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O-Heterocycles by the Cyclization of Side-Chain Bromomethoxylated 2′-Acetoxychalcones

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Summary. The title chalcone derivatives react with aqueous sodium hydroxide of various concentrations to form aurones as the major product, together with small amounts of flavones. However, the introduction of 4′-nitro or 4′-chloro substituents resulted in the formation of flavones as the major product.

Keywords. Aurone; α-Bromochalcone; 3-Bromoflavanone; α-Bromo-β-methoxydihydrochalcone; Cyclization; Flavone.

O-Heterocyclen mittels Cyclisierung von an der Seitenkette brommethoxylierten 2′-Acetoxychalconen

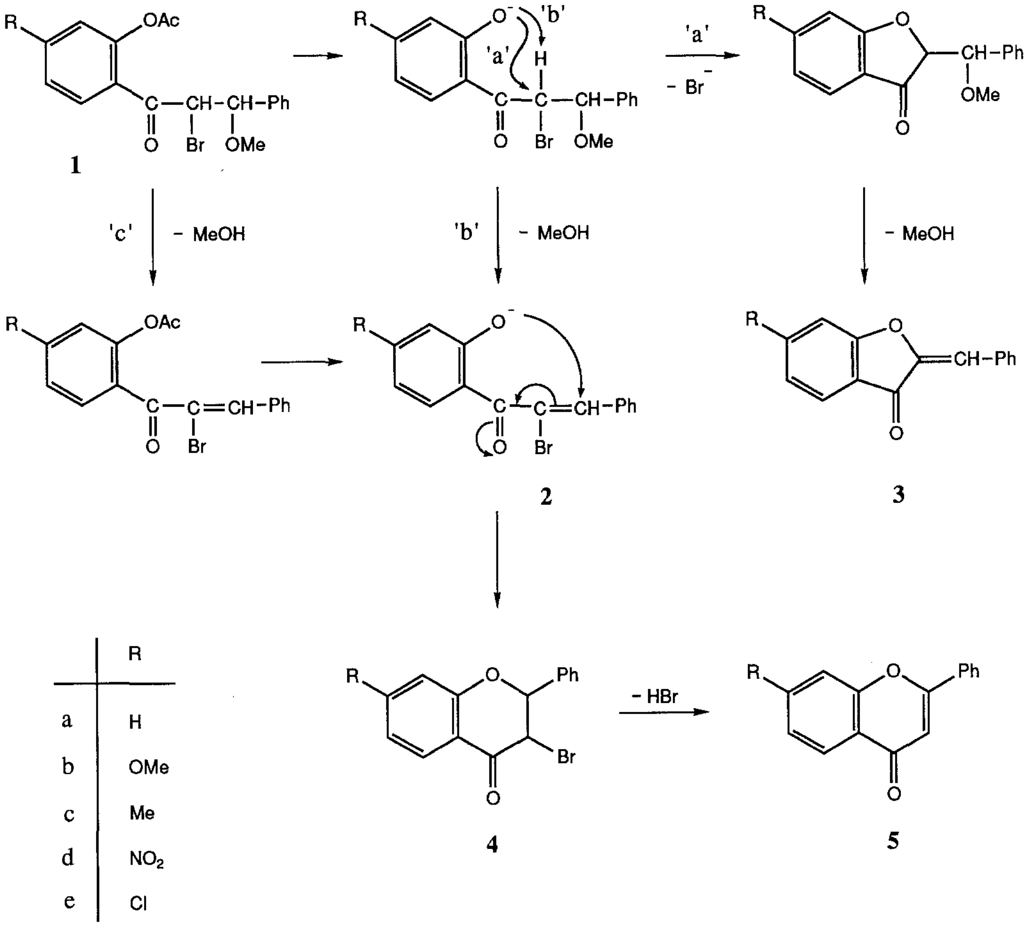
Zusammenfassung. Die im Titel genannten Chalconderivate reagieren mit Natronlauge in verschiedenen Konzentrationen, wobei Aurone zusammen mit geringen Mengen an Flavonen entstehen. Die Einführung von 4′-Nitro- oder 4′-Chlor-Substituenten führte jedoch zur bevorzugten Bildung von Flavonen.

Introduction

Side-chain derivatives of *o*-hydroxychalcones (or their acetates) are readily available precursors of several classes of naturally occurring *O*-heterocycles. For instance, in 1898, von Kostanecki introduced the base-catalysed cyclization of 2′-hydroxychalcone dibromides for the synthesis [1] of flavones and, even earlier, of 2-hydroxychalcone dibromides for the synthesis [2] of benzofurans; a 3-aminoflavanone was prepared by Litkei et al. [3] via a chalcone aziridine; it was for long believed that chalcone epoxides were always intermediates in the Algar-Flynn-Oyamada synthesis [4] of flavonols; the Wheeler reaction for the synthesis [5] of aurones **3** employs the base-catalysed cyclization of α-bromo-β-alkoxydihydrochalcones **1**. In a broader context, the hydroxy substituent in *o*-hydroxydihydrochalcones is a useful probe for the study of the reactions of α,β-disubstituted ketones [6]. Reported here is a study by liquid chromatography of the heterocyclic products of the Wheeler reaction, using different hydroxide concentrations, of a series of dihydrochalcones **1** substituted in the position *para* to the side-chain carbonyl group.

Results and Discussion

The principal observation (Table 1) was the formation of flavones in addition to aurones. Like the parent dihydrochalcone **1 a**, the *p*-methoxy **1 b** and *p*-methyl **1 c** substituted bromomethoxydihydrochalcones gave excellent yields of aurones **3 b, c**, particularly at low base concentrations. On the other hand, the dihydrochalcones **1 d, e** with positive Hammett σ value substituents in the *para* position gave flavones **5 d, e** as the major product. With all dihydrochalcones **1** there was a general decrease in aurone **3** formation and a general increase in flavone **5** formation with increasing concentration of added hydroxide, together with an overall decrease in heterocycle production. The last-mentioned effect was probably due to increasing base-induced fragmentation of the ketonic products and intermediates.



	R
a	H
b	OMe
c	Me
d	NO_2
e	Cl

The success of the Wheeler reaction as a general synthesis of aurones (Scheme, path "a") is undoubtedly due to the considerably greater effectiveness of bromide, compared with alkoxide, as a nucleofuge. Flavone **5** formation, usually minor, presumably occurs by initial elimination of methanol (Scheme, paths "b" and "c"), followed by cyclization of the resulting α-bromochalcone **2** to a 3-bromoflavanone **4** which then eliminates hydrogen bromide to form a flavone. This is in agreement with the exceptionally large amounts of flavones **5 d, e** formed by the 4′-nitro **1 d** and 4′-chloro **1 e** dihydrochalcones. These substituents should help to stabilize any developing negative charge on the α-carbon atom due to catalytic removal of the α-hydrogen atom.

Experimental Part

^{1}H nmr spectra were obtained at 270 MHz in $CDCl_3$ with Si*Me*$_4$ as internal reference. M.p.s were taken with a Kofler hot stage apparatus and are uncorrected. Merck silica gel $PF_{254+366}$ was used for preparative thin layer chromatography (plc). The data in Table 1 were obtained using a Waters Associates HPLC fitted with a μ-Bondapak (100 × 8 mm) C_{18} reverse phase cartridge, connected to an LCD/Milton Roy C 1-108 integrator and a fixed wavelength (214 nm) detector. The mobile phase was *Me*OH/H_2O 80:20.

General Procedure for Cyclizing 2'-Acetoxy-α-bromo-β-methoxydihydrochalcones **1 a–e**

A suspension of the dihydrochalcone (ca. $6.5 \cdot 10^{-5}$ mol) in *Me*OH (5 ml) was stirred for 15 min at 25 °C. Aqueous NaOH of the stated concentrations (1 ml) was then added and the solution was stirred for 1 h at 25 °C, diluted with water, acidified with dilute hydrochloric acid, and extracted with $CHCl_3$ (5 · 10 ml). The extract was washed with water (10 ml) and dried over anhydrous magnesium sulphate. Removal of the solvent gave an oil which was examined by liquid chromatography for its content of aurone **3** and flavone **5**.

General Procedure for the Preparation of α-Bromo-β-methoxydihydrochalcones **1**

N-Bromosuccinimide ($1.1 \cdot 10^{-3}$ mol) was added to a solution of a 2'-acetoxychalcone ($1.0 \cdot 10^{-3}$ mol) in methanol (40 ml, approx.), kept in the dark for 3 days, and the precipitate collected and crystallized from methanol.

2'-Acetoxy-4'-methoxychalcone gave **1 b**, white needles (61% yield), m.p. 131–132 °C. Found: C 55.76, H 4.56, Br 19.62. $C_{19}H_{19}BrO_5$ requires: C 56.04, H 4.70, Br 19.62%. ^{1}H nmr δ 2.39 (s, Ac), 3.18 (s, β-O*Me*), 3.87 (s, 4'-O*Me*), 4.77 (d, β-H, *J*=10 Hz), 5.06 (d, α-H, *J*=10 Hz), 6.67 (d, 3'-H, *J*=3 Hz), 6.87 (q, 5'-H, *J*=9 and 3 Hz), 7.36–7.45 (m, *Ph*), 7.89 (d, 6'-H, *J*=9 Hz).

2'-Acetoxy-4'-methylchalcone gave **1 c**, white needles (62% yield), m.p. 108–109 °C. Found: C 58.62, H 5.03, Br 20.72. $C_{19}H_{19}BrO_4$ requires: C 58.33, H 4.89, Br 20.42%. ^{1}H nmr δ 2.37 (s, *Ac*), 2.42 (s, 4'-*Me*), 3.18 (s, O*Me*), 4.76 (d, β-H, *J*=10 Hz), 5.05 (d, α-H, *J*=10 Hz), 7.14–7.45 (m, 7 H), 7.77 (d, 6'-H, *J*=8 Hz).

2'-Acetoxy-4'nitrochalcone gave **1 d**, white crystals (41% yield) from *Et*$_2$O/petrol, m.p. 124–125 °C. Found: C 50.94, H 3.72, Br 18.96, N 3.21. $C_{18}H_{16}BrNO_6$ requires: C 51.20, H 3.82, Br 18.92, N 3.32%. ^{1}H nmr δ 2.42 (s, *Ac*), 3.20 (s, O-*Me*), 4.75 (d, β-H, *J*=10 Hz), 4.93 (d, α-H, *J*=10 Hz), 7.41 (s, *Ph*), 7.94 (d, 6'-H, *J*=8 Hz), 8.09 (d, 3'-H, *J*=2 Hz), 8.20 (q, 5'-H, *J*=8 and 2 Hz).

2'-Acetoxy-4'-chlorochalcone gave **1 e**, white crystals (89% yield), m.p. 98–99 °C. Found: C 52.93, H 4.02, Br 19.34, Cl 8.25. $C_{18}H_{16}BrClO_4$ requires: C 52.52, H 3.92, Br 19.41, Cl 8.61%. ^{1}H nmr δ

Table 1. Yields (%) of aurone **3** and flavone **5** from the reactions of α-bromo-β-methoxydihydrochalcones **1** with aqueous sodium hydroxide

Added base	**1**	*R*=H [5]		*R*=O*Me*		*R*=*Me*		*R*=NO_2		*R*=Cl	
	3, 5	A [5]	F	A	F	A	F	A	F	A	F
1.0 *M*		96	4	95	5	80	4	23	39	48	15
2.0 *M*		85	6	75	5	85	4	20	40	38	29
3.0 *M*		61	8	75	7	78	9	19	52	23	29
4.0 *M*		63	11	68	4	62	9	21	43	17	29
5.0 *M*		51	25	72	7	63	9	17	35	8	37
10.0 *M*		14	47	59	7	20	28	–	–	4	39

2.38 (s, *Ac*), 3.18 (s, O*Me*), 4.74 (d, β-H, *J*=10 Hz), 4.98 (d, α-H, *J*=10 Hz), 7.22 (d, 3′-H, *J*=2 Hz), 7.34 (q, 5′-H, *J*=8 and 2 Hz), 7.41 (s, *Ph*), 7.79 (d, 6′-H, *J*=8 Hz).

2′-Acetoxy-4′-methylchalcone and Its Dibromide

Anhydrous NaO*Ac* (10.0 g) was added to a solution of 2′-hydroxy-4′-methylchalcone (5.0 g) in Ac_2O (20 ml), heated on a steambath for 2 h, and poured into water (100 ml). The precipitate was crystallized from *Et*OH, giving the acetate, needles (4.2 g), m.p. 82–83 °C. Found: C 77.08, H 5.92. $C_{18}H_{16}O_3$ requires: C 77.12, H 5.75%. ^{1}H nmr δ 2.24 (s, *Ac*), 2.42(s, *Me*), 6.98–7.59 (m, 9 H), 7.65 (d, 6′-H, *J*=8 Hz).

Br_2 (1.1 g) in $CHCl_3$ (20 ml) was added dropwise to a solution of the acetate (1.75 g) in $CHCl_3$ (50 ml). Removal of the solvent after 24 h gave an oil which crystallized from *Et*OH, giving 2′-acetoxy-4′-methylchalcone dibromide, white crystals (1.16 g), m.p. 94–96 °C. Found: C 48.97, H 3.64, Br 36.44. $C_{18}H_{16}Br_2O_3$ requires: C 49.12, H 3.66, Br 36.31%. ^{1}H nmr δ 2.41 (s, *Ac*), 2.42 (s, *Me*), 5.57 (d, α-H, *J*=11 Hz), 5.78 (d, β-H, *J*=11 Hz), 7.02–7.49 (m, 7 H), 7.88 (d, 6′-H, *J*=8 Hz).

Aurones **3 b–e**

Aqueous NaOH (5 *M*; 1 ml) was added to a suspension of **1 d** (0.088 g) in *Me*OH (5 ml), stirred for 1 h, diluted with water (20 ml), and extracted with $CHCl_3$. The extract was washed with water, dried, and evaporated to dryness. The residue was fractionated by plc using petrol/chloroform (1 : 20) as eluent. The fraction with the larger R_f value, 6′-nitroaurone **3 d** crystallized from aqueous *Me*OH in yellow flakes (0.02 g), m.p. 139–141 °C. Found: C 66.98, H 3.27, N 5.05. $C_{15}H_9NO_4$ requires: C 67.42, H 3.39, N 5.24%. ^{1}H nmr δ 6.85 (s, CH*Ar*), 7.27–8.21 (m, 8 H). The other fraction gave **5 d** [7] (0.02 g), m.p. 235–237 °C.

Similarly, **1 b** (0.1 g) gave **3 b** [8] (0.05 g), m.p. 145–146 °C. ^{1}H nmr δ 3.94 (s, O-*Me*), 6.83 (s, CH*Ar*), 6.74–7.92 (m 8 H). In this and the following two preparations, the precipitate obtained by adding water to the reaction mixture, was purified by crystallization from *Et*OH. **1 c** (0.3 g) gave **3 c** [9] (0.16 g), m.p. 153–154 °C. ^{1}H nmr δ 2.48 (s, *Me*), 6.85 (s, CH*Ar*), 7.00–7.92 (m, 8 H). **1 e** (0.2 g) gave **3 e** [9] (0.11 g), m.p. 157–159 °C. ^{1}H nmr δ 6.93 (s, CH*Ar*), 7.09–7.93 (m, 8 H).

Flavones **5 a–c**

Aqueous NaOH (2 *M*; 2 ml) was added to a suspension of 2′-acetoxy-4′-methylchalcone dibromide (0.3 g) in *Me*OH (7 ml), stirred for 1 h, and diluted with water (20 ml). The precipitate crystallized from aqueous *Me*OH giving 7-methylflavone **5 c** [10], yellow granules (0.14 g), m.p. 121–123 °C. ^{1}H nmr δ 2.48 (s, *Me*), 6.76 (s, 3-H), 7.18–7.90 (m, 7 H), 8.08 (d, 5-H, *J*=8 Hz).

The other flavones **5 d, a, b, e** were similarly prepared [7, 11–13] *via* the corresponding chalcone dibromides.

References

[1] Emilewicz T., Kostanecki S. von (1898) Chem. Ber. **31**: 696; see also Donnelly J. A., Doran H. J. (1974) Tetrahedron Lett.: 4083
[2] Kostanecki S. von, Tambor J. (1896) Chem. Ber. **29**: 237
[3] Litkei G., Bognar R., Szigeti P., Trapp V. (1972) Acta Chim. Acad. Sci. (Hung.) **73**: 95
[4] Dean F. M., Podimuang V. (1965) J. Chem. Soc.: 3978
[5] Donnelly J. A., Fox M. J., Sharma T. C. (1979) Tetrahedron **35**: 875
[6] David S. K., Main L., Old K. B. (1981) J. Chem. Soc. Perkin 2: 1367
[7] Donnelly D. J., Donnelly J. A., Philbin E. M. (1972) Tetrahedron **28**: 1867
[8] Auwers K. von, Pohl P. (1914) Liebigs Ann. **405**: 243

[9] Mulholland T. P. C., Preston H. D., Rosevear D. T. (1965) J. Chem. Soc.: 4939
[10] Cramer F. D., Elschnig G. H. (1956) Chem. Ber. **89**: 1
[11] Warriar A. M., Khanolkar A. P., Hutchins W. A., Wheeler T. S. (1937) Current Sci.: 475
[12] Emilewicz T., Kostanecki S. von (1899) Chem. Ber. **32**: 309
[13] Shah N. M., Parikh S. R. (1959) J. Indian Chem. Soc. **36**: 726

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