Dihydro-1,2-oxazole Derivatives. Part IX[1]. Stereoselective Synthesis of Tetrahydro-1,2-oxazoles by Sodium Borohydride Reduction of 4,5-Dihydro-1,2-oxazolium Tetrafluoroborates

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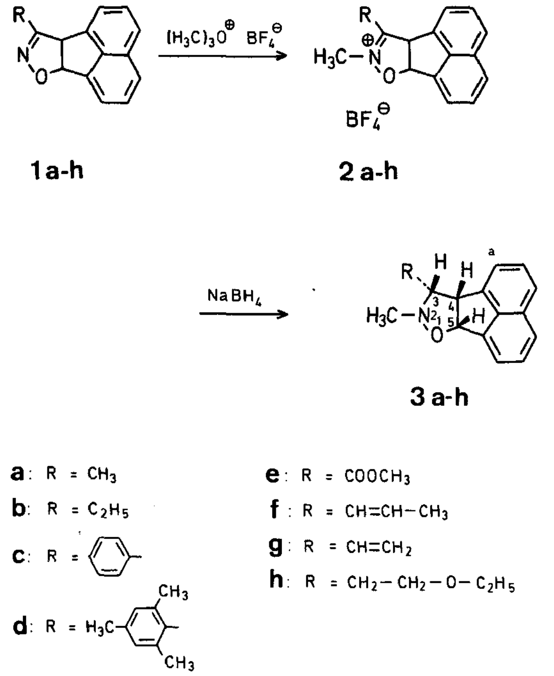
Pursuing our study of 4,5-dihydro-1,2-oxazoles, we now report their reaction with excess trimethyloxonium tetrafluoroborate in nitromethane at room temperature to give the corresponding 4,5-dihydro-1,2-oxazolium tetrafluoroborates in nearly quantitative yields Recently French authors reported[2] preparation of some 4,5-dihydro-1,2-oxazolium perchlorates in fairly good yields via methylation of 4,5-dihydro-1,2-oxazoles with dimethyl sulphate followed by treatment with sodium perchlorate; spectroscopic data were also reported.

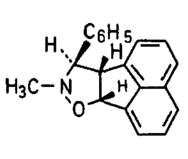
Trimethyloxonium tetrafluoroborate is a highly effective alkylating agent and even the less reactive 4,5-dihydro-1,2-oxazoles can be transformed into the corresponding salts under mild reaction conditions. The crude dried salts, dissolved or suspended in ethanol, undergo sodium borohydride reduction at room temperature to give the related tetrahydro-1,2-oxazoles in very good yields. The use of purified salts did not result in an improvement of yields. Purification of salts **2a**, **2c**, and **2f** was carried out by dissolution of the crude compounds in dry acetone followed by precipitation on addition of diethyl ether. Sodium borohydride reduction can be carried out either in ethanol or in methanol or in dichloromethane or in mixtures of the same solvents.



1a-h **2a-h** **3a-h**

a: $R = CH_3$
b: $R = C_2H_5$
c: R =
d: R =
e: $R = COOCH_3$
f: $R = CH{=}CH{-}CH_3$
g: $R = CH{=}CH_2$
h: $R = CH_2{-}CH_2{-}O{-}C_2H_5$

The reduction tested on several carbocyclic condensed 4,5-dihydro-1,2-oxazolium salts showed to be 100% stereoselective (T.L.C., N.M.R.). The reducing agent entered only the less hindered face of the 4,5-dihydro-1,2-oxazolium ion to give compounds to which we attributed structures **3**, **5**, and **6** where protons at 3- and 4-positions of the tetrahydro-1,2-oxazole ring are *cis* to each other. This stereochemical assignement was corroborated by ^{1}H-N.M.R. spectral data. Thus, proton H-a of **3c** and of **3d** absorbed at higher field than the other aromatic protons (H-a at $\delta = 6.05$; H-aromatic from $\delta = 6.70$ to $\delta = 7.85$ for **3c**), owing to the shielding by the aromatic ring in 3-position. A similar shielding by the naphthalenic system shifted one signal of the *ortho*-methyls of the mesitylene group in **3d** to higher field (at $\delta = 1.05$) than the other two ($\delta = 2.25$ and $\delta = 2.52$).



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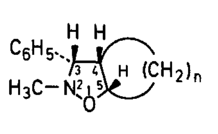
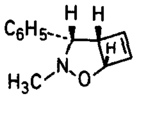


5a n = 2
b n = 3
c n = 4



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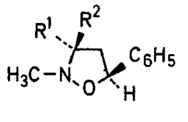
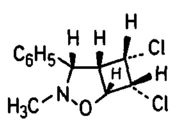


7a: $R^1 = H$, $R^2 = C_6H_5$
b: $R^1 = C_6H_5$, $R^2 = H$

Previously the $J_{3,4}$ values, ≥ 6.0 Hz for the *cis* and ≤ 1.0 Hz for the *trans* isomer, respectively, made possible the attribution of the correct structure to the tetrahydro-1,2-oxazoles with the heterocyclic ring condensed at position 4 and 5 on the rigid four[3] or five[4] membered rings; structure **6** has been attributed on similar basis[3]. This argument was not useful for compounds **3** as shown by the two diastereoisomeric tetrahydro-1,2-oxazoles **3c** (*cis*) and **4** (*trans*) in which protons H-3 and H-4 showed a coupling constant of 7.3 and 8.0 Hz, respectively. The tetrahydro-1,2-oxazole **4** was obtained along with **3c** (ratio **4**/**3c** = 4 : 1; 90% yield) by cycloaddition of *C*-phenyl-*N*-methyl nitrone with excess acenaphthylene in refluxing benzene[5].

Worth mentioning is the behaviour of **2g**. Left aside in ethanol for 24 h, it underwent addition of one molecule of ethanol to yield **2h** (not isolated), which on sodium borohydride reduction gave **3h**. On the other hand reduction of **2g** in dichloromethane gave a mixture of the 3-vinyl (**3g**) (67%) and the 3-ethyl-tetrahydro-1,2-oxazole (**3b**) (25%).

Reduction of 3,5-diphenyl-4,5-dihydro-1,2-oxazolium salt was partially stereoselective and gave the two diastereoisomeric tetrahydro-1,2-oxazoles **7a** and **7b** (ratio **7a**/**7b** = 4 : 1; 90% yield) whose structures were already known[7]. Here again the preferred attack by sodium borohydride was on the less hindered face of the 4,5-dihydro-1,2-oxazolium salt.



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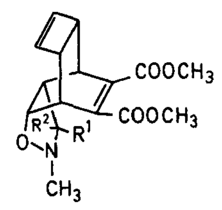
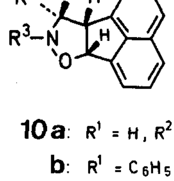


9a: $R^1 = C_6H_5$, $R^2 = H$
b: $R^1 = H$, $R^2 = C_6H_5$



10a: $R^1 = H$, $R^2 = C_6H_5$, $R^3 = C_2H_5$
b: $R^1 = C_6H_5$, $R^2 = CH_3$, $R^3 = CH_3$
c: $R^1 = CH_3$, $R^2 = C_6H_5$, $R^3 = CH_3$

Sodium borohydride reduction of 4,5-dihydro-1,2-oxazolium salts should be considered a useful method of preparation of *N*-methyltetrahydro-1,2-oxazoles not otherwise obtainable. For instance, while the cycloaddition of *C*-phenyl-*N*-methyl nitrone with *cis*-3,4-dichlorocyclobutene gave only three of the four possible stereoisomers[8], the lacking isomer **8** was synthetized following this method from the corresponding 4,5-dihydro-1,2-oxazole. The same argument holds for the synthesis of **9a**: the cycloaddition of *C*-phenyl *N*-methyl nitrone on the unsubstituted cyclohexadiene double bond of the dimethyl tricyclo[4.2.2.$0^{2,5}$]deca-2,7,9-triene-7,8-dicarboxylate gave only **9b**[3].

The use of triethyloxonium tetrafluoroborate instead of trimethyloxonium tetrafluoroborate makes possible the preparation of *N*-ethyltetrahydro-1,2-oxazole such as **10a**. 3,3-Disubstituted-*N*-alkyltetrahydro-1,2-oxazoles, like **10b** and **10c**,

Table. Yields, Physical Properties, and ^{1}H-N.M.R. Data for Tetrahydro-1,2-oxazoles and 4,5-Dihydro-1,2-oxazolium Tetrafluoroborates

Compound[a]	Yield (%)	Recrystallization Solvent	M.p.[b]	^{1}H-N.M.R. data[c]					
				δ H-3	δ H-4	δ H-5	δ N—CH$_3$	$J_{3,4}$	$J_{4,5}$
2a	100	Acetone/Ether	168—172°		6.05 (m)	6.95 (d)	3.88 (m)		8.8
2c	100	Acetone/Ether	188—189°		—[d]	—[d]	4.10 (d)[e]		
2f	100	Acetone/Ether	189—191°		6.41 (m)	7.06 (d)	3.98 bs		8.6
3a	89	Cyclohexane	99—101°	2.88 (m)	4.36 (dd)	5.90 (d)	2.60 (s)	7.3	6.7
3b	96	Petrol Ether	99—100°	2.50 (m)	4.15 (dd)	5.57 (d)	2.40 (s)	7.1	6.5
3c	97	Cyclohexane	166—168°	3.92 (d)	4.47 (dd)	5.95 (d)	2.53 (s)	7.3	6.3
3d[f]	88	Ethanol	168—169°	4.28 (d)	4.58 (dd)	6.02 (d)	2.54 (s)	7.7	6.6
3e	98	Cyclohexane	135—137°	3.75 (d)	4.80 (dd)	6.01 (d)	2.77 (s)	7.3	6.4
3f	93	Cyclohexane	141—143°	3.22 (m)	4.37 (dd)	5.88 (d)	2.51 (s)	7.6	6.5
3g		Petrol Ether	97—99°	3.25 (m)	4.40 (dd)	5.89 (d)	2.55 (s)	7.3	6.7
3h	95	Petrol Ether	49—50°	2.88 (m)	4.39 (dd)	5.78 (d)	2.59 (s)	7.3	6.7
4		Ethanol	132—133°	3.36 (d)	4.43 (dd)	6.01 (d)	2.50 (s)	8.0	6.8
5a	94	Petrol Ether	66—67°	3.42 (s)	3.42 (m)	4.69 (m)	2.67 (s)		
5b	94	Petrol Ether	54—55°	3.67 (d)	3.10 (m)	4.72 (m)	2.59 (s)	7.3	
5c	97		oil	4.10 (d)	—[d]	4.60 (m)	2.80 (s)	5.3	
8	91	Cyclohexane	119—120°	3.72 (d)	3.90 (m)	4.76 (m)	2.90 (s)	6.0	
9a[g]	90	Cyclohexane	118—120°	—[d]	—[d]	4.68 (dd)	2.51 (s)		8.4
10a	95	Ethanol	131—133°	4.06 (d)	4.48 (dd)	5.91 (d)		8.0	7.3
10b	42	Ethanol	173—175°		4.70 (d)	6.06 (d)	2.44 (s)		7.1
10c[h]	30	Ethanol	126—128°		4.12 (d)	5.87 (d)	2.48 (s)		6.7

[a] All compounds gave satisfactory C, H, N ($\pm 0.3\%$) analyses.

[b] Uncorrected.

[c] Recorded on a Perkin Elmer R-12 instrument at 60 MHz, acetone-d_6 being used as solvent for compounds **2a**, **2c**, and **2f** and CDCl$_3$ for the other compounds with TMS as internal reference; δ in ppm, J in Hz.

[d] Signal cannot be identified with certainty.

[e] $J_{4,NCH_3} = 0.75$ Hz.

[f] $\delta = 6.16$ (d, 1H, H-a).

[g] $\delta = 3.82$ (s, 3H, O—CH$_3$), 3.46 (s, 3H, O—CH$_3$). The latter methoxy group was shielded by the benzene ring.

[h] $\delta = 5.87$ (d, 1H, H-a).

have been prepared by the 100% stereoselective reaction of the appropriate Grignard reagent on the 4,5-dihydro-1,2-oxazolium salt.

From the above results it can be seen that the sodium borohydride reduction of 4,5-dihydro-1,2-oxazolium salt is indeed a superior method of preparation of almost all tetrahydro-1,2-oxazoles, which often either are not obtainable or prepared in low yields via 1,3-dipolar cycloaddition. Furthermore the high stereoselectivity of this reduction represents a useful tool in structure elucidation problems.

The 4,5-dihydro-1,2-oxazoles **1a**[9], **1b**[9], **1c**[10], **1e**[9], **1f**[9], **1g**[9], and those corresponding to tetrahydro-1,2-oxazoles **5a**[11], **5b**[10], **5c**[12], **6**[13], **7**[14], **8**[13], **9a**[13], were prepared by literature methods. The hitherto unknown 4,5-dihydro-1,2-oxazole **1d** has been synthesized by cycloaddition of mesitonitriloxide to acenaphthylene, m.p. 215—216° (from methanol).

Synthesis of Tetrahydro-1,2-oxazoles; General Procedure:

A solution of the 4,5-dihydro-1,2-oxazole **1** (1.00 mmol) and a two-fold excess trimethyloxonium fluoroborate (2.00 mmol) in anhydrous nitromethane (10 ml) was left at room temperature for ~ 48 h, until T.L.C. analysis showed the total disappearance of the 4,5-dihydro-1,2-oxazole. The solvent was removed in vacuo and the oily residue was dissolved in anhydrous ethanol. To the resulting stirred solution (or suspension) an excess of sodium borohydride was added in small portions at room temperature during 30 min. Stirring was continued for 30 min, the solvent was removed in vacuo, the residue was diluted with water and extracted with ether. The ether extracts were dried, filtered, and evaporated to dryness to give the crude tetrahydro-1,2-oxazoles which were purified either by crystallization or by column chromatography. Yields (of crude products), physical and N.M.R. data are given in the Table.

During the syntheses of **3e** and **9a** the reduction was carried out in dichloromethane/methanol (10:1). The separation of the mixtures of tetrahydro-1,2-oxazoles (**7a** and **7b**; **3b** and **3g**; **3c** and **4**) was performed by column chromatography (Silicagel H, Merck; eluent: cyclohexane/ethyl acetate 9:1).

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