Facile reduction of benzopyrones with nickel boride: a new method for synthesis of 2*H*-1-benzopyran-4-ols

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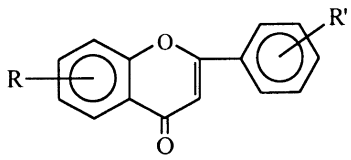
Reduction of various benzopyrones to the corresponding 2*H*-1-benzopyran-4-ols by nickel boride in methanol at ambient temperature is reported

Keywords: benzopyrones, nickel boride, 2H-1-benzopyran-4-ols

Benzopyrones and 2*H*-1-benzopyran-4-ols are important classes of naturally occurring compounds. Benzopyrones *e.g.*, flavones (I), flavanones (II), chromones (III), chromanones (IV), isoflavones (V) and isoflavanones (VI) can be reduced to give different products with different reagents but also undergo ring opening, hydrogenolysis and other side reactions which lower the yields of 2*H*-1-benzopyran-4-ols.[6] The use of sodium borohydride (SBH) with or without the presence of Lewis acids has been attempted for reductions of benzopyrones in different solvents under various conditions. It is reported in the literature that flavones (I) are resistant to SBH reduction as compared to flavanones (II) due to the conjugation of the 2-phenyl group with the enone group. Although LAH,[7] and SBH/Lewis acid[6] have been reported to reduce a few flavones (I), the reaction times are long and the flavan-4-ols (VII) are obtained in poor yields. Similarly chromones (III) and isoflavones (V) are reduced with difficulty as compared to their dihydro derivatives, *i.e.* chromanones (IV) and isoflavanones (VI), due to double bond conjugation.

The stereochemistry of the 2*H*-1-benzopyran-4-ols depends on the nature of the reducing agent. Reductions of flavanones (II) with Pt–H_2, Raney Ni–EtOH, anhyd. $AlCl_3$, LAH and SBH gave 2,4-*cis*- (β)-isomers whereas Al–Hg reduction gave 2,4-*trans*- (α)-isomers.[5g,16] The isoflavan-4-ols (IX) formed by reduction of isoflavones (V) with SBH are also reported to be 3,4-*cis* compounds based on $J_{3,4}$ values.[16,17] Reduction of chromanones (IV) with LAH, SBH and catalytic hydrogenation in the presence of Raney Ni, Pd and Pt[18] yielded *cis*-2-substituted 4-chromanols (VIII). In view of the unpredictable nature of the reduced products from benzopyrones, we have investigated the reductions of (I–VI) with nickel boride[19] to determine the selectivity and stereochemistry (if applicable) of the products.

Benzopyrones (I–VI) are reported to undergo reduction with nickel boride in dry methanol at ambient temperature to give 2*H*-1-benzopyran-4-ols in good yields (Table 1). The nickel boride was generated *in situ* from anhydrous nickel chloride and sodium borohydride. The reactions were sluggish in tetrahydrofuran and dioxan and did not proceed to completion. Flavones (I) and chromones (III) which are resistant to reduction were reduced readily to give the corresponding 2*H*-1-benzopyran-4-ols in methonol. The involvement of nickel boride as a reducing agent was confirmed by carrying out reactions with sodium borohydride alone, since flavone, 2-methylchromone and 7-methoxyisoflavone did not undergo



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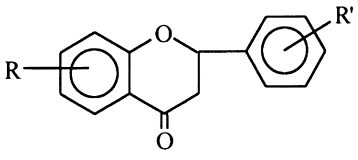

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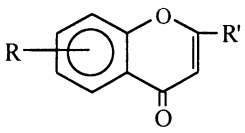

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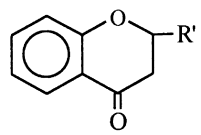

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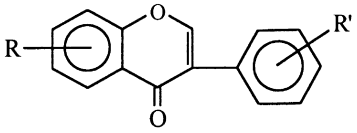

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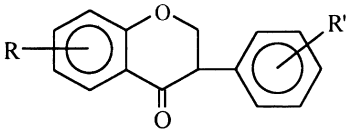

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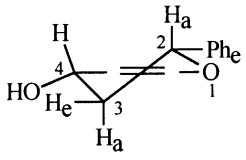

(X)

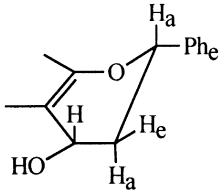

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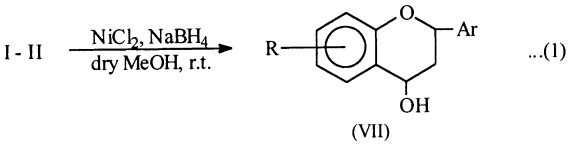
Table 1 Facile reduction of benzopyrones with nickel boride in MeOH[a] at ambient temperature

Run no.	Substrate	Substrate: $NiCl_2$: $NaBH_4$	Time min	Yield/ %	M.p. / °C	Lit.m.p. /°C
1	Flavone	1:1:3	–	–[b]	–	–
2	Flavone	1:2:6	10	55	146	148[1c]
3	Flavone	1:0:6	–	–[c]	–	–
4	4′-Methoxyflavone	1:4:12[d]	130	61	151–152	150–151[1c]
5	3′,4′-Dimethoxyflavone	1:3:9	10	73	158	157–158[5f]
6	4′-Methoxy-6-methylflavone	1:3:9[e]	130	76	138	138[1c]
7	6,4′-Dimethoxyflavone	1:4:12[f]	255	75	146–148	148–149[5d]
8	2-Methylchromone	1:1:3	10	75	84	84–86[18b]
9	2-Methylchromone	1:0:3	–	–[c]	–	–
10	Chromone	1:1:3	10	68	38	41[20]
11	6-Methylchromone	1:1:3	10	67	39	41[8b]
12	2,6-Dimethylchromone	1:1:3	10	85	92	95–97[8a]
13	7-Methoxychromone	1:1:3	10	66	–	–[21]
14	7-Methoxyisoflavone	1:2:6[g]	130	69	132–136	138–140[15]
15	7-Methoxyisoflavone	1:0:6	–	–[c]	–	–
16	7,3′,4′-Trimethoxyisoflavone	1:3:9[e]	135	83	116–118	120–122[15]
17	Flavanone	1:1:3	10	56	148	148[1c]
18	4′-Methoxyflavanone	1:1:3	15	85	150	150–151[1c]
19	7-Methoxyisoflavanone	1:2:6[g]	130	76	134–138	138–140[15]
20	7,4′-Dimethoxyisoflavanone	1:2:6[g]	135	89	136–138	141–143[15]
21	7,3′,4′-Trimethoxyisoflavanone	1:2:6[g]	130	86	120	120–122[15]
22	Chromanone	1:1:3	10	85	38	41[20]
23	2-Methylchromanone	1:1:3	10	91	84	84–86[18b]

[a] 25 ml of dry MeOH/g of substrate was used.
[b] Reduction was incomplete even after 3.5 h but showed the formation of flavan-4-ol.
[c] Reaction was incomplete even after 2 days.
[d] Reaction was started with 1:3:9 molar ratio, 1:3 molar ratio of $NiCl_2$ to $NaBH_4$ was added after 2 h.
[e] Reaction was started with 1:2:6 molar ratio, 1:3 molar ratio of $NiCl_2$ to $NaBH_4$ was added after 2 h.
[f] Reaction was initially started with 1:2:6 molar ratio, two lots of 1:3 molar ratio of $NiCl_2$ to $NaBH_4$ were added at intervals of 2 h.
[g] Reaction was started with 1:1:3 molar ratio, 1:3 molar ratio of $NiCl_2$ to $NaBH_4$ was added after 2 h.



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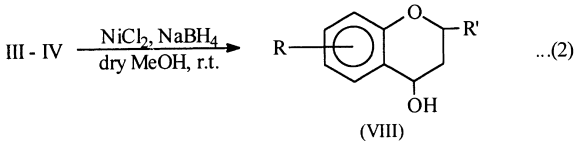

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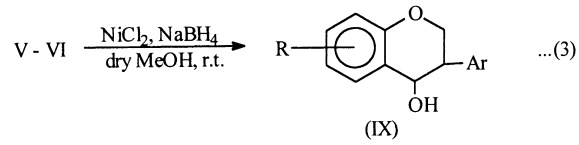

(IX)

complete reduction with sodium borohydride even after 48 h (runs 3, 9, 15).

Selective reduction of the double bond in flavones (I), chromones (III) and isoflavones (V) could not be achieved despite changing various reaction conditions. The reductions of flavanones (II) are faster than those of flavones (I). The 2*H*-1-benzopyran-4-ols obtained in all the reactions have been identified as the corresponding *cis*-stereoisomers by ^1H NMR (300 MHz). The coupling constants for the flavan-4-ols (VII) are consistent with the half chair (X) or sofa conformation (XI) of the heterocyclic ring in which the 2-aryl group is equatorial.[5a] The formation of *cis*-products in case of flavones (I), chromones (III) and isoflavones (V) is obviously due to hydrogenation from same side of the enone group while in case of flavanones (II), chromanones (IV) and isoflavanones (VI), the hydrogenation is from less hindered side of carbonyl group thus leading to the formation of the *cis*-isomer.

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