EXPEDIENT SYNTHESIS OF 4-AMINOCHROMANS AND 4-AMINOTHIOCHROMANS

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Dedicated to Prof. Dr. László Pallos on the occasion of his 70th birthday

Abstract: The reduction of 4-chromanone and 4-thiochromanone oximes is investigated. Based on the product distributions (4-aminochromans *vs.* 1,5-benzoxazepines) for the reductions of several 4-chromanone oximes by different reducing agents, the Raney-Ni/H_2 system proved to be practically useful for selective production of 4-aminochromans and 4-aminothiochromans.

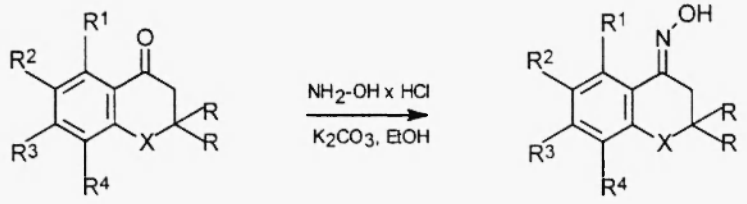
Introduction

1-Benzopyrans are well known six-membered heterocyclic compounds and, owing to their diverse bioactivities (1-4) they are important substances in the pesticide and drug research. Since the introduction of substituted-4-aminochroman derivatives as promising drug candidates in the field of potassium channel openers (5-6) there has continuously been increasing interest in developing practical syntheses for the production of these compounds. Recently we reported on the synthesis of 2,2-dimethylbenzoxazepinones by the Schmidt reaction of 2,2-dimethyl-4-chromanones (7) and by the Beckmann rearrangement of 2,2-dimethyl-4-chromanone oximes (8). As a continuation of our work in the field of benzopyran derivatives (9-11), some additional series of 4-chromanone and 4-thiochromanone oximes (**2a-k**) were prepared and further reduction studies of these oximes into the corresponding amino derivatives (**3a-i**) were undertaken.

Results and Discussion

4-Chromanone oximes are well known compounds (12) obtained by the reaction of 4-chromanones with hydroxylamine. However, as only few 2,2-dimethyl-4-chromanone oximes (**2**) have been described prior to our works, a few years ago we performed a detailed study devoted to the synthesis and stereochemistry of these derivatives (8). The use of this former procedure involving 2,2-dimethyl-4-chromanones, hydroxylamine hydrochloride and sodium acetate in refluxing ethanol provided the desired oximes in moderate yields. As depicted in Scheme 1, we have recently found that the use of potassium carbonate instead of sodium acetate significantly improves the yields in 4-chromanone oximes and 4-thiochromanone oximes (**2**) (Table 1).

Scheme 1



1a-k **2a-k**

Entry	X	R	R^1	R^2	R^3	R^4
a	S	H	H	H	H	H
b	S	Me	H	H	MeO	H
c	O	H	H	H	H	H
d	O	Me	H	H	H	H
e	O	Me	H	H	MeO	H
f	O	Me	H	H	MeO	Me
g	O	Me	H	MeO	MeO	H
h	O	Me	H	*t*-Bu	MeO	H
i	O	Me	H	Cl	MeO	H
j	O	Me	MeO	H	MeO	H
k	O	Me	H	Br	MeO	H

Table 1. Compounds **2** Prepared

Compound	Yield (%)	mp (°C)	^{1}H-NMR ($CDCl_3$/TMS) δ, *J* (Hz)	MS (70 eV) *m/z* (%)
2a	89	97-99	2.95 (m, 2H), 3.20 (m, 2H), 7.05-7.30 (m, 3H), 7.85 (m, 1H), 8.60 (s, 1H)	179 (M^+, 100), 162 (65), 147 (32), 134 (65)
2b	95	> 250 (dec.)	1.43 (s, 6H), 3.00 (s, 2H), 3.80 (s, 3H), 6.65 (m, 2H), 7.85 (d, *J* = 9, 1H)	-
2c	93	139-141	3.00 (t, *J* = 7, 2H), 4.25 (t, *J* = 7, 2H), 6.95 (m, 2H), 7.25 (m, 1H), 7.80 (dd, J_1=2, J_2=8, 1H), 8.15 (s, 1H)	163 (M^+, 100), 145 (15), 131 (33), 91 (56)
2d	90	121-123	1.40 (s, 6H), 2.90 (s, 2H), 6.90 (m, 2H), 7.25 (m, 1H), 7.75 (dd, J_1=2, J_2=8, 1H), 8.30 (br s, 1H)	191 (M^+, 52), 176 (100), 159 (15), 133 (32), 119 (28)
2e	92	132-133	See ref. 8.	-
2f	98	185-186	1.38 (s, 6H), 2.08 (s, 3H), 2.88 (s, 2H), 3.82 (s, 3H), 6.50 (d, *J* = 8, 1H), 7.62 (d, *J* = 8, 1H)	235 (M^+, 90), 220 (100), 204 (28), 162 (45)
2g	98	112-114	1.38 (s, 6H), 2.85 (s, 2H), 3.85 (s, 6H), 6.38 (s, 1H), 7.21 (s, 1H), 8.10 (br s, 1H)	251 (M^+, 90), 236 (100), 220 (28), 204 (15)

Table 1. continued

Compound	Yield (%)	mp (°C)	^{1}H-NMR ($CDCl_3$/TMS) δ, *J* (Hz)	MS (70 eV) *m/z* (%)
2h	95	159-161	1.35 (s, 9H), 1.40 (s, 6H), 2.85 (s, 2H), 3.80 (s, 3H), 6.35 (s, 1H), 7.65 (s, 1H)	277 (M^+, 33), 262 (100), 247 (90), 191 (77), 162 (15)
2i	96	169-171	1.30 (s, 6H), 2.78 (s, 2H), 3.82 (s, 3H), 6.60 (s, 1H), 7.65 (s, 1H), 11.15 (s, 1H)	257/255 (M^+, 21/63), 240 (100), 222 (38), 183 (32)
2j	90	218-220	1.41 (s, 6H), 2.95 (s, 2H), 3.78 (s, 3H), 3.90 (s, 3H), 6.05 (d, *J* = 2, 1H), 6.14 (d, *J* = 2, 1H)	251 (M^+, 67), 234 (100), 220 (18) , 190 (34)
2k	90	164-166	1.30 (s, 6H), 2.88 (s, 2H), 3.82 (s, 3H), 6.60 (s, 1H), 7.80 (s, 1H), 11.15 (s, 1H)	300 (M^+, 35), 84 (55), 239 (15), 187 (25)

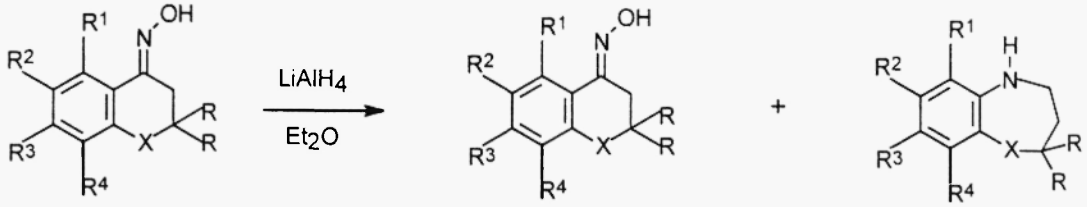
The elemental analyses for C, H and N were within ± 0.35 % of the theoretical value.

There are several reports on the reduction of flavanone and isoflavanone oximes (13, 14) as well as chromanone oximes (12, 15). A wide variety of reducing agents were applied, such as Pd-C/AcOH (over reduced PtO_2), $LiAlH_4/Et_2O$, Al-Hg/80% EtOH, Zn dust/AcOH (12,13,14), and also Na-Hg/AcOH (15). Depending on the substitution pattern of the starting oximes and the applied reducing agents the corresponding 4-amino derivatives and 1,5-benzoxazepines were formed in different ratio.

For chromanone oximes it is established that the position (C2 and C3) and the size of the substituents exert remarkable influence on the rearrangement reaction (12). Thus, chromanone oximes without C2 substituent and with C3 substituent give only the corresponding 1,5-benzoxazepine (the rearrangement product) when reduced with $LiAlH_4$. Chromanone oximes with C2 substituent give a mixture of the 4-aminochroman and 1,5-benzoxazepine. It is also stated that the more bulky substituent at C2 gives more "normal" reduction product and the smaller quantity of the rearrangement derivative.

However, no data were found on the reduction of the parent compounds **2a** and **2c**. Consequently, we first decided to investigate the reduction of these two oximes as well as that of their 2,2-disubstituted congeners **2b** and **2e** by using $LiAlH_4$ in anhydrous ether (Scheme 2). In each case two products: the 4-aminochroman and 1,5-benzoxazepine (**3a** and **4a**, **3b** and **4b**, **3c** and **4c** or **3e** and **4e**, respectively) were isolated in low to moderate yields. The structures of the obtained products were unequivocally established by ^{1}H NMR and MS analysis. These results clearly indicate that the rules previously stated (12) do not apply for the parent compounds since 4-aminochromans **3a** or **3c** were formed. In addition, the reduction of oximes **2a** or **2b** afforded mainly the corresponding amines **3a** or **3b** besides the expected rearrangement products **4a** or **4b**.

Scheme 2



2a, **2b**, **2c**, **2e**

3a (30 %)
3b (20 %)
3c (8 %)
3e (20 %)

4a (17 %)
4b (10 %)
4c (38 %)
4e (25 %)

2e —Pd/C, H_2, 5 bar, ×→ **3e**

2e —$NaBH_4$, MeOH, ×→ **3e**

2e —$NaBH_4$, $NiCl_2$, MeOH→ **3e** (55 %)

2e —Raney-Ni, H_2, MeOH, 5 bar→ **3e** (85 %)

Based on our own preliminary observation outlined above and on the relevant literature data (12-15) we investigated the reduction of 2,2-dimethyl-7-methoxy-4-chromanone oxime (**2e**), as a model compound with several reducing agents (Scheme 2). The use of Pd/C, H_2, (5 bar) or $NaBH_4$/MeOH provided no result. However, the $NaBH_4$-$NiCl_2$/MeOH system allowed us to isolate the corresponding amine (**3e**) in 55 % yield. The application of Raney-Ni/H_2 (5 bar) proved to be practically useful and led to the formation of 4-amino-2,2-dimethyl-7-methoxychroman (**3e**) in 85 % yield. This latter system was then used for the preparation of a large number of 4-aminochromans and 4-aminothiochromans (**3a-i**) (Table 2). Structures of the final products have been elucidated by elemental analyses, ^{1}H NMR and MS methods. In the course of this study some scopes and limits of this methodology are also disclosed. When reducing the 2,2-dimethyl-6-chloro-7-methoxy-4-chromanone oxime (**2i**) small amount of 4-amino-2,2-dimethyl-7-methoxychroman (**3e**) was also formed. The reduction of 2,2-dimethyl-5,7-dimethoxy-4-chromanone oxime (**2j**) could not be accomplished as 2,2-dimethyl-5,7-dimethoxy-4-chromanone was isolated in 89 % yield instead of the corresponding amine. In the case of the reduction of 6-bromo-2,2-dimethyl-7-methoxy-4-chromanone oxime (**2k**) the exclusive formation of 2,2-dimethyl-4-hydroxy-7-methoxychroman was observed.

Table 2. Compounds **3** Prepared

Compound	Yield (%)	mp (°C)	^{1}H-NMR ($CDCl_3$/TMS) δ, *J* (Hz)	MS (70 eV) *m/z* (%)
3a	76	103-105	1.07 (s, 2H), 2.30 (m, 2H), 2.90 (m, 1H), 3.25 (m, 1H), 4.05 (m, 1H), 7.10 (m, 3H), 7.35 (m, 1H)	165 (M^+, 33), 147 (92), 136 (100)
3b	65	oil	1.40 (s, 3H), 1.44 (s, 3H), 1.82 (m, 1H), 2.18 (m, 1H), 2.25 (s, 2H), 3.85 (s, 3H), 4.05 (m, 1H), 6.65 (m, 2H), 7.50 (d, *J* = 8, 1H)	223 (M^+, 32), 208 (20), 191 (28), 166 (100)
3c	77	118-120	1.75 (m, 1H), 1.95 (m, 1H), 3.85 (m, 1H), 4.10-4.30 (m, 3H), 6.70 (m, 1H), 6.85 (m, 1H), 7.09 (m, 1H), 7.35 (m, 1H)[x]	149 (M^+, 28), 132 (45), 121 (100), 93 (45)
3d	80	oil	1.25 (s, 3H), 1.43 (s, 3H), 1.65 (m, 1H), 2.10 (m, 3H), 4.05 (m, 1H), 6.75 (m, 1H), 6.90 (m, 1H), 7.13 (m, 1H), 7.45 (m, 1H)	177 (M^+, 15), 145 (10), 121 (100), 93 (25)
3e	85	oil	1.28 (s, 3H), 1.43 (s, 3H), 1.63 (m, 1H), 1.82 (s, 2H), 2.09 (m, 1H), 3.75 (s, 3H), 3.95 (m, 1H), 6.34 (d, *J* = 2, 1H), 6.51 (dd, J_1=2, J_2=8, 1H), 7.35 (d, *J* = 8, 1H)	-
3f	76	oil	1.23 (s, 3H), 1.43 (s, 3H), 1.62 (m, 1H), 2.10 (m, 3H), 2.60 (s, 3H), 3.79 (s, 3H), 4.05 (m, 1H), 6.45 (d, *J* = 9, 1H), 7.25 (d, *J* = 9, 1H)	221 (M^+, 40), 189 (88), 165 (100), 136 (44)
3g	72	169-170	1.25 (s, 3H), 1.42 (s, 3H), 1.65 (m, 1H), 2.09 (m, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 4.00 (m, 1H), 6.35 (s, 1H), 7.00 (s, 1H)	237 (M^+, 28), 205 (78), 181 (75), 166 (100)
3h	74	84-86	1.26 (s,3H), 1.35 (s, 9H), 1.43 (s, 3H), 1.65 (m, 1H), 2.10 (m, 1H), 3.78 (s, 3H), 4.00 (m, 1H), 6.30 (s, 1H), 7.30 (s, 1H)	263 (M^+, 18), 231 (48), 207 (20), 192 (100)
3i	60[a]	oil	1.25 (s,3H), 1.40 (s, 3H), 1.60 (m, 1H), 1.80 (s, 2H), 2.08 (m, 1H), 3.82 (s, 3H), 3.95 (m, 1H), 6.35 (s, 1H), 7.44 (s, 1H)	243/241 (M^+, 6/18), 209 (17), 185 (100), 143 (12)
3j	0[b]			
3k	0[c]			

[a] 4-amino-2,2-dimethyl-7-methoxychroman **3e** was also formed in 15 % yield.

[b] 2,2-dimethyl-5,7-dimethoxy-4-chromanone was obtained in 89 % yield. For physical and spectral data see ref.16.

[c] 2,2-dimethyl-4-hydroxy-7-methoxychroman was isolated in 84 % yield. mp.: 184-185 °C; ^{1}H-NMR 1.27 (s,3H), 1.49 (s, 3H), 2.09 (m, 1H), 2.43 (m, 1H), 3.75 (s, 3H), 4.55 (m, 1H), 6.35 (d, *J* = 2, 1H), 6.55 (dd, J_1=2, J_2=8, 1H), 7.55 (d, *J* = 8, 1H); MS: 206 (M^+, 12), 175 (33), 151 (100)

The elemental analyses for C, H and N were within ± 0.35 % of the theoretical value.

Experimental

Melting points were determined with a Koffler hot-stage apparatus and are uncorrected. Analytical thin-layer chromatography was performed on precoated aluminium-backed 0.2 mm silica gel plates. Column chromatography was carried out with Kieselgel 60 silica gel. ^{1}H NMR spectra were determined for solutions in deuteriochloroform with TMS as the internal reference on a Varian Gemini-200 instrument. MS data were obtained on a VG TRIO-2 spectrometer in EI mode at 70 eV. Microanalyses were performed by Microlaboratory, L. Kossuth University, Debrecen, Hungary. Solvents were used either as purchased or dried and purified by standard methods.

General procedure for the preparation of oximes **2a-k**

A mixture of 2,2-dimethyl-4-chromanone (**1a-k**, 10 mM), hydroxylamine hydrochloride (1.4 g, 20 mM), potassium carbonate (2.8 g, 20 mM) and ethanol (30 ml) was refluxed for 1-4 hours (TLC monitoring; until the starting material was consumed). The reaction mixture was then poured onto crushed ice, the precipitate was filtered, washed with water and dried. The crude material was satisfactorily pure for further steps. Analytical samples were recrystallized from methanol. Yields, physical and spectral data are summarized in Table 1.

General procedure for the reduction of oximes **2a-c** or **2e** ($LiAlH_4$ / Et_2O)

A mixture of 4-chromanone oximes (**2a-c** or **2e**, 20 mM), lithium aluminum hydride (1.14 g, 30 mM) and diethyl ether was refluxed for 4-6 hours (TLC monitoring; until the starting material was consumed). The excess of lithium aluminum hydride was decomposed by the careful addition of water under cooling with ice. The mixture was extracted with diethyl ether. The organic layer was washed with water, brine and dried over magnesium sulphate. The solvent was evaporated and the residue was subjected to column chromatography (eluent: chloroform-methanol = 5 : 1) to give 4-aminochromans (**3a-c** or **3e**) and 1,5-dibenzoxazepines (**4a-c** or **4e**). For yields, physical and spectral data of **3a-c** or **3e** see Scheme 2 and Table 2.
Spectral data of 1,5-benzoxazepines (**4**) prepared:

4a: (oil)	^{1}H NMR [$CDCl_3$/TMS, δ, *J* (Hz)]: 2.10 (m, 2H), 2.85 (m, 2H), 3.28 (m, 2H), 6.78 (m, 2H), 7.09 (m, 1H), 7.40 (m, 1H) MS [70 eV, m/z (%)] : 165 (M^+, 38), 136 (100), 120 (10), 109 (18)
4b: (oil)	^{1}H NMR [$CDCl_3$/TMS, δ, *J* (Hz)]: 1.30 (s, 6H), 1.98 (m, 2H), 3.10 (m, 2H), 3.73 (s, 3H), 6.75 (m, 2H), 7.01 (d, *J* = 2, 1H) MS [70 eV, m/z (%)] : 223 (M^+, 61), 208 (10), 166 (100), 152 (35)
4c: (mp. 51-52 °C)	^{1}H NMR [$CDCl_3$/TMS, δ, *J* (Hz)]: 2.00 (m, 2H), 3.22 (m, 2H), 4.11 (m, 2H), 6.70-7.05 (m, 4H) MS [70 eV, m/z (%)] : 149 (M^+, 32), 120 (100), 95 (20), 65 (28)
4e: (oil)	^{1}H NMR [$CDCl_3$/TMS, δ, *J* (Hz)]: 1.32 (s, 6H), 1.95 (m, 2H), 3.30 (m, 2H), 3.70 (s, 3H), 6.50 (m, 2H), 6.60 (d, *J* = 8, 1H) MS [70 eV, m/z (%)] : 207 (M^+, 52), 164 (12), 152 (100), 136 (64)

General procedure for the reduction of oximes **2** (Raney-Ni/H_2)

A mixture of 4-chromanone oximes (**2** 2.5 mM), Raney-Ni (Degussa) (2 g) and methanol (50 ml) was stirred under hydrogen pressure (5 bar) for 1-10 hours (TLC monitoring) at room temperature. The catalyst was filtered off, washed with methanol and the solvent was removed in vacuum. The residue was subjected to column chromatography (eluent: chloroform-methanol = 5 : 1) to give 4-aminochromans (**3a-i**). Yields, physical and spectral data are summarized in Table 2.

Acknowledgement

The authors gratefully acknowledge the financial support from ICN Hungary Co. Ltd. (Tiszavasvari, Hungary). Our thank is also due to Mrs. Fazekas Lajos and Mrs. Kovach Álmos for their technical assistance.

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Received on October 24, 1998