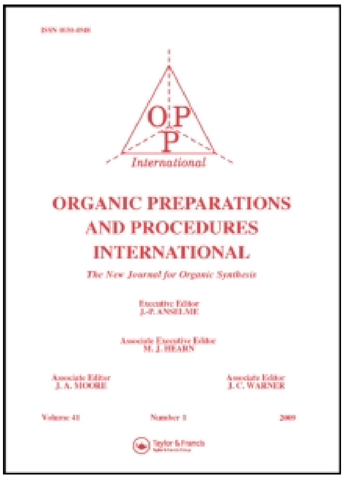

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4-PHENYL-Δ^3-DIHYDROPYRANS BY REDUCTION OF PYRILIUM SALTS WITH SODIUM BOROHYDRIDE IN ACETIC ACID

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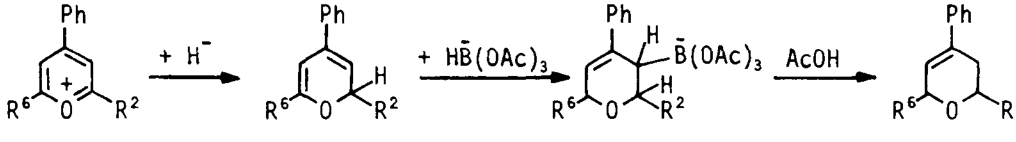
Reductions with sodium borohydride in carboxylic acid media have been reviewed in this Journal.[1] We have recently applied this synthetically useful reduction to pyrylium salts and observed[2] that for 2,4,6-trisubstituted pyrylium salts having at least one α-(2- or 6-)alkyl substituent, the reduction products are different from those obtained by reduction with $NaBH_4$ in aqueous or alcoholic media.[3] Δ^3-Dihydropyrans are the major reduction products of these pyrylium salts with $NaBH_4$ in acetic acid. When the 4-substituent is a phenyl group (pyrylium salt 1 with R^2 or R^6 being alkyl groups), Δ^3-dihydropyrans 2 are the only products and they are obtained in yields surpassing 95 %.[2]



1

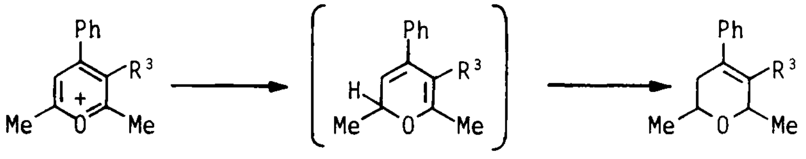
2

	a	b	c
R^2	Me	*i*Pr	Me
R^6	Me	*i*Pr	Ph

Charge delocalization by the 4-phenyl group accounts for the exclusive hydride addition (from $Na^+ \bar{B}(OAc)_3H$) to the α-positions devoid of such delocalization. With 4-alkyl groups other products result as well (tetrahydropyrans and 1,5-diketones) arising from a 4-addition of H$^-$. When both α-substituents are phenyl groups, hydride addition occurs more sluggishly and no Δ^3-dihydropyrans are formed ; in this case the same products result as in neutral media.

We demonstrated by reducing 2,6-dimethyl-4-phenylpyrylium cations 1a with AcOD + NaBH$_4$ and AcOH + NaBD$_4$ that the reaction involves an α-attack of the hydride nucleophile followed by a *cis*-1,4-addition of the triacetoxyborohydride, so that *cis*-2a was obtained stereospecifically.

The fact that Δ^3-dihydropyrans 2 thus become available from pyrylium salts (easily accessible from simple and inexpensive starting materials[4]), prompts us to report a detailed experimental procedure together with hitherto unreported analytical data (see the Experimental Section). Furthermore, we show now that for 2,3,6-trisubstituted 4-phenylpyrylium salts 3 the reduction with NaBH$_4$ + AcOH is also regiospecific affording the Δ^3-dihydropyran 4 with a tetrasubstituted double bond and no detectable ammount (by ^{1}H-NMR) of the isomeric product with a trisubstituted double bond.



3

4

	R^3
a	Me
b	Ph

This regioselectivity implies as the first step of the reduction an attack of the bulky hydride nucleophile in the less crowded α-position (namely the 6-position for 2,3,4,6-tetrasubstituted pyrylium salts). Assuming that the second step involves a 1,4-addition to the intermediate 2*H*-pyran, this mechanism was verified by reducing 2,3,6-trimethyl-4-phenylpyrylium perchlorate 3a with NaBH$_4$ + AcOD, when 5-deuterated-4a was obtained.

EXPERIMENTAL SECTION

All reagents and glassware were thoroughly dried in order to ensure anhydrous conditions ; if water is present the reduction of pyrylium salts takes other routes and complex mixtures result. Δ^3-Dihydropyrans with a 4-phenyl group are affected progressively by light and oxygen so that prolonged storage should be avoided, especially if undistilled. Elemental analyses were also performed on undistilled samples and were found in most cases satisfactory. Distillation from slightly alkaline medium over a trace of hydroquinone under argon and storage in a sealed vial has kept samples of Δ^3-dihydropyrans unaltered for more than a year. Sample purities of the crude reaction product were greater than 90% (by NMR), and were checked by HPLC runs using methanol-water eluents (Hewlett-Packard instrument equipped with a reverse phase C_8 10μ column and a UV detector calibrated at λ_{max}) ; in each case a single peak was found, thus indicating the absence of stereoisomers. ^{1}H-NMR spectra were run at 60 MHz on a Varian A-60A spectrometer in $CDCl_3$ with TMS as internal standard. IR spectra were recorded on a Zeiss UR 20 spectrometer as neat film between NaCl plates. UV spectra were run on a Zeiss instrument in cyclohexane.

2,6-Dimethyl-4-phenyl-5,6-dihydro-2*H*-pyran (**2a**). General Procedure.- A 500 ml four-necked round-bottom flask equipped with a mechanical stirrer, a reflux condenser protected against moisture with a calcium chloride tube, a Y-connection fitted with thermometer and argon inlet, and a flexible wide-bore tube obturated by a clamp, was flamed under dry argon for 0.5 hr and then allowed to cool. 2,6-Dimethyl-4-phenylpyrylium sulfoacetate[5] (15.0 g, 46.3 mmol) was suspended in 100 ml anhydrous acetic acid (1.67 mol); coarsely ground sodium borohydride (7.0 g, 185 mmol) was gradually added to the stirred suspension from an ampoule *via* the flexible connection. The exothermic addition of $NaBH_4$ was conducted in the beginning at such a rate that the abrupt temperature rise did not exceed 40° ; afterwards a cooling water bath was applied and the addition of $NaBH_4$ continued as rapidly as possible while the temperature was maintained at 40°. The initial red color faded into orange and later became an opaque light tan. Towards the end of the addition, foaming occured and the sodium borohydride reacted more slowly. The mixture was stirred at 35° for 2 hrs after completion of addition and then it was decomposed with 250 ml of water containing 1 ml of conc. HCl. The mixture was stirred for 5 min and then transferred to a separatory funnel. The reaction flask, stirrer and thermometer were rinsed with 15 ml of ether which was added to the funnel from which the aqueous layer was run off and extracted separately twice with ether (a 50 ml and then a 15 ml portion). The combined ethereal layers were neutralized with aqueous sodium carbonate and dried over anhydrous magnesium sulfate. Solvent evaporation afforded 8.6 g (99 % yield) of crude yellow oil with a clean ^{1}H-NMR spectrum and satisfactory elemental analysis. Distillation under argon with a trace of hydroquinone in the receiver flask gave a pale yellow, fragrant oil, bp. 105°/2 Torr., lit.[6] bp. 133-6°/12 Torr.

^{1}H-NMR, δ(ppm) : 1.32 (3H, d, J = 6.8 Hz, 2-Me), 1.33 (3H, d, J = 6.0 Hz, 6-Me), 2.33 (2H, m, 5-H_2), 3.77 (1H, sextet, J = 6 Hz, 6-H), 4.37 (1H, m, 2-H), 6.00 (1H, q, J = 1.5 Hz, 3-H), 7.34 (5H, s, 4-Ph) ; IR (cm^{-1}) : 702(s), 760(s), 1058(s), 1070(s), 1098(s), 1145(s), 1175(s), 1365-1380(s), 1440(s), 1590(m), 2960(s), 3025(m), 3050(m), 3078(mw) ; UV, λ_{max} (nm) : 221 and 252.

Anal. Calcd. for $C_{13}H_{16}O$: C, 82.92 ; H, 8.57

Found : C, 82.74 ; H, 8.47

2,6-Diisopropyl-4-phenyl-5,6-dihydro-2*H*-pyran (2b).- 2,6-Diisopropyl-4-phenylpyrylium perchlorate[7] (1.90 g, 5.6 mmol) was similarly reduced with $NaBH_4$ (1.10 g, 29.1 mmol) in 10 ml of anhydrous acetic acid, yielding a crude light brown oil (1.35 g, 99 % yield) with a single HPLC peak.

^{1}H-NMR, δ (ppm) : 0.99 (6H, dd, J = 6.75 Hz, 2-$CH\underline{Me}_2$), 1.06 (6H, d, J = = 6.25 Hz, 6-$CH\underline{Me}_2$) 1.82 (2H, m, 2- and 6-$\underline{CH}Me_2$), 2.33 (2H, m, 5-H_2), 3.30 (1H, q, J = 6.25 Hz, 6-H), 4.02 (1H, m, 2-H), 6.08 (1H, q, J = 1.25 Hz, 3-H) 7.39 (5H, closely spaced m, 4-Ph) ; IR (cm^{-1}) : 705(s), 760(s), 1080(m), 1360-1380(s), 1460(s), 1590(m), 2930-2960(s), 3020(m), 3052(m), 3078(mw) ; UV, λ_{max} (nm) : 220 and 251.

Anal. Calcd. for $C_{17}H_{24}O$: C, 83.54 ; H, 9.91

Found : C, 83.34 ; H, 9.89

2,4-Diphenyl-6-methyl-5,6-dihydro-2*H*-pyran (2c).- 2,4-Diphenyl-6-methyl-pyrylium sulfoacetate[8] (3.2 g, 8.3 mmol) was reduced analogously with $NaBH_4$ (1.6 g, 42.1 mmol) in anhydrous acetic acid (15 ml). The usual workup gave a yellow-orange oil (2.05 g, 99 % yield) with satisfactory spectral and analytical data. Bp. 145-8°/0.7 Torr., the distillation in vacuum was accompanied by partial decomposition. ^{1}H-NMR, δ (ppm) : 1.38 (3H, d, J = 6.4 Hz, 6-Me), 2.32-2.52 (2H, m, 5-H_2), 3.94 (1H, sextet, J = 6.5 Hz, 6-H), 5.28 (1H, m, 2-H), 6.10 (1H, q, J = 1.75 Hz, 3-H), 7.32 (10H, 2- and 4-Ph) ; IR, (cm^{-1}) in CS_2 : 705(s), 763(s), 1045(s), 2900-3080(m) ; in CCl_4 1445(m). UV, λ_{max} (nm) : 220 and 250.

Anal. Calcd. for $C_{18}H_{18}O$: C, 86.35 ; H, 7.25

Found : C, 86.14 ; H, 7.57

2,3,6-Trimethyl-4-phenyl-5,6-dihydro-2*H*-pyran (4a).- 2,3,6-Trimethyl-4-phenyl-pyrylium perchlorate[9] (3.0 g, 10.0 mmol) was reduced with $NaBH_4$ (1.9 g, 50.0 mmol) in 15 ml anhydrous acetic acid yielding 4a (1.90 g, 93.5 %) as an orange-yellow oil with satisfactory spectral and analytical data. Bp. 117°/5 Torr. ^{1}H-NMR, δ(ppm) : 1.26 (3H, d, J = 6 Hz, 2-Me), 1.35 (3H, d, J = 6.5 Hz, 6-Me), 1.52 (3H, closely-spaced m, 3-Me), 2.22 (2H, m, 5-H_2), 3.80 (1H, sextet, J = 6.5 Hz, 6-H), 4.27 (1H, m, 2-H), 7.30 (5H, closely-spaced m, 4-Ph) ; IR (cm^{-1}) : 705(s), 760(s), 1120-1140(s), 1488(m) 1590(mw), 2800-3070(s) ; UV, λ_{max} (nm) : 220 and 243.

Anal. Calcd. for $C_{14}H_{18}O$: C, 83.11 ; H, 8.98

Found : C, 82.86 ; H, 9.06

[5-^{2}H]-2,3,6-Trimethyl-4-phenyl-5,6-dihydro-2*H*-pyran (5*d*-4a).- In the above procedure, by using AcOD instead of AcOH we obtained 5*d*-4a. ^{1}H-NMR : same as above except that the 3-Me signal (1.52 ppm) is a singlet, the 2.24 ppm multiplet corresponds to about 1.2 protons (instead of two), the 2- and 6-protons are both poorly resolved quartets. IR : same as above except for two additional weak bands at 2128 and 2180 cm^{-1}.

2,6-Dimethyl-3,4-diphenyl-5,6-dihydro-2*H*-pyran (4b).- Pyrylium perchlorate 3b[9] (0.92 g, 2.6 mmol) was reduced in 5 ml anhydrous acetic acid with $NaBH_4$ (0.56 g, 14.8 mmol). The resulted crude yellow oil (0.66 g, 98.3 % yield) degraded faster than other 4-phenyl-5,6-dihydro-2*H*-pyrans and although ^1H-NMR data advocate its structure, a satisfactory and reproducible elemental analysis could not be obtained. ^1H-NMR, δ(ppm) : 1.09 (3H, d, J = 6.75 Hz, 2-Me), 1.33 (3H, d, J = 6.3 Hz, 6-Me), 1.6-2.6 (2H, m, 5-H_2), 3.95 (1H, m, 6-H), 4.74 (1H, m, 2-H), 7.05 (10H, closely-spaced m, Ph_2) ; UV, λ_{max} (nm) : 220, 250 and 320(sh).

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