An Efficient Synthesis of 2,2-Dimethylchromans from 4-Methoxy-2,2-dimethylchromans[1]

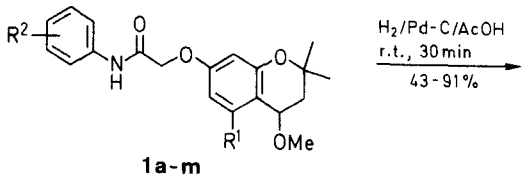
Albert Lévai,[a] Tibor Timár[b]

[a] Department of Organic Chemistry, Lajos Kossuth University, H 4010 Debrecen, Hungary

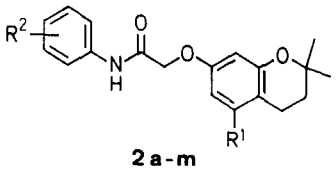
[b] Alkaloida Chemical Factory, H 4440 Tiszavasvári, Hungary

2,2-Dimethylchromans functionally substituted at C-7 were prepared by dealkoxylation of the corresponding 2,2-dimethyl-4-methoxychromans by catalytic hydrogenation on palladium on charcoal in acetic acid.

2,2-Dimethylchromans are natural products which have been shown to exhibit various bioactivities. Several procedures for their synthesis have been developed. The most frequently used method is based on the reaction of phenols with isoprene affording 2,2-dimethylchromans having various substitution patterns in the aromatic ring.[2-6] A similar procedure[7,8] utilizes the reaction of phenols with 1,3-dichloro-3-methylbutane. 3,4-Dihydrocoumarin is converted into 2,2-dimethylchroman on reaction with methylmagnesium halide.[9] Since these methods afford 2,2-dimethylchromans only in low or moderate yields, new procedures would be of interest.



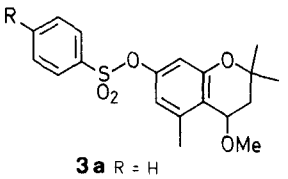
1a-m



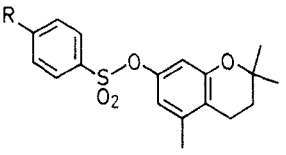
2a-m

1, 2	R^1	R^2	1, 2	R^1	R^2
a	H	H	h	H	3-Br
b	H	2-CH_3	i	H	4-Br
c	H	4-CH_3	j	CH_3	H
d	H	2-Cl	k	CH_3	2-Cl
e	H	3-Cl	l	CH_3	3-Cl
f	H	4-Cl	m	CH_3	4-Cl
g	H	2-Br			

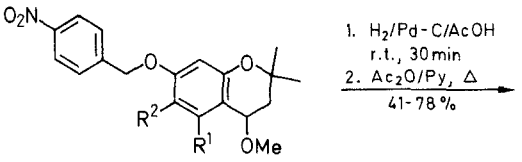
Recently, we synthesized a series of 2,2-dimethyl-4-methoxychromans[1] and investigated their chemical transformations. Hydrogenation of these compounds was systematically studied in acetic acid using 10% palladium on charcoal as catalyst and it was found that 2,2-dimethylchromans (**2**, **4**, **6**) possessing various substituents in the aromatic ring can conveniently be pre-



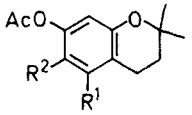
3a R = H
b R = CH_3



4a 55%
b 72%



5a R^1 = R^2 = H
b R^1 = CH_3, R^2 = H
c R^1 = H, R^2 =



6a R^1 = R^2 = H
b R^1 = CH_3, R^2 = H
c R^1 = H, R^2 = AcO

Downloaded by: Chinese University of Hong Kong. Copyrighted material.

Table. Compounds **2**, **4**, and **6** Prepared

Product	Yield (%)	mp. (°C)	Molecular Formula[a]	^{1}H-NMR ($CDCl_3$/TMS)[b] δ, J(Hz)
2a	91	139–140	$C_{19}H_{21}NO_3$ (311.4)	1.36 (s, 6H), 1.76 (t, 2H, J = 6.0), 2.72 (t, 2H, J = 6.0), 4.58 (s, 2H), 6.42–7.60 (m, 8H_{arom}), 8.24 (s, 1H)
2b	51	89–90	$C_{20}H_{23}NO_3$ (325.4)	1.36 (s, 6H), 1.84 (t, 2H, J = 6.3), 2.25 (s, 3H), 2.75 (t, 2H, J = 6.3), 4.62 (s, 2H), 6.46–8.04 (m, 7H_{arom}), 8.28 (s, 1H)
2c	69	145–146	$C_{20}H_{23}NO_3$ (325.4)	1.35 (s, 6H), 1.82 (t, 2H, J = 6.0), 2.34 (s, 3H), 2.72 (t, 2H, J = 6.0), 6.42–7.50 (m, 7H_{arom}), 8.20 (s, 1H)
2d	91	121–122	$C_{19}H_{20}ClNO_3$ (345.8)	1.35 (s, 6H), 1.80 (t, 2H, J = 6.1), 2.73 (t, 2H, J = 6.1), 4.58 (s, 2H), 6.44–8.46 (m, 7H_{arom}), 9.06 (s, 1H)
2e	63	136–137	$C_{19}H_{20}ClNO_3$ (345.8)	1.34 (s, 6H), 1.80 (t, 2H, J = 6.3), 2.72 (t, 2H, J = 6.3), 4.56 (s, 2H), 6.40–7.80 (m, 7H_{arom}), 8.28 (s, 1H)
2f	81	137–138	$C_{19}H_{20}ClNO_3$ (345.8)	1.36 (s, 6H), 1.82 (t, 2H, J = 6.0), 2.74 (t, 2H, J = 6.0), 4.55 (s, 2H), 6.42–7.56 (m, 7H_{arom}), 8.30 (s, 1H)
2g	54	110–111	$C_{19}H_{20}BrNO_3$ (390.3)	1.36 (s, 6H), 1.80 (t, 2H, J = 6.0), 2.72 (t, 2H, J = 6.1), 4.56 (s, 2H), 6.44–8.42 (m, 7H_{arom}), 9.06 (s, 1H)
2h	74	139–140	$C_{19}H_{20}BrNO_3$ (390.3)	1.34 (s, 6H), 1.80 (t, 2H, J = 6.0), 2.73 (t, 2H, J = 6.0), 4.54 (s, 2H), 6.42–7.84 (m, 7H_{arom}), 8.25 (s, 1H)
2i	55	151–152	$C_{19}H_{20}BrNO_3$ (390.3)	1.35 (s, 6H), 1.82 (t, 2H, J = 6.2), 2.72 (t, 2H, J = 6.2), 4.54 (s, 2H), 6.40–7.46 (m, 7H_{arom}), 8.26 (s, 1H)
2j	77	135–136	$C_{20}H_{23}NO_3$ (325.4)	1.34 (s, 6H), 1.80 (t, 2H, J = 6.0), 2.22 (s, 3H), 2.58 (t, 2H, J = 6.0), 4.5 (s, 2H), 6.30–7.62 (m, 7H_{arom}), 8.28 (s, 1H)
2k	54	108–109	$C_{20}H_{22}ClNO_3$ (359.8)	1.32 (s, 6H), 1.80 (t, 2H, J = 6.2), 2.22 (s, 3H), 2.56 (t, 2H, J = 6.2), 4.58 (s, 2H), 6.30–8.46 (m, 6H_{arom}), 9.06 (s, 1H)
2l	65	122–123	$C_{20}H_{22}ClNO_3$ (359.8)	1.34 (s, 6H), 1.80 (t, 2H, J = 6.2), 2.23 (s, 3H), 2.58 (t, 2H, J = 6.2), 4.54 (s, 2H), 6.32–7.80 (m, 6H_{arom}), 8.27 (s, 1H)
2m	43	151–152	$C_{20}H_{22}ClNO_3$ (359.8)	1.36 (s, 6H), 1.80 (t, 2H, J = 6.0), 2.22 (s, 3H), 2.57 (t, 2H, J = 6.0), 4.54 (s, 2H), 6.30–7.56 (m, 6H_{arom}), 8.28 (s, 1H)
4a	55	91–92	$C_{18}H_{20}O_4S$ (332.3)	1.28 (s, 6H), 1.80 (t, 2H, J = 6.4), 2.12 (s, 3H), 2.54 (t, 2H, J = 6.4), 6.25 (d, 1H), 6.40 (d, 1H), 7.48–7.82 (m, 5H_{arom})
4b	72	111–112	$C_{19}H_{22}O_4S$ (346.4)	1.26 (s, 6H), 1.78 (t, 2H, J = 6.4), 2.12 (s, 3H), 2.42 (s, 3H), 2.54 (t, 2H, J = 6.4), 6.28 (d, 1H), 6.40 (d, 1H), 7.30 (d, 2H), 7.72 (d, 2H)
6a	78	78–79	$C_{13}H_{16}O_3$ (220.3)	1.33 (s, 6H), 1.78 (t, 2H, J = 6.2), 2.24 (s, 3H), 2.74 (t, 2H, J = 6.2), 6.52–7.04 (m, 3H_{arom})
6b	41	63–64	$C_{14}H_{18}O_3$ (234.3)	1.36 (s, 6H), 1.82 (t, 2H, J = 6.1), 2.22 (s, 3H), 2.28 (s, 3H), 2.60 (t, 2H, J = 6.1), 6.38 (d, 1H), 6.48 (d, 1H)
6c	47	123–124	$C_{15}H_{18}O_5$ (278.3)	1.32 (s, 6H), 1.80 (t, 2H, J = 6.2), 2.25 (s, 6H), 2.74 (t, 2H, J = 6.2), 6.62 (s, 1H), 6.84 (s, 1H)

[a] Satisfactory microanalyses obtained: C ±0.14, H ±0.09.

[b] Recorded at 200 MHz on a Bruker WP 200 SY spectrometer.

pared in this way. The reduction products of compounds **5a–c** were purified as the acetates to afford 7-acetoxy-2,2-dimethylchromans **6a–c**.

The structure of the compounds prepared was proven by microanalyses and ^{1}H-NMR spectra (Table). All characteristic signals of the hetero ring of the starting materials disappeared and in the spectra of the hydrogenation products two triplets appeared at $\delta \approx 1.8$ and 2.8, respectively; they are attributable to the two adjacent methylene groups of the hetero ring. Other signals remained unchanged. Thus, we have worked out a new efficient procedure for the preparation of 2,2-dimethylchromans.

2,2-Dimethylchromans 2, 4, and 6; General Procedure:

A solution of the appropriate 4-methoxy-2,2-dimethylchroman **1**, **3**, or **5** (0.01 mol) in AcOH (100 mL) solution is hydrogenated at ambient temperature and pressure in the presence of 10% Pd-C (1.0 g) until no more H_2 is taken up (ca. 30 min). The catalyst is then filtered off, the solvent evaporated, and the residue crystallized from MeOH to afford compounds **2a–m** or **4a,b**. In the case of the hydrogenation of compounds **5a–c**, the residue is acetylated by heating in Ac_2O (5.0 mL)/anhydrous pyridine (5.0 mL) to give compounds **6a–c** (Table).

The present studies were sponsored by the Alkaloida Chemical Factory (Tiszavasvári, Hungary) and by the Hungarian Academy of Sciences for which our gratitude is expressed. Our thanks are due to Mrs. E. Hajnal for the technical assistance and to the staff of our NMR laboratory for the ^{1}H-NMR spectra.

Received: 30 May 1989; revised: 13 September 1989

(1) Part 12 of the series on Synthesis of Benzopyran Derivatives. Part 11: Lévai, A.; Timár, T. *Heterocycles*, in press.
(2) Bolzoni, L.; Casiraghi, G.; Casnati, G.; Sartori, G. *Angew. Chem.* **1978**, *90*, 727; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 684.
(3) Ahluwalia, V.K.; Ghazanfari, F.A.; Arora, K.K. *Synthesis* **1981**, 526.
(4) Ahluwalia, V.K.; Jolly, R.S.; Tehim, A.K. *Tetrahedron* **1982**, *38*, 3673.
(5) Ahluwalia, V.K.; Arora, K.K.; Jolly, S.S. *J. Chem. Soc., Perkin Trans. 1* **1982**, 335.
(6) Ahluwalia, V.K.; Khanna, M.; Singh, R.P. *Synthesis* **1983**, 404.
(7) Camps, F.; Coll, J.; Messeguer, A.; Pericas, M.A.; Ricart, S. *Synthesis* **1979**, 126.
(8) Camps, F.; Colomina, O.; Coll, J.; Messeguer, A. *Tetrahedron* **1982**, *38*, 2955.
(9) Fatope, M.O.; Abraham, D.J. *J. Med. Chem.* **1987**, *30*, 1973.

Downloaded by: Chinese University of Hong Kong. Copyrighted material.