Conversion of 3-Formylchromones into Pyrrole and Thiophene Derivatives

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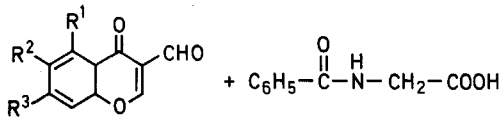
3-Formylchromones react with phenylhydrazine to give pyrazoles[1], and yield isoxazoles with hydroxylamine[2], pyridones with cyanoacetamide anion[3], benzophenones with ethyl acetoacetate anion[4] and pyrimidines with formamidine[5]. We now report the practicable conversion of 3-formylchromones[6] into pyrrole and thiophene derivatives by treatment of their azlactone[7] or rhodanine[8] condensates, **3**, **6**, with base[9]. The azlactones (**3a–d**) were readily obtained from the appropriate chromon-3-aldehyde (**1**) and hippuric acid (**2**), and when heated with methanolic or ethanolic sodium carbonate gave either the pyrroles (**4a–c**) directly (from azlactones **3a, b**, $R^1 = H$) or the intermediate acrylic esters (**5a–c**) when the azlactones carried a 5-substituent (**3c, d**, $R^1 \neq H$). All the azlactones and the acrylic esters were, however, converted into the corresponding pyrroles on treatment with methanolic sodium methoxide.



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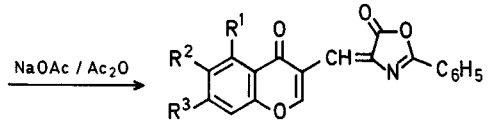
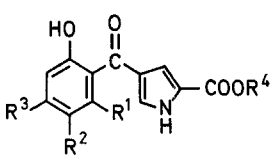


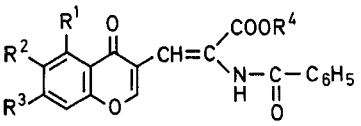
3 a-d

1, 3	R^1	R^2	R^3
a	H	H	H
b	H	OCH_3	H
c	CH_3	H	CH_3
d	OCH_3	H	H



4 a-e

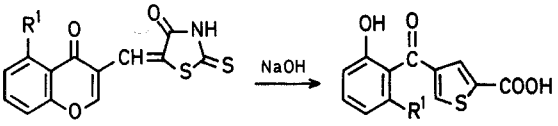
4	R^1	R^2	R^3	R^4
a	H	H	H	CH_3
b	H	H	H	C_2H_5
c	H	OCH_3	H	CH_3
d	CH_3	H	CH_3	CH_3
e	OCH_3	H	H	CH_3



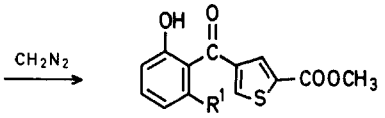
5 a-c

5	R^1	R^2	R^3	R^4
a	CH_3	H	CH_3	CH_3
b	CH_3	H	CH_3	C_2H_5
c	OCH_3	H	H	CH_3

On treatment with 15% aqueous sodium hydroxide, the rhodanine condensates (**6a, b**) gave the thiophen-2-carboxylic acids (**7a, b**) directly, which for identification purposes were converted into their methyl esters (**8a, b**) by treatment with ethereal diazomethane. The esters gave spectra closely related to those obtained for the pyrrole esters (**4**).



6a,b **7a,b**



$R^1 = H, OCH_3$ **8a,b**

Mechanistic aspects of these transformations and the substituent effects observed during pyrrole formation are being investigated. All compounds gave spectra consistent with their assigned structures.

Preparation of 4'-[(Chromon-3-yl)-methylene]-5-oxo-2-phenyl-4,5-dihydro-1,3-oxazole (3a); General Procedure for 3a–d:

To an intimately ground mixture of 3-formylchromone (**1a**; 4 g, 0.024 mol), hippuric acid (**2**; 4.1 g, 0.024 mol), and sodium acetate (1.6 g, 0.020 mol) was added acetic anhydride (10 ml, 0.1 mol). The mixture was heated at 100° for 1 h, then cooled, and added to water (250 ml). The crude product was filtered off and gave 4'-[(chromon-3-yl)methylene]-5-oxo-2-phenyl-4,5-dihydro-1,3-oxazole (**3a**), as yellow prisms (see Table).

Preparation of 2-Methoxycarbonyl-4-(2-hydroxybenzoyl)-pyrrole (4a); General Procedure for 4a–c:

A solution of 4'-[(chromon-3-yl)-methylene]-5-oxo-2-phenyl-4,5-dihydro-1,3-oxazole (**3a**;) (2 g, 0.0063 mol) in methanol (50 ml) was heated under reflux for 45 min in the presence of anhydrous sodium carbonate (1 g, 0.01 mol), then filtered. The filtrate was evaporated to yield a red oil which solidified on trituration with aqueous acetic acid. The crude product gave 2-methoxycarbonyl-4-(2-hydroxybenzoyl)-pyrrole (**4a**) as white needles (see Table).

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Table. Preparation of Azlactones **3**, Pyrroles **4**, Acrylic Esters **5**, Rhodanine Condensates **6**, and Thiophenes **7** and **8**

Compound	Yield [%]	m.p.	Crystallisation solvent	Molecular formula[a]	Mass Spectrum *m/e* $M^{\oplus}$
3a	41	184–186°	CCl_4	$C_{19}H_{11}NO_4$ (317.3)	317
3b	47	243–245°	$CHCl_3$	$C_{20}H_{13}NO_5$ (347.3)	347
3c	52	253–254°	$CHCl_3$	$C_{21}H_{15}NO_4$ (361.4)	
3d	40	247°	$CHCl_3$	$C_{20}H_{13}NO_5$ (347.3)	347
4a	74	149–150°	CH_3OH	$C_{13}H_{11}NO_4$ (245.2)	245
4b	37	112–113°	C_2H_5OH/H_2O	$C_{14}H_{13}NO_4$ (259.3)	259
4c	78	125–127°	CH_3OH/H_2O	$C_{14}H_{13}NO_5$ (275.3)	275
4d	46	182–183°	$CHCl_3$/pet. ether	$C_{15}H_{15}NO_4$ (273.3)	273
4e	55	158°	$CHCl_3$/pet. ether	$C_{14}H_{13}NO_5$ (275.3)	275
5a	55	162–163°	CH_3OH	$C_{22}H_{19}NO_5$ (377.4)	377
5b	73	144–145°	C_2H_5OH	$C_{23}H_{21}NO_5$ (391.4)	391
5c	50	186°	CH_3OH	$C_{21}H_{17}NO_6$ (379.4)	379
6a	66	245°	C_5H_5N	$C_{13}H_7NO_3S_2$ (289.3)	289
6b	43	258–259°	DMSO	$C_{14}H_9NO_4S_2$ (319.4)	319
7a	44	161–163°	C_2H_5OH/H_2O	$C_{12}H_8O_4S$ (248.3)	248
7b	80	202°	C_2H_5OH/H_2O	$C_{13}H_{10}O_5S$ (278.3)	278
8a	57	79–80°	CCl_4/pet. ether	$C_{13}H_{10}O_4S$ (262.3)	262
8b	60	125–126°	CCl_4/pet. ether	$C_{14}H_{12}O_5S$ (292.3)	292

[a] All products gave satisfactory microanalyses (C ± 0.3%, H ± 0.2%, N ± 0.3%).

Preparation of 4-(4,6-Dimethyl-2-hydroxybenzoyl)-2-methoxycarbonylpyrrole (4d); General Procedure for 4d, e:
4'-[5,7-Dimethylchromon-3-yl)-methylene]-5-oxo-2-phenyl-4,5-dihydro-1,3-oxazole (**3c**; 1.1 g, 0.0032 mol) was added to a solution of sodium methoxide in methanol [from sodium (0.1 g, 0.0043 g. atom) in methanol (25 ml)]. The mixture was heated under reflux for 0.5 h, then cooled, and the solvent was evaporated. The residue was dissolved in water and the solution was extracted with chloroform (3 × 25 ml). The combined extracts were dried and evaporated to yield methyl benzoate (0.22 g). After acidification with concentrated hydrochloric acid, the aqueous phase was extracted with chloroform (3 × 50 ml). Evaporation of the combined extracts yielded an oil which was chromatographed on silica gel. Elution with ether gave 4-(4,6-dimethyl-2-hydroxybenzoyl)-2-methoxycarbonylpyrrole (**4d**) as white needles (see Table).

Preparation of Methyl 2-Benzamido-3-(5,7-dimethylchromon-3-yl)-acrylate (5a); General Procedure for 5a–d:
A solution of 4'-[(5,7-dimethylchromon-3-yl)-methylene]-5-oxo-2-phenyl-4,5-dihydro-1,3-oxazole (**3c**; 1 g, 0.0029 mol) in methanol (50 ml) was heated under reflux in the presence of anhydrous sodium carbonate (1 g) for 45 mins, then cooled and filtered. The filtrate was evaporated and the residual oil solidified on trituration with aqueous acetic acid. The crude product gave methyl 2-benzamido-3-(5,7-dimethylchromon-3-yl)-acrylate (**5a**) as white needles (see Table).

Preparation of 4-(4,6-Dimethyl-2-hydroxybenzoyl)-2-methoxycarbonylpyrrole (4d) from Methyl 2-Benzamido-3-(5,7-dimethylchromon-3-yl)-acrylate (5a); General Procedure for 4d, e:
To a solution of sodium (0.1 g, 0.0043 g. atom) in methanol (20 ml) was added methyl 2-benzamido-3-(5,7-dimethylchromon-3-yl)-acrylate (**5a**; 0.75 g, 0.002 mol) and the mixture was heated under reflux for 1 h. The solvent was evaporated and excess of 2 normal hydrochloric acid was added to the residue. Extraction with chloroform and evaporation of the dried extracts gave an oil which was column-chromatographed on silica gel. Elution with ether/light petroleum [b. p. 60–80°] (9:1) gave 4-(4,6-dimethyl-2-hydroxybenzoyl)-2-methoxycarbonylpyrrole (**4d**) (see Table).

Preparation of 5'-[(Chromon-3-yl)-methylene]rhodanine (6a); General Procedure for 6a, b:
To an intimately ground mixture of 3-formylchromone (**1a**; 1 g, 0.006 mol), rhodanine (0.76 g, 0.006 mol), and sodium acetate (0.5 g, 0.006 mol) was added acetic anhydride (5 ml, 0.05 mol) and the mixture was heated at 100° for 0.5 h, then added to water (250 ml). The crude product was filtered off and gave 5-[(chromon-3-yl)-methylene]rhodanine (**6a**) as yellow needles (see Table).

Preparation of 2-Carboxy-4-(2-hydroxybenzoyl)-thiophene (7a); General Procedure for 7a, b:
A solution of 5'-[(chromon-3-yl)-methylene]rhodanine (**6a**; 3.3 g, 0.115 mol) in 15% aqueous sodium hydroxide (50 ml) was heated under reflux for 1 h, then cooled and poured into water (250 ml). The mixture was acidified with concentrated hydrochloric acid and the precipitate was filtered off. It gave 2-carboxy-4-(2-hydroxybenzoyl)-thiophene (**7a**) as light brown powder (see Table).

Preparation of 4-(2-Hydroxybenzoyl)-2-methoxycarbonylthiophene (8a); General Procedure for 8a, b:
A solution of 2-carboxy-4-(2-hydroxybenzoyl)-thiophene (**7a**; 0.5 g, 0.002 mol) in ether (30 ml) was added dropwise to ethereal diazomethane (0.6 g, in ~50 ml ether) over 10 min. The solution was allowed to stand at room temperature for a further 10 min before the excess of diazomethane was destroyed by cautious addition of acetic acid. The solvent was evaporated under reduced pressure, and the residue gave 4-(2-hydroxybenzoyl)-2-methoxycarbonylthiophene (**8a**) as pale yellow needles (see Table).

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