

AMINE-EFFECTED CYCLIZATION OF CHALCONE DIHALIDES TO AURONES

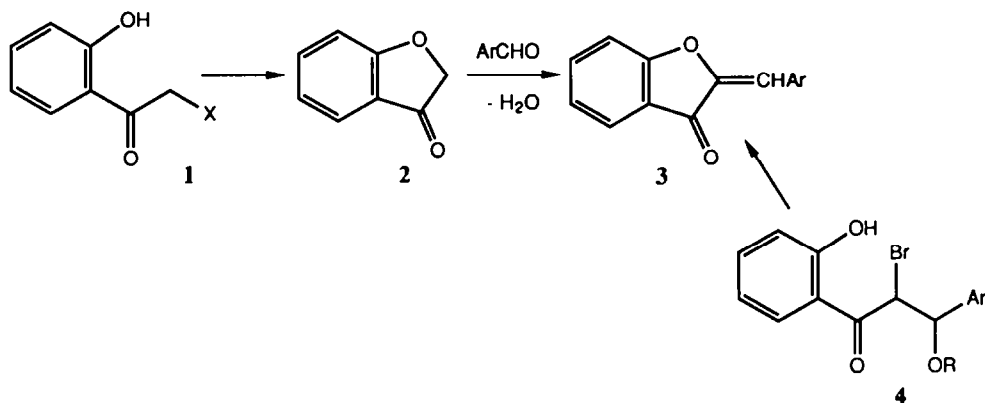
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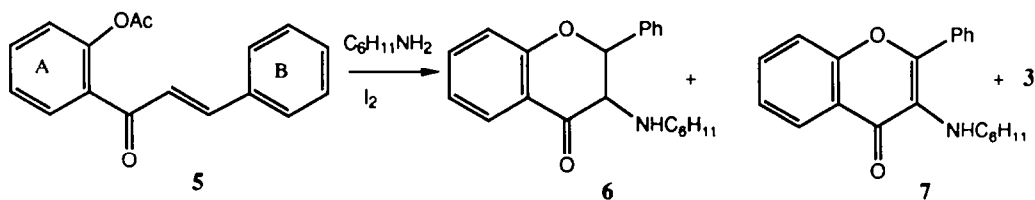
(Received in UK 25 June 1990)

Abstract - The possibility of employing the amine-catalysed cyclization of α,β -dibromodihydrochalcones and α -bromochalcones as a general synthesis of aurones was studied using cyclohexylamine and the most representative member of each class of these α,β -disubstituted ketones and α -halogeno chalcones. Overall yields of heterocyclic products were generally poor except from 4',6'-dimethoxy- and 3-nitro- substituted chalcone systems; aurones were obtained in fair yield from the former and in excellent yield from the latter. 2,2'-Diacetoxychalcone dibromide and 2,2'-diacetoxy- α -bromochalcone cyclised to a 2-benzoylbenzofuran, to the exclusion of the corresponding aurone and flavone.

Aurones **3** are one of the least common ¹ of the flavonoids; they are not widely distributed in nature. Not surprisingly, therefore, general methods for their synthesis are few. The most common ² is the condensation of suitably substituted coumaranones **2** with aromatic aldehydes in warm ethanolic base or acid. However, the synthesis of 2'-hydroxy-2-halogenoacetophenones **1** and their cyclization to coumaranones **2** are often complicated by side-reactions such as nuclear halogenation ³ and intermolecular substitution ⁴ for the side-chain halogen. Aurones **3** are sometimes, depending on the substitution pattern, the co-products from typical syntheses of six-membered-ring flavonoids, for example, the Emilewicz-von Kostanecki synthesis ⁵ of flavones by the reaction of chalcone dihalides with aqueous alcoholic alkali and the Algar-Flynn-Oyamada synthesis ⁶ of flavonols by the action of chalcones with alkaline hydrogen peroxide.



The generalisation of the Wheeler aurone synthesis ⁷, *i.e.* the base-catalysed cyclization of α -bromo- β -methoxylated 2'-hydroxychalcones 4, has made available a convenient, practical method for the preparation of these five-membered-ring heterocycles - though it has been observed ⁸ recently that, unless the concentration of the basic catalyst is kept low, flavones are formed as by-products. Bognar, Litkei et al have observed ⁹ that 2'-acetoxychalcone 5 reacts with cyclohexylamine in the presence of iodine to form a small amount (10%) of aurone 3; the major product is 3-cyclohexylaminoflavanone 6 which is autoxidised, in part, to 3-aminoflavanone 7; they concluded ^{9, 10} that a chalcone aziridine (*e.g.* 14) is an intermediate in this reaction. Some aurone formation was also observed in the reaction of the dibromide of this chalcone with cyclohexylamine. Reported here is a quantitative study, using liquid chromatography, of the effect of amine concentration on the production of aurones by the Bognar-Litkei reaction of 2'-hydroxy- and 2'-acetoxychalcone dibromides (Table 1) and α -bromo-chalcones (Table 2) with cyclohexylamine. For comparison purposes, the reaction of these compounds with aqueous methanolic sodium hydroxide, the Emilewicz-von Kostanecki flavonoid synthesis, was also studied.

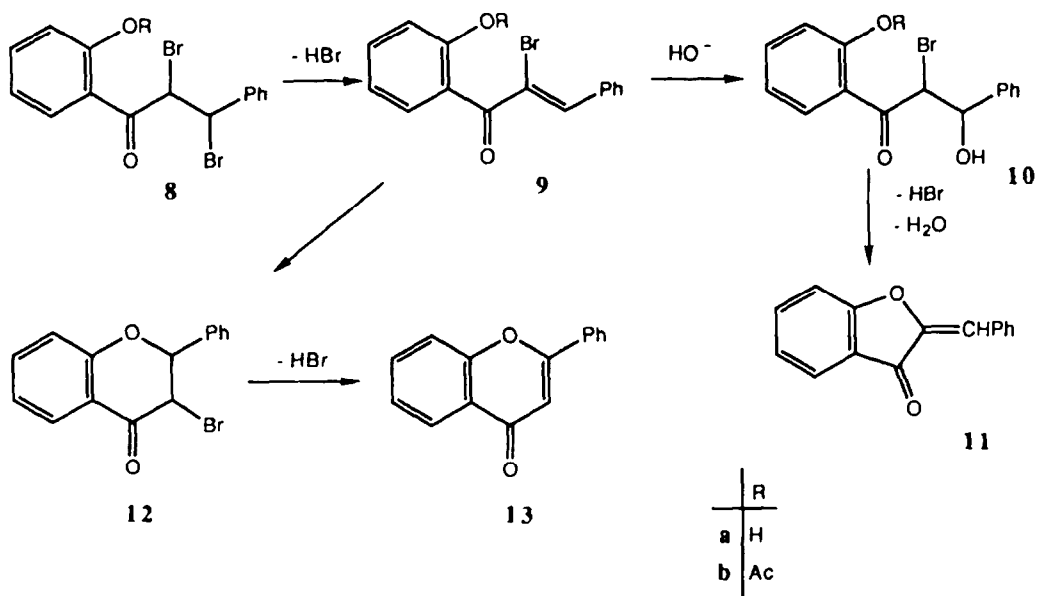


The reactions of α,β -disubstituted dihydrochalcones are controlled to a large extent by the substituents on the aromatic nuclei and α,β -dibromodihydrochalcones, *i.e.* chalcone dibromides, have been classified* accordingly ¹¹. The present study was made of the most representative member of each class, and its

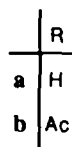
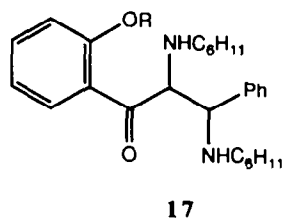
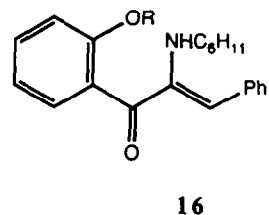
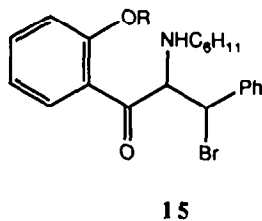
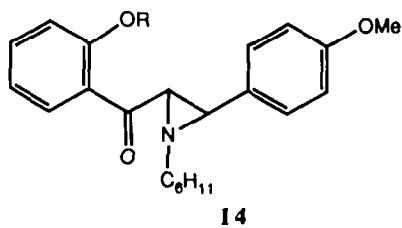
* It is convenient to extend the chalcone dihalide classification to all α,β -disubstituted dihydrochalcones and to add two further classes: class 0 (zero), those α,β -disubstituted dihydrochalcones having no cyclizable functional group in an *ortho* position of either aromatic ring; class 3, those α,β -disubstituted dihydrochalcones having a cyclizable functional group in the 2-position, *i.e.* the *ortho* position of the B-ring.

dehydrobrominated derivative (α -bromo-chalcone), and the acetates of both. In addition, a class 1/3 dihydrochalcone system, i.e. one having the characteristics of classes 1 and 3, has been included.

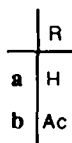
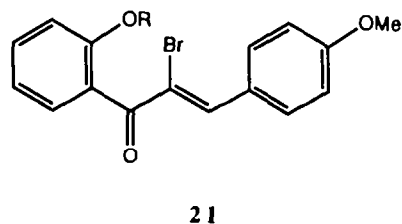
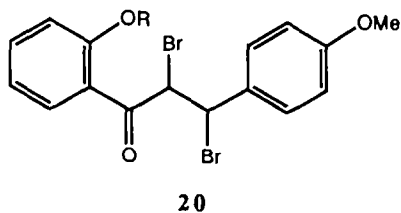
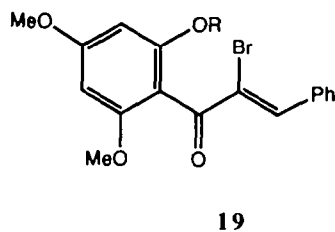
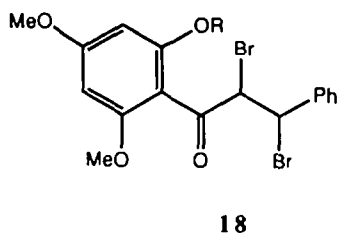
2'-Hydroxychalcone dibromide **8a** and its derivative **8b**, dihydrochalcones of class 1 (a class which is not known to form aurones in the Emilewicz-von Kostanecki reaction) and their α -bromo-chalcones **9a,b** were observed to form trace amounts of aurone **11** on reaction with aqueous ethanolic sodium hydroxide - probably not by direct cyclosubstitution ¹² of the 2'-phenoxide for the α -bromine atom but *via* an α -bromo-chalcone **9a,b** which were shown (Table 2) to be slightly more productive of aurone **11**, presumably by the initial formation of an α -bromo- β -hydroxydihydrochalcone **10**, followed by cyclosubstitution for the α -bromine and dehydration.

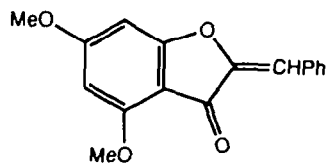


As previously observed for the dibromides **8a,b**, a major product of the Bognar-Litkei reaction of these halogeno ketones **8a,b**, **9a,b** with cyclohexylamine was 3-cyclohexylaminoflavanone **6**. Without taking into account possible intermediates resulting from amine attack on the carbonyl group, there are many routes to the 3-aminoflavanone **6**; they involve the chalcone aziridine **14** proposed by Litkei *et al*⁹ and intermediates such as **12**, **15-17**. Surprisingly, no 3-aminoflavanones were detected (the crude reaction products were examined by Hmr spectroscopy) in the products of the Bognar-Litkei reaction of any other class of chalcone dibromide or α -bromo-chalcone. Another major product was now found to be flavone **13**, the formation of which from chalcone dibromides requires extensive dehydrobromination to an α -bromo-chalcone **9**, followed by cyclization to 3-bromoflavanone **12** and further dehydrobromination.

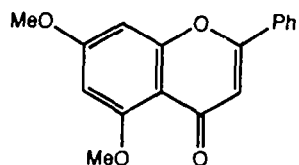


Both 2'-hydroxy-4',6'-dimethoxychalcone dibromide **18a** and 2'-hydroxy-4-methoxychalcone dibromide **20a**, representing dihydrochalcones of classes 2a and 2b, respectively, and their derivatives **18b**, **19a,b**, **20b**, **21a,b** often gave, in addition to the corresponding flavones **23**, **25**, fair yields of the corresponding aurones **22**, **24** and, bearing in mind the greater insolubility of aurones over flavones in ethanol, the solvent most commonly used for crystallising flavonoids, it is probable that the Bognar-Litkei reaction represents a practical method for their large scale preparation.

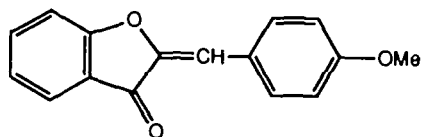




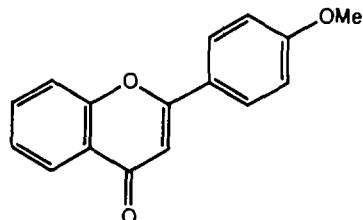
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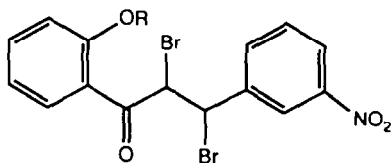


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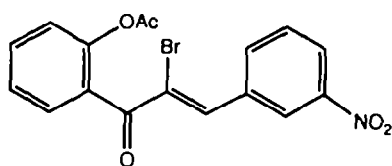


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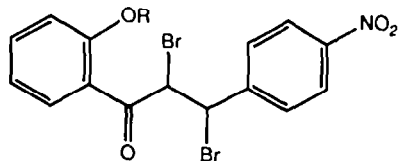
By far the outstanding aurone-producing systems were the 3-nitrodihydrochalcones **26a,b** and the α -bromo-3-nitrochalcone **27**. However, they can have little, if any, use in the synthesis of naturally occurring aurones. The co-product of the aurone **30** in these reactions was 3'-nitroflavone **31**. The 4-nitrochalcone dibromides **28a,b**, representing dihydrochalcones of class 2c, and the 4-nitro- α -bromo-chalcones **29a,b** usually yielded approximately equal amounts of 4'-nitroaurone **32** and 4'-nitroflavone **33**.



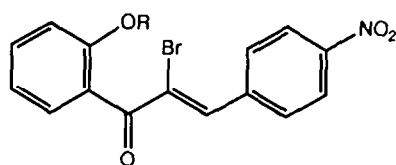
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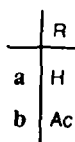
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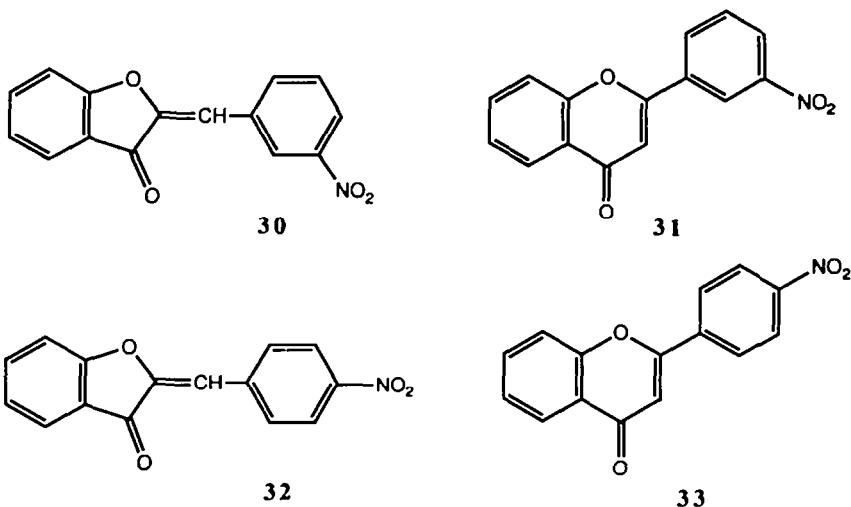


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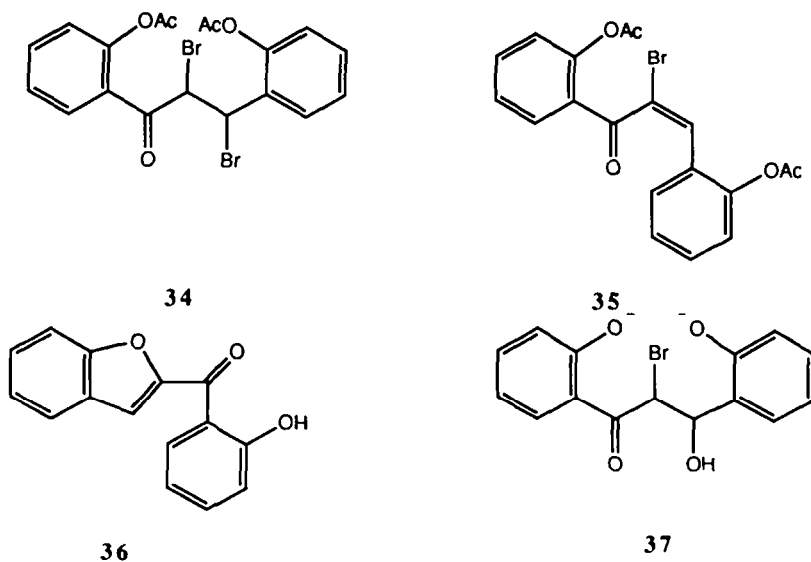


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The cyclizations of the class 1/3 dihydrochalcone, 2,2'-diacetoxychalcone dibromide **34**, and 2,2'-diacetoxy- α -bromochalcone **35** were interesting in that any or all of three heterocyclic systems could be formed. In fact, 2-(2-hydroxybenzyl)benzofuran **36** was obtained, to the exclusion of any aurone or flavone; undoubtedly reflecting the greater nucleophilicity of the 2-phenoxide over the carbonyl-conjugated 2'-phenoxide in the probable intermediate **37**.



EXPERIMENTAL

Melting points were determined with a Reichert Thermovar hot-block and are uncorrected. The Hmr spectra of all products were recorded on a Perkin-Elmer R12 spectrometer in CDCl_3 solutions containing Me_4Si

as internal standard. Merck silica gel PF₂₅₄₊₃₆₆ was used for preparative thin layer chromatography (PLC). Liquid chromatography was carried out using a Waters Associates instrument incorporating a model 455 variable wavelength uv detector, a model 745 data module, and a model 501 solvent delivery system, with a μ -Bondapak (10 x 8 cm) C₁₈ reverse phase cartridge and using external standards.

General procedure for the cyclization with sodium hydroxide of (i) 2'-hydroxy- and 2'-acetoxy- chalcone dibromides (Table 1) and (ii) 2'-hydroxy- and 2'-acetoxy- α -bromo-chalcones (Table 2). A suspension of the halogeno ketone (25 mg) in MeOH (5 ml) was stirred for 15 min. at 25°C. Aqueous sodium hydroxide (1 ml) of the appropriate concentration was added and the solution stirred for 1 h. at 25°C. Water (20 ml) and hydrochloric acid (1 ml) were then added and the solution was extracted with CHCl₃ (5 x 10 ml). The extract was washed with water and dried over anhydrous magnesium sulphate. Removal of the solvent gave a residue which was examined by liquid chromatography.

General procedure for the cyclization with cyclohexylamine of (i) 2'-hydroxy- and 2'-acetoxy- chalcone dibromides (Table 1) and (ii) 2'-hydroxy- and 2'-acetoxy- α -bromo-chalcones (Table 2). A suspension of the halogeno ketone (25 mg) in benzene (10 ml) was treated with the appropriate amount of cyclohexylamine. The solution was stirred for 20 h. and then washed with water (3 x 10 ml) and dried over anhydrous magnesium sulphate. Removal of the solvent gave a residue which was examined by liquid chromatography.

2,2'-Diacetoxychalcone Dibromide (34)

Br₂ (1.8 g) in CHCl₃ (20 ml) was added to a solution of 2,2'-diacetoxychalcone (3.0 g) in CHCl₃ (200 ml). After 18 h., the solvent was removed and the residual solid crystallised from light petroleum (b.p. 60-80°C) in white needles of the *dibromide* **34** (2.8 g), m.p. 127-128°C. Hmr δ 2.32 (s, 2-OAc), 2.41 (s, 2'-OAc), 5.87 (d, α -H, J 12 Hz), 5.99 (d, β -H, J 12 Hz), 7.12-8.13 (m, 8 H). Found: C, 46.74; H, 3.28; Br, 33.04. C₁₉H₁₆Br₂O₅ requires: C, 47.14; H, 3.33; Br, 33.01%.

2,2'-Diacetoxy- α -bromo-chalcone (35)

A solution of 2,2'-diacetoxychalcone dibromide **34** (1.0 g) in acetone (50 ml) containing anhydrous potassium acetate (0.44 g) was stirred overnight. It was diluted with water and extracted with CHCl₃. The extract was washed with water and dried over anhydrous magnesium sulphate. Purification by PLC gave (*E*)-2,2'-diacetoxy- α -bromo-chalcone **35** (0.42 g) as a yellow solid, m.p. 63-65°C. Hmr δ 2.40 (s, 2-OAc), 2.42 (s, 2'-OAc), 6.84-8.41 (m, 9 H). Found: C, 56.95; H, 3.82; Br, 19.49. C₁₉H₁₅BrO₅ requires: C, 56.60; H, 3.75; Br, 19.82%.

2-(2-Hydroxybenzoyl)benzofuran (36)

Aqueous NaOH (4 M; 4 ml) was added to a suspension of 2,2'-diacetoxychalcone dibromide **34** (1.22 g) in MeOH (40 ml). After 1 h, water was added and the mixture was acidified with hydrochloric acid and extracted with CHCl₃. The extract was washed with water and dried over anhydrous magnesium sulphate. Removal of the solvent gave an oil which crystallised from EtOH in yellow needles of the *benzofuran* **36** (0.28 g),

Table 1

Reactions of chalcone dibromides with cyclohexylamine and sodium hydroxide

2'-Hydroxychalcone Dibromide	Conc. of base (M)	% Yield from B-L reaction ^a				% Yield from E-K reaction ^b		
		A ^c	F ^d	Af ^e	Bf ^f	A ^c	F ^d	Bf ^f
8a ¹³	0.04	8	11	37		0.02	55	
	0.4	19	26	13		0.01	65	
	2	23	27	9		0	72	
18a ⁵	0.04	58	26	0		2	67	
	0.4	48	22	0		4	66	
	2	37	5	0		10	44	
20a ¹⁴	0.04	10	24	0		17	64	
	0.4	6	26	0		6	62	
	2	5	44	0		3	62	
26a ¹⁵	0.04	92	6	0		10	70	
	0.4	89	7	0		30	63	
	2	32	20	0		35	56	
28a ¹⁵	0.04	50	17	0		4	79	
	0.4	30	23	0		15	79	
	2	17	25	0		33	63	
2'-Acetoxychalcone Dibromide								
8b ¹⁷	0.04	3	18	63		0	61	
	0.4	6	27	54		0.8	62	
	2	9	28	3		2	61	
18b ⁵	0.04	40	5	0		2	89	
	0.4	29	7	0		4	82	
	2	26	9	0		27	71	
20b ¹⁴	0.04	12	20	0		77	19	
	0.4	10	21	0		46	46	
	2	4	23	0		45	53	
26b ¹⁸	0.04	26	20	0		9	72	
	0.4	44	15	0		11	58	
	2	48	9	0		15	44	
28b ¹⁸	0.04	22	18	0		53	43	
	0.4	22	18	0		44	39	
	2	16	15	0		43	27	
34	0.04	0	0	0	20	0	0	64
	0.4	0	0	0	21	0	0	59
	2	0	0	0	38	0	0	54

^a The Bogner-Litkei reaction of the chalcone dibromide with cyclohexylamine. ^b The Emilewicz-von Kostanecki reaction of the chalcone dibromide with sodium hydroxide. ^c Aurones: **11** ⁷, **22** ²², **24** ²³, **30** ²⁴ (m.p. 194-196°C. Found: C, 67.78; H, 3.62; N, 5.48. Calc. for C₁₅H₉NO₄: C, 67.42; H, 3.39; N, 5.24%), **32** ¹⁸. ^d Flavones: **13** ²⁰, **23** ²¹, **25** ¹⁶, **31** ¹⁸, **33** ¹⁸. ^e As the 3-aminoflavanone (**6**) was observed by LC to steadily autoxidise to the 3-aminoflavone (**7**), the figures in this column are the sum of the yields of these two products. ^f 2-(2-Hydroxybenzoyl)benzofuran (**36**).

Table 2

Reactions of α -bromo-chalcones with cyclohexylamine and sodium hydroxide

2'-Hydroxy- α -bromo-chalcone	Conc. of base (M)	% Yield from B-L reaction ^a				% Yield from E-K reaction ^b		
		A ^c	F ^d	Af ^e	Bf ^f	A ^c	F ^d	Bf ^f
9a ¹⁶	0.04	2	21	4		5	85	
	0.4	3	52	5		3	69	
	2	10	54	13		2	60	
19a ¹⁹	0.04	43	17	0		11	78	
	0.4	35	14	0		10	80	
	2	34	10	0		7	84	
21a ¹⁶	0.04	10	15	0		1	57	
	0.4	33	24	0		2	64	
	2	40	25	0		2	80	
29a ¹⁵	0.04	44	45	0		1	87	
	0.4	44	41	0		2	75	
	2	29	31	0		13	19	
2'-Acetoxy- α -bromo-chalcone								
9b ¹⁶	0.04	3	13	30		2	75	
	0.4	5	36	12		2	75	
	2	5	40	11		3	92	
19b ¹⁹	0.04	43	10	0		1	88	
	0.4	27	72	0		1	86	
	2	11	76	0		3	85	
21b ¹⁶	0.04	46	31	0		25	62	
	0.4	10	34	0		25	63	
	2	5	38	0		26	64	
27 ¹⁵	0.04	88	12	0		37	6	
	0.4	65	14	0		37	6	
	2	60	27	0		37	6	
29b ¹⁵	0.04	26	16	0		54	45	
	0.4	31	17	0		61	37	
	2	41	54	0		61	34	
35	0.04	0	0	0	10	0	0	60
	0.4	0	0	0	20	0	0	76
	2	0	0	0	24	0	0	87

^a The Bogнар-Litkei reaction of the α -bromo-chalcone with cyclohexylamine. ^b The Emilewicz-von Kostanecki reaction of the α -bromo-chalcone with sodium hydroxide. ^c Aurones: **11**, **22**, **24**, **30**, **32**. ^d Flavones: **13**, **23**, **25**, **31**, **33**. ^e As the 3-aminoflavanone (**6**) was observed by LC to steadily autoxidise to the 3-aminoflavone (**7**), the figures in this column are the sum of the yields of these two products. ^f 2-(2-Hydroxy-benzoyl)benzofuran (**36**).

m.p. 68-69°C. Hmr δ 6.97-8.39 (m, 8 H), 7.66 (s, 3-H), 12.04 (s, OH). Found: C, 75.70; H, 4.28. C₁₅H₁₀O₃ requires: C, 75.62; H, 4.23%.

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