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NEW SYNTHESIS OF CHALCOGENOCHROMONES

ANDRÉ J. LUXEN, LÉON E.E. CHRISTIAENS and MARCEL J. RENSON

Organic Heterocyclic Chemistry, University of Liège, Chemistry Institute, B.6., Sart-Tilman, 4000 Liège (Belgium)

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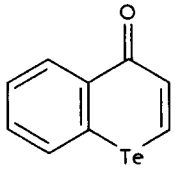
Summary

We describe a new synthesis of chalcogenochromones and of some of their oxygen, sulfur, selenium and tellurium derivatives. The synthesis involves acidic cyclisation of (*o*-alkylchalcogenophenyl) ethynyl ketones.



(A)

The chemistry of chromones and flavones and their sulfur and selenium analogs [1–4] is well documented. Tellurochromone (**A**) was synthesized by our group [5] and very recently the first telluroflavone derivatives were described [6]. However, of the numerous syntheses of chalcogenochromones published in the literature, none provides a general method. Four years ago [7], we reported the electrophilic cyclisation of β-arylchalcogenopropenoïc acids **1** and **3** (Scheme 1) (obtained [8,9] through a Michael addition of an arylchalcogenate anion to the corresponding propiolic acids or esters) as an alternative method for production of chalcogenochromone derivatives. Recently, this method was extensively studied by Detty and co-workers [6,8,10], and the results were in agreement with those we obtained with other substrates. However, this electrophilic cyclisation suffers from two important limitations: (1) competitive cyclisation on the R substituted aromatic ring in **3** when R bears electron-releasing substituents [8]; and (2) *ipso* carbodechalcogenation in the selenium series (when there is electron enrichment) and in the tellurium series, with formation of 1-aroyl-2-chlorochalcogenoethylene derivatives **2** and **4** [6,10]. With the aim of providing a general synthesis of chalcogenochromone

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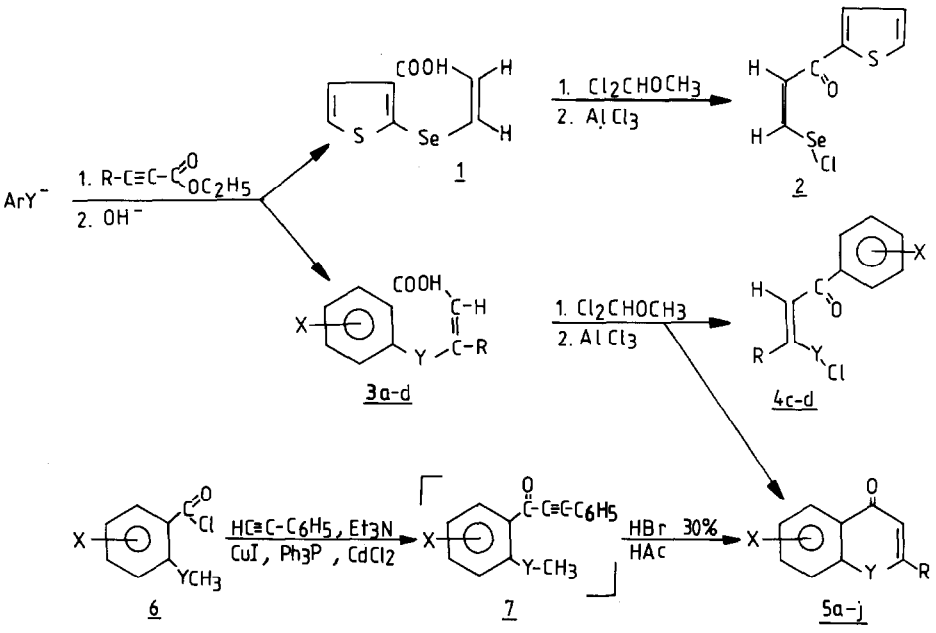

derivatives, we have examined another reaction, namely the hydrobromic acid induced ring closure of *o*-alkylchalcogenophenylethynyl ketones, parallel to that of *o*-alkylchalcogeno chalcones [11,12] to give flavanone derivatives.

As expected, when an *o*-chalcogenophenylphenylethynyl ketone **7** is treated with the same reagent, cyclisation occurs to give chalcogenoflavones **5**. The yields of isolated pure products are fairly good and the method is simple. The ethynyl ketones are readily synthesized by use of heavy metal catalysts [13] or electrophilic cleavage of trimethylsilylacetylenes [14], and, the substituted chalcogeno acids, precursors of chlorides **6**, are also readily available [15,16]. Unfortunately our method suffers from two limitations: the first is the impossibility of locating directly a substituent on the three position of the heterocycle and the second arises from the fact that that *o*-ethyltellurobenzoyl chloride does not condense with phenylacetylene under our conditions.

Experimental

All the new compounds gave satisfactory analytical data $\pm 0.4\%$ for C and H) and correct low resolution mass spectra. Their purities were checked by TLC and GLC, and their structures established by comparison with known compound or ^{1}H NMR spectroscopy ($CDCl_3$, HMDS, δ(ppm), J Hz); m = multiplet s = singlet; d = doublet). Yields given are for pure isolated compounds. Analyses for the new compounds are given in Table 4.

(a) 3-Arylchalcogenopropenoïc acids 1 and 3

A solution of 50 mmol of the diaryldichalcogenide in 150 ml of ethanol is treated with successive small amounts of sodium borohydride ($NaBH_4$) until decoloration is complete. A solution of the ethylpropynoate (0.1 mol) in the minimum amount of

TABLE 1

YIELDS, MELTING POINTS AND ^{1}H NMR DATA FOR COMPOUNDS 1 AND 3

Compound	R	X	Y	Yield (%)	M.p. (°C)	^{1}H NMR (δ(ppm), J(Hz))
1	–	–	Se	21	115	7.8 H_β $J(H_\alpha-H_\beta)$ 9.4 7.4 H_3 J(H(3)–H(4)) 3.6 7.2 H_5 J(H(3)–H(5)) 1.2 7.0 H_4 J(H(4)–H(5)) 5.2 6.3 H_α
3a	H	H	Se	95	129–132 ref. 17: 125–126	7.5–7.1 (m,ArH,5H) 7.8 H_β $J(H_\alpha-H_\beta)$ 9.6 6.3 H_α
3b	C_6H_5	H	Se	95	170 ref. 8: 171–173	–
3c	H	4-CH_3	Se	75	120	7.06 (d, H(2,2′), 2H) 7.4 (d, H(3,3′), 2H) $J_{2\text{-}3}$ 7.6; $J(H_\alpha-H_\beta)$ 9.6 7.8 : H_β 2.3 (s, CH_3) 6.3 : H_α
3d	H	H	Te	80	140–145 ref. 10: 150–153	–

the same solvent, is then added, and the mixture is refluxed for 4 h. Subsequently a solution of 6 g of sodium hydroxide in water (50 ml) is added and the mixture is refluxed for 4 h. After removal of most of the alcohol, the residue is taken up in 100 ml of water, treated with Norit, filtered and acidified in the cold. The precipitate is filtered off, dried, and recrystallized (toluene/ethanol) (see Table 1).

TABLE 2

YIELDS, MELTING POINTS, ^{1}H NMR AND IR DATA FOR COMPOUNDS **2**, **4c**, **4d**, **5a** AND **5b**

Compound	R	X	Y	Yield (%)	M.p. (°C)	^{1}H NMR (δ(ppm), J (Hz))	IR(a) ν(C=O) (cm^{-1})
2	–	–	Se	56	95–96	9 H_β $J(H_\alpha-H_\beta)$ 6.8 7.8 H_3&H_5; J(H(3)–H(4)) 3.8 7.5 H_α J(H(3)–H(5)) 1.2 7.2 H_4 J(H(4)–H(5)) 5.0	1530
4c	H	4-CH_3	Se	28	130	9.8 H_β; 2.3 (s,3H,-CH_3) 7.8 (d,2H,ArH(2)&ArH(6)) 7.7 H_α 7.2 (d,2H,ArH(3)&ArH(5))	1590
d	H	H	Te	56	90–92 ref. 10: 96–98	–	–
5a	H	H	Se	66	92 ref. 4: 93–94	–	–
5b	C_6H_5	H	Se	43	133 ref. 4: 133	–	–

[a] ν(C=O) for the rearranged product is very low, and characteristic of such compounds [6,10].

TABLE 3

YIELDS, MELTING POINTS AND ^{1}H NMR DATA FOR COMPOUNDS **5b**, **5e–5j**

Compound	R	X	Y	Yield (%)	M.p. (°C)	^{1}H NMR (δ(ppm), J(Hz))
5b	C_6H_5	H	Se	50	133 ref. 4: 133	–
5e	C_6H_5	H	O	71	95 comm.: 97–98	–
5f	C_6H_5	H	S	58	131–133 ref. 3: 127–130	–
5g	C_6H_5	7-F	Se	51	138	8.8–8.4 (m,ArH,1H) 7.6–7.1 (m,ArH,8H)
5h	C_6H_5	6-NO_2	Se	51	196–198	9.03 (d,ArH(4),1H); 8 (dd,ArH(6),1H); 7.4 (d,ArH(7),1H); 7.3–7.2 (m,ArH,5H); 7 (s,H(2),1H); J(H(6)–H(7)) 7; J(H(4)–H(6)) 2
5i	C_6H_5	6-CH_3	Se	52	142 ref. 4: 138	8.4 (m,ArH,1H); 7.7–7.2 (m,ArH,8H); 2.4 (s,CH_3,3H)
5j	C_6H_5	6-OCH_3	Se	21	120–22	8.1 (s,ArH,1H); 7.9–7.0 (m,ArH,8H); 3.9 (s,OCH_3,3H)

(b) Cyclisation or rearrangement of 3-arylchalcogenopropenoïc acids chlorides

A suspension of 5 mmol of 3-arylchalcogenopropenoïc acid in 50 ml of dry carbon tetrachloride containing 100 mg of anhydrous zinc(II) chloride is treated with 20 ml of α,α-dichloromethylmethyl ether and the mixture is left overnight. The excess of solvent and reagent is removed under vacuum, and the residue is dissolved in 100 ml of dry dichloromethane. The solution is stirred at −80°C and 0.7 g (5 mmol) of dry aluminium chloride is added in one portion. After 15 min, the mixture

TABLE 4

ELEMENTAL ANALYSES OF THE NEW COMPOUNDS

Compound	Analysis (Found (calcd.) (%))	
	C	H
1	36.0 (36.05)	2.6 (2.58)
3c	50.0 (49.79)	4.4 (4.15)
2	33.5 (33.40)	2.0 (1.99)
4c	46.4 (46.24)	3.5 (3.47)
5g	61.2 (59.41)	2.8 (2.97)
5i [a]	54.7 (54.55)	2.7 [a] (2.73)
5j	61.3 (60.95)	3.9 (3.81)

[a] N, 4.1 (4.20).

is allowed to warm to room temperature and hydrolysed. After the usual work-up, the crystalline solid is recrystallized (hexane/benzene) (see Table 2) or used immediately in the reaction described below.

(c) Phenylethynyl ketones 7 and their cyclisation to chalcogenoflavones

Cuprous iodide (20 mg) and dichlorobis(triphenylphosphine)palladium(II) (20 mg) are added under argon to a solution of 50 mmol of acid chloride **6** [15,16] in 50 ml of dry and freshly distilled triethylamine. A solution of 5 g (50 mmol) of phenyl acetylene in 10 ml of triethylamine is then added and the mixture is stirred for 6 h at 60°C. After the usual work-up, the pressure of **7** in the residue is confirmed by GLC-MS and the crude ketones **7** are dissolved in 50 ml of a 30% solution of hydrobromic acid in acetic acid. After refluxing for 2 h, the mixture is diluted with ice-water and extracted with methylene chloride. The extract is washed with sodium hydrogenocarbonate, dried, filtered, and concentrated in vacuum. The residue is purified by column chromatography (silica gel, eluent cyclohexane/ethyl acetate 70/30) and recrystallized (hexane/benzene) (see Table 3).

Acknowledgments

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