 1 H).

Treatment of the above product with thallium(III) nitrate in methanol[10] gives *2′-benzyloxy-3′,4′,7-trimethoxyisoflavone*; yield: 67%; m.p. 141-143 °C (methanol).

$C_{25}H_{22}O_6$	calc.	C 71.46	H 5.22
(418.5)	found	71.40	5.12

I.R. (KBr): ν = 1612, 1600 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 3.92, 3.95 (2 s, 6 H); 5.04 (s, 2 H); 6.8-7.3 (m, 9 H); 7.70 (s, 1 H); 8.20 ppm (d, 1 H, J = 8.5 Hz).

Reduction of the above compound with DIBAH gives *2′-benzyloxy-3′,4′,7-trimethoxyisoflavan-4-one*; yield: 56%; m.p. 124-126 °C (methanol).

$C_{25}H_{24}O_6$	calc.	C 71.41	H 5.75
(420.5)	found	71.18	5.56

I.R. (KBr): ν = 1680, 1600 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 3.84, 3.87, 3.88 (3 s, 9 H); 4.0-4.6 (m, 3 H); 5.11 (s, 2 H); 6.40 (d, 1 H, J = 2.5 Hz); 6.58 (q, 1 H, J = 2.5 Hz, 8.5 Hz); 6.67 (d, 1 H, J = 8.5 Hz); 6.80 (d, 1 H, J = 8.5 Hz); 7.85 ppm (d, 1 H, J = 8.5 Hz).

Debenzylation of the above product by catalytic hydrogenation gives *2′-hydroxy-3′,4′,7-trimethoxyisoflavan-4-one* (**12**); yield: 65%; m.p. 155-156 °C (methanol); Lit.[8], m.p. 155-157 °C.

I.R. (KBr): ν = 1680, 1600 cm^{-1}.

^{1}H-N.M.R. (CD_3—CO—CD_3): δ = 3.81, 3.83, 3.90 (3 s, 9 H); ~4.0 (1 H); 4.6 (m, 2 H); 6.50 (q, 1 H, J = 2.0 Hz, 8.5 Hz); 6.60 (d, 1 H, J = 2 Hz); 6.76 (s, 2 H); 7.86 ppm (d, 1 H, J = 8.5 Hz).

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Table. Reduction of α,β-Unsaturated Carbonyl Compounds with Diisobutylaluminium Hydride

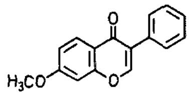
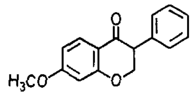
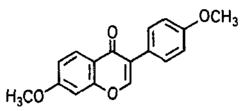
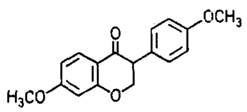
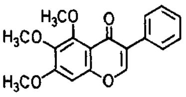
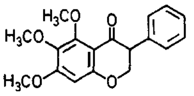
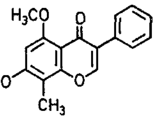
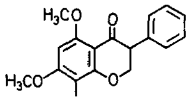
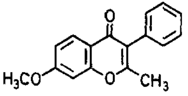
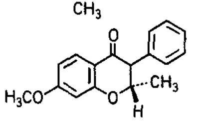
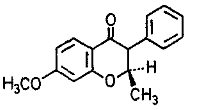
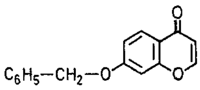
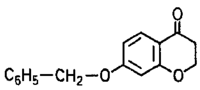
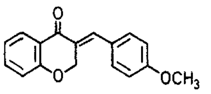
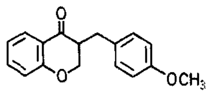
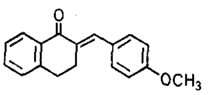
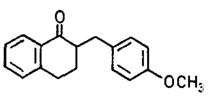
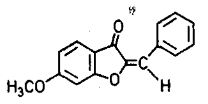
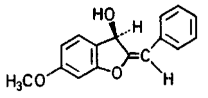
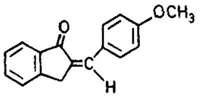
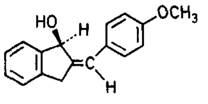
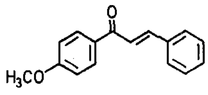
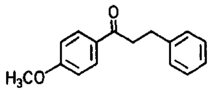
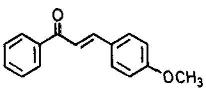
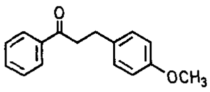
Substrate	Product	Yield [%][a]	m.p. [°C] (solvent)	Molecular formula[b] or Lit. m.p. [°C]	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. (CDCl$_3$) δ [ppm]
1a 	**4a** 	90	98-99° (CH_3OH)	92-95°[11]	1680, 1600	3.70 (s, 3H); 3.77 (t, 1H, J=6.5 Hz); 4.50 (d, 2H, J=6.5 Hz); 6.27 (d, 1H, J=2 Hz); 6.44 (q, 1H, J=2 Hz, 8 Hz); 7.76 (s, 5H); 7.73 (d, 1H, J=8 Hz)
1b 	**4b** 	87	130-132° (CH_3OH/ n-C_6H_{14})	130-131°[12]	1695, 1600	3.72, 3.80 (2s, 6H); ~3.9 (1H); 4.60 (d, 2H, J=6.5 Hz); 6.4-6.7 (m, 2H); 6.81 (d, 2H, J=8.5 Hz); 7.17 (d, 2H, J=8.5 Hz); 7.81 (d, 1H, J=8.5 Hz)
1c 	**4c** 	89	160-161° (CH_3OH)	$C_{18}H_{18}O_5$ (314.3)	1680, 1590, 1560	3.83, 3.88, 3.92 (3s, 9H); ~3.9 (1H); 4.62 (d, 2H, J=6.5 Hz); 6.32 (s, 1H); 3.37 (s, 5H)
1d 	**4d** 	75	130-131° (CH_3OH)	131°[13]	1675, 1600	2.02 (s, 3H); 3.90 (s, 6H); ~3.9 (1H); 4.64 (d, 2H, J=6.5 Hz); 6.12 (s, 1H); 7.32 (s, 5H)
1e 	**4e** 	21[c]	107-109° (CH_3OH)		1660, 1595	1.30 (d, 3H, J=6.5 Hz); 3.58 (d, 1H, J=3.5 Hz); 3.87 (s, 3H); 4.85 (q, 1H, J=6.5 Hz, 3.5 Hz); 6.50 (d, 1H, J=2 Hz); 6.64 (q, 1H, J=2 Hz, 8.5 Hz); 7.1-7.3 (m, 5H); 7.88 (d, 1H, J=8.5 Hz)
	+			122-122.5°		
	4f 	42[c]	116-117° (CH_3OH)		1660, 1595	1.33 (d, 3H, J=6 Hz); 3.67 (d, 1H, J=11 Hz); 4.73 (q, 1H, J=6 Hz, 11 Hz); 6.46 (d, 1H, J=2.5 Hz); 6.61 (q, 1H, J=2 Hz, 8.5 Hz); 7.1-7.4 (m, 5H); 7.86 (d, 1H, J=8.5 Hz)
5 	**8** 	57	102-103° (CH_3OH)	153-155°[15]	1650, 1600	2.66 (t, 2H, J=6.5 Hz); 4.51 (t, 2H, J=6.5 Hz); 4.98 (s, 2H); 6.38 (d, 1H, J=2 Hz); 6.52 (q, 1H, J=2 Hz, 8.5 Hz); 7.30 (s, 5H); 7.75 (d, 1H, J=8.5 Hz)
6a 	**9a** 	50	93-95° (CH_3OH)	98-99°[16]	1680, 1600	2.72 (d, 1H, J=12.2 Hz); 2.84 (m, 1H); 3.21 (t, 1H, J=12 Hz, 2.8 Hz); 4.18 (q, 1H, J=15.4 Hz, 4.1 Hz); 4.37 (q, 1H, J=15.4 Hz, 7.5 Hz); 6.98 (m, 2H); 7.49 (m, 1H); 7.93 (m, 1H)
6b 	**9b** 	71	97-98° (n-C_6H_{14})	98°[17]	1680, 1600	2.0 (m, 2H); 2.5-3.0 (m, 4H); 3.3 (m, 1H); 3.73 (s, 3H); 6.80 (d, 2H, J=8.5 Hz); 7.13 (d, 2H, J=8.5 Hz); 7.0-7.5 (m, 3H); 8.0 (m, 1H)

Table. (continued).

Substrate		Product		Yield [%][a]	m.p. [°C] (solvent)	Molecular formula[b] or Lit. m.p. [°C]	I.R. (KBr) ν [cm⁻¹]	¹H-N.M.R. (CDCl₃) δ [ppm]
6c		**10a**		65	122-123° (n-C_6H_{14})	$C_{16}H_{14}O_3$ (254.3)	3450, 1608, 1595	2.44 (d, 1H, J=9.5 Hz)[d]; 3.70 (s, 3H); 5.50 (d, 1H, J=9.5 Hz)[d]; 5.83 (s, 1H); 6.4-6.6 (m, 2H); 7.1-7.7 (m, 6H)
6d		**10b**		42	95-97° (CH_3OH)	$C_{17}H_{16}O_2$ (252.3)	3350, 1600	2.14 (d, 1H, J=7 Hz)[d]; 3.72 (s, 3H); ~3.7 (2H); 5.50 (d, 1H, J=7 Hz)[d]; 6.74 (s, 2H); 6.82 (d, 2H, J=8.5 Hz); 7.1-7.5 (m, 6H)
7a		**11a**		59	97–100° (CH_3OH)	96-97°[18]	1665, 1600	2.9-3.2 (m, 4H); 3.82 (s, 3H); 6.90 (d, 2H, J=8.5 Hz); 7.20 (s, 5H); 7.92 (d, 2H, J=8.5 Hz)
7b		**11b**		44	65-67° (ether)	59-60°[18]	1680, 1600	2.9-3.2 (m, 4H); 3.73 (s, 3H); 6.70 (d, 2H, J=8.5 Hz); 7.05 (d, 2H, J=8.5 Hz); 7.2-7.5 (m, 3H); 7.8 (m, 2H)

[a] Yield after crystallization.

[b] Satisfactory microanalyses obtained for all products: C ±0.3, H ±0.28.

[c] Separated by preparative layer chromatography.

[d] Exchanged with D_2O.

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