Monatshefte für Chemie 115, 327—332 (1984)

Monatshefte für Chemie
Chemical Monthly

The Reaction of 4-Methoxycoumarins with Prenyl Bromide: Synthesis of 4′,4′,5′-Trimethyl-dihydrofurano-coumarins and 2,2-Dimethyl-chromenopyrans

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(Received 15 June 1983. Accepted 29 September 1983)

The reaction of 7-hydroxy-4-methoxy- (**1a**), 7-hydroxy-4,5-dimethoxy- (**1b**) and 5-hydroxy-4,7-dimethoxy (**1c**) -2*H*-1-benzopyran-2-ones with prenyl bromide in acetone in the presence of anhydrous potassium carbonate gave the corresponding prenyloxycoumarins **1d**, **1e**, and **1f**. The prenyloxy coumarins **1d**, **1e**, **1f** on *Claisen* migration by refluxing in *N*,*N*-dimethyl aniline gave the corresponding 4′,4′,5′-trimethyl-dihydrofuranocoumarins **2a**, **2b**, and **3**. However, the reaction of **1a**, **1b**, and **1c** with 3-chloro-3-methyl-but-1-yne in acetone in presence of potassium carbonate and potassium iodide gave the corresponding propargyl ethers **1g**, **1h**, **1i**, which on refluxing in *N*,*N*-dimethyl aniline gave the corresponding 2,2-dimethylchromenopyrans **4a**, **4b**, and **5**. These can also be obtained directly if the reaction is carried out in the presence of dioxan.

(Keywords: 3-Chloro-3-methylbut-1-yne; Claisen migration; Propargl ethers)

Die Reaktion von 4-Methoxycumarinen mit Prenylbromid: Synthese von 4′,4′,5′-Trimethyl-dihydro-furanocumarinen und 2,2-Dimethyl-chromenopyranen

Die Reaktion von 7-Hydroxy-4-methoxy- (**1a**), 7-Hydroxy-4,5-dimethoxy- (**1b**) und 5-Hydroxy-4,7-dimethoxy-2*H*-1-benzopyran-2-onen (**1c**) mit Prenylbromid in Aceton in der Gegenwart von wasserfreiem Kaliumcarbonat ergab die entsprechenden Prenylcumarine **1d**, **1e** und **1f**. Diese ergaben durch *Claisen*-Wanderung bei Rückfluß in *N*,*N*-Dimethylanilin die entsprechenden 4′,4′,5′-Trimethyldihydrofuranocumarine **2a**, **2b** und **3**. Die Reaktion von **1a**, **1b** und **1c** mit 3-Chlor-3-methyl-1-butin in Aceton in Gegenwart von wasserfreiem Kaliumcarbonat und Kaliumjodid ergab die entsprechenden Propargylether **1g**, **1h** und **1i**, die ihrerseits bei Rückfluß in *N*,*N*-Dimethylanilin die jeweiligen 2,2-Dimethylchromenopyrane **4a**, **4b** und **5** ergaben. Letztere können auch direkt erhalten werden, wenn die Reaktion in Gegenwart von Dioxan durchgeführt wird.

Introduction

The isoprenyl unit as 2,2-dimethylchromene ring or as 3,3-dimethyl allyl unit is a frequently occurring arrangement in natural products. The study of 4-hydroxycoumarin and its derivatives is of special importance in view of their being in tautomeric[2,3] equilibrium with the ketoform and its important physiological properties[4,5]. In view of this and due to the presence of coumarins with different modifications of isopentenyl group in nature, the reaction of 4-methoxycoumarins, viz., 7-hydroxy-4-methoxy-2*H*-1-benzopyran (**1 a**), 7-hydroxy-4,5-dimethoxy-2*H*-1-benzopyran-2-one (**1 b**) and 5-hydroxy-4,7-dimethoxy-2*H*-1-benzopyran-2-one (**1 c**) with prenyl bromide and 3-chloro-3-methyl-but-1-yne has been carried out with a view to synthesize 4′,4′,5′-trimethyldihydrofuranocoumarins and 2,2-dimethylchromenopyrans.

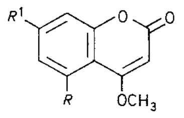
Results and Discussion

The reaction of 7-hydroxy-4-methoxy-2*H*-1-benzopyran-2-one (**1 a**) with prenyl bromide in dry acetone in the presence of anhydrous potassium carbonate gave an alkali insoluble product **A**. Its ^{1}H-NMR spectrum showed besides onther signals the presence of two singulets at δ 1.75 and 1.80 integrating for three protons each, which could be assigned to the gem. dimethyl group i.e., $—CH_2—CH=C(CH_3)_2$, δ 4.57 ($J = 8$ Hz) integrating for two protons i.e. methylene protons and a multiplet at δ 5.54 integrating for one methyne proton. Hence, **A** was assigned the structure of 4-methoxy-7-prenyloxy-2*H*-1-benzopyran-2-one (**1 d**). Similarly 7-hydroxy-4,5-dimethoxy-2*H*-1-benzopyran-2-one (**1 b**) and 5-hydroxy-4,7-dimethoxy-2*H*-1-benzopyran-2-one (**1 c**) gave 4,5-dimethoxy-7-prenyloxy-2*H*-1-benzopyran-2-one (**1 e**) and 4,7-dimethoxy-5-prenyloxy-2*H*-1-benzopyran-2-one (**1 f**). Similar results were obtained when the reaction was carried out in dioxan. **1 d** on *Claisen* migration in boiling *N*,*N*-dimethylaniline gave a compound **2 a** which was insoluble in alkali.

In the ^{1}H-NMR spectrum it showed the presence of three methyl groups, among which one appeared as a doublet at δ 1.32 ($J = 7$ Hz) indicating it to be a secondary methyl group and the other two methyl groups as two singlets at δ 1.40 and 1.52. Further one hydrogen resonated as a quartet at 4.50 ($J = 7$ Hz), which can be adjacent to ring oxygen atom. Finally two *ortho* coupled aromatic protons with $J = 10$ Hz each appeared at δ 6.65 and 7.58.

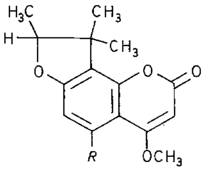
Hence compound **2 a** was assigned the structure of a 4-methoxy-4′,4′,5′-trimethyl-dihydrofurano(2′,3′,7,8)-2*H*-1-benzopyran-2-one.

However prenylation of 7-hydroxy-4-methoxy-2*H*-1-benzopyran-2-one (**1 a**) with 3-chloro-3-methyl-but-1-yne in acetone in the presence of anhydrous potassium carbonate and potassium iodide gave the propargyl ether **1 g** as can be deduced from its ^{1}H-NMR spectrum which indicated the presence of two methyl groups as a singlet at δ 1.70 and acetylenic protons at δ 2.61 besides other signals. On refluxing with *N,N*-dimethylaniline **1 g** gave 4-methoxy-8,8-dimethyl-2-oxo-2*H*,8*H*-chromeno[2,3—*h*]-pyran (**4 a**). Chromene **4 a** could also be obtained in one step by carrying out the reaction with 3-chloro-3-methyl-but-1-yne in presence of potassium carbonate and potassium iodide in dioxan.



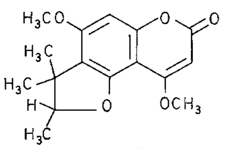
1

	R	R'
a	H	OH
b	OCH$_3$	OH
c	OH	OCH$_3$
d	H	OCH$_2$CH=C(CH$_3$)$_2$
e	OCH$_3$	OCH$_2$CH=C(CH$_3$)$_2$
f	OCH$_2$CH=C(CH$_3$)$_2$	OCH$_3$
g	H	OC(CH$_3$)$_2$-C≡CH
h	OCH$_3$	OC(CH$_3$)$_2$-C≡CH
i	OC(CH$_3$)$_2$-C≡CH	OCH$_3$

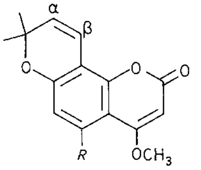


2

a R = H
b R = OCH$_3$

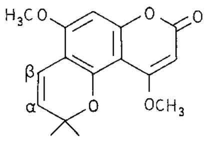


3



4

a R = H
b R = OCH$_3$



5

Identical results were obtained for 7-hydroxy-4,5-dimethoxy-2*H*-1-benzopyran-2-one (**1 b**) and 5-hydroxy-4,7-dimethoxy-2*H*-1-benzopyran-2-one (**1 c**). The structures of these compounds were in agreement with their spectral data which are presented in Table 1 and 2.

The coumarins **1 b** and **1 c**, required for the prenylation studies, have been obtained by catalytic debenzylation of the earlier described[3] 7-benzyloxy-4,5-dimethoxy- and 5-benzyloxy-4,7-dimethoxy-2*H*-1-benzopyran-2-ones.

Experimental

Reaction of Hydroxycoumarins in Acetone and Dioxan with Prenyl Bromide

The appropriate hydroxycoumarin (**1 a**, **1 b** or **1 c**) (1 g) in dry acetone or dioxan (50 ml) was refluxed for 6 h. with prenyl bromide in presence of anhydrous K_2CO_3. The solution was filtered, the residue washed with more

Table 1. *Melting points and* ^{1}H-NMR *spectral data of compounds* **1 d–1 i** *(in* $CDCl_3$*)*

Compound	M. P. (°C)	$—CH_2—CH{=}C\genfrac{}{}{0pt}{}{CH_3}{CH_3}$	$—OCH_3$ (s)	H-3	$—\underset{H_3C}{C}—\underset{CH_3}{C}{\equiv}CH$	Aromatic Protons
1 d	135–136	1.75 and 1.80 [2 s, $(CH_3)_2$] 4.57 (d, $—OCH_2—$, $J = 8$) 5.54 (m, —CH=, H-3)	3.95	5.54 (m, —CH=, H-3)	—	6.80 (m, H-6 and H-8) 7.65 (d, H-5, $J = 10$)
1 e	138–139	1.75 and 1.80 [2 s, $(CH_3)_2$] 4.53 (d, $—OCH_2—$, $J = 8$) 5.40 (m, —CH=, H-3)	3.82 and 3.88	5.40 (m, H-3 and —CH=)	—	6.25 and 6.30 (2 d, H-6, H-8, $J = 2.5$)
1 f	151–152	1.75 and 1.80 [2 s, $(CH_3)_2$] 4.53 (d, $—OCH_2—$, $J = 8$) 5.40 (m, —CH=, H-3)	3.80 and 3.90	5.40 (m, H-3 and —CH =)	—	6.25 and 6.30 (2 d, H-6, H-8, $J = 2.5$)
1 g	147–155	—	3.97	5.60 (s)	1.70 [s, $(CH_3)_2$] 2.67 (s, ≡CH)	7.05 (dd, H-6, $J = 10$ and 2.5), 7.30 (d, H-8, $J = 2.5$) 7.70 (d, H-5, $J = 10$)
1 h	154–155	—	3.90 and 3.96	5.46 (s)	1.78 [s, $(CH_3)_2$] 2.70 (s, ≡CH)	6.47 and 6.95 (2 d, H-6, H-8, $J = 2.5$)
1 i	142–143	—	3.82 and 3.88	5.45 (s)	1.65 [s, $(CH_3)_2$] 2.55 (s, ≡CH)	6.55 and 7.00 (2 d, H-6 and H-8, $J = 2.5$)

All compounds gave satisfactory C, H values; chemical shift are given in δ values (ppm) from internal *TMS*; coupling constants in Hz.

Table 2. *Melting points and* ^{1}H-NMR *spectral data of compounds* **2**, **3**, **4**, *and* **5** *(in* $CDCl_3$*)*

Compound	M. P. (°C)	*Me* groups for **2**, **3** or *Me* + olefinic H for **4**, **5**	OCH_3 (s)	H-3 (s)	Aromatic protons
2a	140–141	1.32 (d, CH_3, $J = 7$) 1.45 and 1.55 [2 s, $(CH_3)_2$], 4.50 (q, =CH—, $J = 7$)	3.92	5.50	6.66 (d, H-6, $J = 10$) 7.58 (d, H-5, $J = 10$)
2b	110–111	1.30 (d, CH_3, $J = 7$) 1.40 and 1.50 [2 s, $(CH_3)_2$]	3.80 and 3.90	5.45	6.25 (s, H-6)
3	150–151	1.32 (d, CH_3, $J = 7$) 1.40 and 1.50 [2 s, $(CH_3)_2$] 4.15 (q, =CH—, $J = 7$)	3.80 and 3.90	5.35	6.20 (s, H-8)
4a	130–131	1.46 [s, $(CH_3)_2$] 5.68 (d, α-H, $J = 10$) 6.85 (d, β-H, $J = 10$)	3.95	5.55	6.70 (d, H-6, $J = 10$) 7.52 (d, H-5, $J = 10$)
4b	144–145	1.42 and 1.44 [2 s, $(CH_3)_2$] 5.50 (d, α-H, $J = 10$) 6.75 (d, β-H, $J = 10$)	3.82 and 3.88	5.42	6.19 (s, H-6)
5	135–136	1.25 and 1.45 [2 s, $(CH_3)_2$] [2 s, $(CH_3)_2$] 5.55 (d, α-H, $J = 10$) 6.60 (d, β-H, $J = 10$)	3.85 and 3.90	5.45	6.35 (s, H-8)

All compounds gave satisfactory C, H values; chemical shifts are given in δ values (ppm) from internal *TMS*; coupling constants in Hz.

acetone or dioxan and the combined filtrate distilled. On crystallization from benzene — petroleum ether the respective prenyloxy coumarins (**1 d**, **1 e** or **1 f**) (Table 1) were ontained.

Claisen Rearrangement of Prenyloxycoumarins

The above prenyloxycoumarins (0.5 g) in *N*,*N*-dimethylaniline (5 ml) were refluxed for 15 h at 200–210 °C. The solution was cooled, diluted with Et_2O, the ether extract washed with dil. HCl (to remove dimethyl aniline) and then with sodium hydroxide solution. The remaining ether solution was dried ($MgSO_4$), distilled and the residue crystallised from methanol to give the appropriate 4′,4′,5′-trimethyl dihydrofuranocoumarins (**2 a**, **2 b** and **3**) (Table 2).

Reaction of Hydroxycoumarins in Acetone with 3-Chloro-3-methyl-but-1-yne

The appropriate hydroxycoumarin (**1 a**, **1 b** or **1 c**) (1 g) in dry acetone (50 ml) was refluxed for 6 h with 3-chloro-3-methyl-but-1-yne in presence of anhydrous K_2CO_3 and potassium iodide. The solution was filtered, the residue washed with more acetone and the combined filtrate distilled. Crystallisation of the residue from benzene—petroleum ether yielded respective propargyl ethers (**1 g**, **1 h** or **1 i**) (Table 1).

Claisen Rearrangement of Propenyloxycoumarins (**1 g**, **1 h** and **1 i**)

The above propenyloxy coumarins (0.5 g) were refluxed with *N*,*N*-dimethylaniline (5 ml) for 6 h at 180–190°. Working up of the reqction mixture (as above) and crystallisation from methanol yielded the appropriate 2,2-dimethylchromopyran (**4 a**, **4 b**, and **5**) (Table 2).

Reaction of the Hydroxycoumarins in Dioxan with 3-Chloro-3-methyl-but-1-yne

The appropriate hydroxy coumarin (1 g) was refluxed with 3-chloro-3-methyl-but-1-yne in dioxan for 12 h in presence of anhydrous K_2CO_3 and potassium iodide. The solution was filtered, the residue washed with more dioxan and the combined filtrate distilled. The product, on crystallisation from methanol, yielded the 2,2-dimethyl chromenopyrans (**4 a**, **4 b**, or **5**) (Table 2).

Acknowledgement

Our thanks are due to the CSIR, New Delhi, India, for financial assistance.

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