Amberlyst-15-Catalyzed Novel Synthesis of Tetrahydropyranols

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Abstract: The cross-coupling reaction of homoallyl alcohols with aldehydes in the presence of Amberlyst-15 resulted in the formation of 4-hydroxy-2,6-disubstituted tetrahydropyrans in high yields with high diastereoselectivity. The stereochemistry of these products was assigned with the assistance of coupling constants and nOe studies.

Key words: Amberlyst-15, Prins cyclization, homoallyl alcohols, tetrahydropyranols

The cross-coupling reaction of homoallyl alcohols with aldehydes in the presence of Amberlyst-15 resulted in the formation of 4-hydroxy-2,6-disubstituted tetrahydropyrans in high yields with high diastereoselectivity. The stereochemistry of these products was assigned with the assistance of coupling constants and nOe studies.

The acid catalyzed condensation of olefins with carbonyl compounds known as Prins reaction is an important carbon-carbon bond forming reaction in organic synthesis.2 The tetrahydropyran ring is a part of the backbone of various important carbohydrates and natural products.3 In addition, tetrahydropyrans hydroxylated at the 4-position are found in a number of natural products including avermectins, aplysia toxin, oscillatoxins, latrunculins, talaromycins, and acutiphycins. The synthesis of halogenated tetrahydropyrans is reported using conventional Lewis acids5 which often generate a mixture of products. Recently, Sc(OTf)3 has also been employed for prins type cyclization6 which affords a mixture of tetrahydropyranyl ethers and tetrahydropyranols. The use of solid acidic catalysts7 such as ion-exchange resins, clays and zeolites has received considerable attention in different areas of organic synthesis because of their environmental compatibility, reusability, greater selectivity, experimental simplicity, low cost and ease of isolation of the products. Particularly, ion-exchange resins8 make the reaction processes convenient, more economic, environmentally benign and act as Bronsted acids enabling them to function as efficient catalysts for various organic transformations.

In this report we describe a mild and efficient procedure for the synthesis of tetrahydropyrans through the Prins-type cyclization reaction of homoallylic alcohols with aldehydes in the presence of Amberlyst-15. The reaction of benzaldehyde with 1-phenyl-3-buten-1-ol in the presence of Amberlyst-15 in refluxing 1,2-dichloroethane resulted in the formation of 2,6-diphenyl-4-hydroxy-tetrahydropyran in 88% yield with high diastereoselectivity (Scheme 1). Likewise, several substituted aromatic, aliphatic aldehydes were condensed with homoallyl alcohols to give the corresponding tetrahydropyrans in high yields.

The reactions proceeded smoothly in refluxing 1,2-dichloroethane and the products were obtained in high yields with high cis-diastereoselectivity. Only a single diastereomer was formed in each reaction, the structure of which was confirmed by 1H NMR and nOe studies. The assignment of the stereochemistry was based on the coupling constants of the protons at the C2 and C4 positions. The coupling constants of the benzylic hydrogens H-2 (δ = 4.60, J = 11.5 Hz) as well as the hydrogen on the carbon bearing the hydroxyl group H-4 (δ = 4.18, J = 4.5, 11.5 Hz) in the 1H NMR spectrum of product 2a suggested a structure consistent with two phenyl groups and the hydroxyl group being in the cis-orientation and equatorial. The predominant formation of a single stereoisomer is probably due to thermodynamic factors. In addition, the nOe spectrum of product 2a revealed that the signal at δ = 4.60 (H-2) shows nOe correlation with the signal at δ = 4.18 (H-4) (Scheme 2).

Further, the formation of the products may be explained by hemi-acetal formation and subsequent Prins-type cyclization (Scheme 3).

The reaction of aromatic aldehydes with the corresponding homoallylic alcohols in the presence of Amberlyst-15 gave symmetric 2,6-disubstituted-4-hydroxy tetrahydropyrans in high yields. Similarly, the Prins cyclization between aliphatic aldehydes and the corresponding homoallylic alcohols provided the symmetric hydroxy-
Scheme 3

pyrans in moderate to good yields. Further, the cross coupling between aromatic homoallylic alcohols and aliphatic aldehydes or the cross coupling between aliphatic homoallylic alcohols and aromatic aldehydes gave the corresponding unsymmetrical hydroxy pyrans in good yields. Several examples illustrating this novel and efficient procedure for the preparation of pyranols are summarized in the Table. The nature of the substituents on the aromatic ring show some effect on this conversion. It should be noted that aliphatic, simple aromatic and moderately activated aldehydes like chloro, bromo and meta- phenoxy benzaldehydes gave high yields of products compared to strongly activated or deactivated nitro or cyano substituted aldehydes. The catalyst, Amberlyst-15 was recovered by filtration and reused after activation, for three cycles without significant loss of activity.

In summary, we have demonstrated that Amberlyst-15 is a novel and reusable catalyst for the synthesis of tetrahydro pyranols through the Prins-type cyclization reaction. In addition to its simplicity and milder reaction conditions, the method affords high yields of products with high diastereoselectivity. The catalyst is inexpensive, easily available and reusable which makes the reaction process convenient, more economic and environmentally benign.

A mixture of homoalyl alcohol (5 mmol), aldehyde (5 mmol) and Amberlyst-15 (1 g) was stirred in refluxing 1,2-dichloroethane (20 mL) for an appropriate time (Table). After completion of the reaction as indicated by TLC, the catalyst was recovered by filtration. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, EtOAc–hexane, 2:8) to afford pure 4-hydroxy tetrahydropyran derivative. All NMR spectra were recorded on a 200 MHz Varian Gemini spectrometer at 200 MHz.

2a: White solid, mp: 102–104 °C.
1H NMR (CDCl3): δ = 1.15–1.30 (m, 6H), 1.40 (dd, 2H, J = 12.5, 11.0 Hz), 1.50 (br s, OH), 1.85 (dd, 2H, J = 12.0, 4.5 Hz), 2.75 (dd, 1H, J = 12.0, 6.0 Hz), 2.90 (dd, 1H, J = 12.0, 6.0 Hz), 3.50 (m, 2H), 3.70 (m, 1H), 7.15–7.25 (m, 1H).
EIMS: m/z (%) = M+ 254 (15), 236 (25), 136 (100), 128 (125), 127.8, 128.5, 142.0.
13C NMR (CDCl3, proton decoupled): δ = 43.0, 68.5, 78.5, 126.0, 127.8, 128.5, 142.0.
IR (neat): ν = 3380, 2950, 2900, 1650, 1490, 1365, 1245, 1135, 1070, 970 cm⁻¹.

2b: Semi-solid.
1H NMR (CDCl3): δ = 1.20 (dd, 2H, J = 12.0, 11.0 Hz), 1.50 (br s, OH), 1.85 (dd, 2H, J = 12.0, 4.5 Hz), 2.75 (dd, 1H, J = 12.0, 6.0 Hz), 2.90 (dd, 1H, J = 12.0, 6.0 Hz), 3.50 (m, 2H), 3.70 (m, 1H), 7.15–7.25 (m, 1H).
EIMS: m/z (%) = M+ 268 (20), 250 (45), 191 (25), 174 (58), 130 (60), 118 (20), 91 (100).

2c: Liquid.
1H NMR (CDCl3): δ = 1.15–1.30 (m, 6H), 1.40 (dd, 2H, J = 12.5, 11.0 Hz), 1.50 (br s, OH), 1.75 (m, 4H), 2.00 (m, 2H), 2.25 (dd, 1H, J = 12.5, 4.5 Hz), 3.25 (m, 1H), 3.90 (m, 1H), 4.35 (dd, 1H, J = 11.0, 2.2 Hz), 7.25–7.35 (m, 5H).
EIMS: m/z (%) = M+ 260 (10), 242 (25), 177 (30), 159 (86), 131 (25), 104 (100), 91 (75).

2d: Semi-solid.
1H NMR (CDCl3): δ = 1.50 (dd, 2H, J = 12.5, 11.5 Hz), 1.80 (br s, OH), 2.30 (dd, 2H, J = 12.5, 4.5 Hz), 4.05 (m, 1H), 4.60 (d, 2H, J = 11.5 Hz), 7.20 (m, 2H), 7.45 (m, 4H).
EIMS: m/z (%) = M+ 392 (25), 374 (40), 280 (15), 190 (100), 172 (55), 149 (35), 91 (85), 69 (30).

2e: White solid, mp: 120–122 °C.
1H NMR (CDCl3): δ = 1.50 (dd, 2H, J = 12.5, 11.5 Hz), 2.25 (dd, 2H, J = 12.5, 4.5 Hz), 4.10 (m, 1H), 4.50 (d, 2H, J = 11.5 Hz), 7.25 (m, 3H), 7.45–7.55 (m, 4H).
EIMS: m/z (%) = M+ 402 (20), 384 (30), 184 (65), 172 (100), 149 (10), 103 (15), 77 (20).

2f: White solid, mp: 68–90 °C.
1H NMR (CDCl3): δ = 1.30 (dd, 2H, J = 12.5, 11.5 Hz), 1.55 (br s, OH) 1.90 (dd, 2H, J = 12.5, 4.5 Hz), 2.80 (dd, 1H, J = 12.0, 6.0 Hz), 3.00 (dd, 1H, J = 12.0, 6.0 Hz) 3.40 (m, 2H), 3.70 (m, 1H), 7.15–7.25 (m, 8H).
EIMS: m/z (%) = M+ 337 (25), 303 (15), 191 (20), 173 (50), 129 (45), 117 (20), 91 (100).

2g: White solid, mp: 83–85 °C.
1H NMR (CDCl3): δ = 1.50 (dd, 2H, J = 12.0, 11.5 Hz), 2.20 (dd, 2H, J = 12.0, 4.5 Hz), 2.30 (s, 3H), 4.10 (m, 1H), 4.50 (d, 2H, J = 11.5 Hz), 7.15–7.25 (m, 7H).
EIMS: m/z (%) = M+ 338 (15), 320 (25), 172 (100), 118 (75), 91 (50).

2h: Semi-solid.
1H NMR (CDCl3): δ = 1.50 (br s, OH), 1.55 (dd, 2H, J = 12.5, 11.5 Hz), 2.30 (dd, 2H, J = 12.5, 4.5 Hz), 4.15 (m, 1H), 4.60 (d, 2H, J = 11.5 Hz), 7.35 (m, 8H).
EIMS: m/z (%) = M+ 322 (15), 304 (20), 210 (35), 192 (30), 184 (100), 164 (55), 156 (75).

2i: Semi-solid.
1H NMR (CDCl3): δ = 1.50 (br s, OH), 1.55 (dd, 2H, J = 12.5, 11.5 Hz), 2.25 (dd, 2H, J = 12.5, 4.5 Hz), 4.10 (m, 1H), 4.55 (d, 2H, J = 11.5 Hz), 7.35 (d, 4H, J = 8.4 Hz), 7.60 (d, 4H, J = 8.4 Hz).
EIMS: m/z (%) = [M + 2]+ 414 (20), 396 (35), 184 (75), 129 (55), 103 (100), 77 (50).

2j: White solid, mp: 125–127 °C.
1H NMR (CDCl3): δ = 1.30 (br s, OH), 1.55 (dd, 2H, J = 12.5, 11.5 Hz), 2.25 (dd, 2H, J = 12.5, 4.5 Hz), 2.35 (s, 6H), 4.10 (m, 1H), 4.50 (d, 2H, J = 11.5 Hz), 7.15 (d, 4H, J = 8.0 Hz), 7.25 (d, 4H, J = 8.0 Hz).
## Amberlyst-15-Catalyzed Synthesis of Tetrahydroxypyrans

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<th>Homoallyl Alcohol</th>
<th>Aldehyde</th>
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</table>

All products were characterised by $^1$H, $^{13}$C NMR, IR and MS. Isolated yields after purification.
EIMS: m/z (%) = M+ 282 (20), 264 (45), 136 (100), 119 (75), 91 (85).

2k: Semi-solid.
1H NMR (CDCl3): δ = 1.45 (br s, OH), 1.70 (dd, 2H, J = 12.5, 11.5 Hz), 2.40 (dd, 2H, J = 12.5, 4.5 Hz), 4.20 (m, 1H), 4.75 (d, 2H, J = 11.5 Hz), 7.30–7.40 (m, 8H), 7.70–7.90 (m, 10H).
EIMS: m/z (%) = M+ 438 (15), 420 (20), 214 (30), 196 (55), 105 (100), 83 (25), 40 (10).

2l: Solid, mp: 75–76 °C.
1H NMR (CDCl3): δ = 0.90 (t, 3H, J = 6.8 Hz), 1.25 (dd, 2H, J = 12.0, 11.0 Hz), 1.30 (m, 6H), 1.50 (br s, OH), 1.65 (m, 2H), 2.00 (dd, 2H, J = 12.0, 4.5 Hz), 2.70 (dd, 1H, J = 12.0, 6.0 Hz), 3.30 (m, 1H), 3.50 (m, 2H), 3.80 (m, 1H), 7.25–7.35 (m, 5H).
EIMS: m/z (%) = M+ 262 (20), 244 (15), 171 (30), 127 (100), 109 (80), 91 (45).

2m: Liquid.
1H NMR (CDCl3): δ = 0.90 (t, 3H, J = 6.8 Hz), 1.25 (m, 6H), 1.40 (dd, 2H, J = 12.0, 11.0 Hz), 1.50 (m, 1H), 1.65 (m, 1H), 1.80 (br s, OH), 2.00 (dd, 1H, J = 12.0, 4.5 Hz), 2.20 (dd, 1H, J = 12.0, 4.5 Hz), 2.40 (s, 3H), 3.45 (m, 1H), 3.90 (m, 1H), 4.30 (d, 1H, J = 11.5 Hz), 7.15 (d, 2H, J = 8.0 Hz), 7.25 (d, 2H, J = 8.0 Hz).
EIMS: m/z (%) = M+ 262 (20), 244 (15), 171 (30), 121 (100), 119 (80), 91 (45).

2n: Liquid.
1H NMR (CDCl3): δ = 0.90 (t, 3H, J = 7.0 Hz), 1.25 (m, 6H), 1.40 (dd, 2H, J = 12.0, 11.0 Hz), 1.50 (m, 1H), 1.65 (m, 1H), 1.80 (br s, OH), 2.00 (dd, 1H, J = 12.0, 4.5 Hz), 2.15 (dd, 1H, J = 12.0 Hz), 3.40 (m, 1H), 3.90 (m, 1H), 4.30 (dd, 1H, J = 11.5 Hz), 7.15 (m, 1H), 7.45 (m, 2H).
EIMS: m/z (%) = M+ 316 (10), 298 (15), 227 (25), 185 (30), 175 (70), 137 (20), 100 (35), 73 (50).

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References
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