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A convenient access to 3-cyanoflavones

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Abstract—Reaction of β-bromo α-alkylthiocinnamonitriles with various substituted methyl salicylates followed by treatment with $AlCl_3/PhNO_2$ provides 3-cyanoflavones.

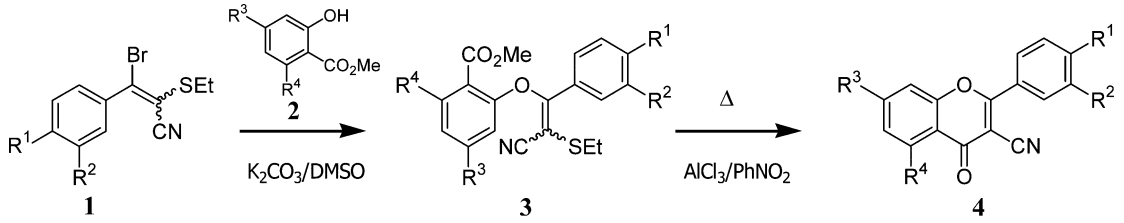
Several C-3 substituted flavones have been found to play an important role in a number of biological processes: the most representative of them are flavonols which are reported to have antiviral and antibiotic effects as well as antioxidant properties.

Among the numerous C-3 functionalized flavones described in the literature[1] only one example of a substituted 3-cyanoflavone has been reported, as a by-product from a reaction starting from a 3-(α-hydroxybenzyl) flavone.[2]

More recently, we have found a novel route to 3-cyanoflavones **4** by reacting β-bromo α-ethylthio cinnamonitrile **1** with methyl salicylate **2** and the subsequent treatment of precursor **3** with $AlCl_3$ (Scheme 1).

Compounds of type **1**, readily obtained in good yields (70–80%) following the literature method,[3] react in alkaline medium with methyl salicylate[4] **2** to give the substitution products **3** as *Z*, *E* mixtures which can be further used as such. These reactions were performed using the following general procedure: a mixture of **1** (6 mmol), methyl salicylate **2** (7.2 mmol) and anhydrous potassium carbonate (6.5 mmol) in dry DMSO (10 mL) was stirred overnight at 70–80°C. After pouring into cold water, diethyl ether extraction and washing with 1 M NaOH solution, compounds **3** (*Z*/*E* mixture) were isolated in good yields (70–90%) as shown in Table 1.

The conversion of **3** into 3-cyanoflavones **4** was carried out as follows. To a stirred solution of precursor **3** (1.5 mmol) in dry nitrobenzene at 150°C (50 mL, inner temp.) was added dropwise, over 2 min, a nitrobenzene solution of $AlCl_3$ (0.88 M, 5.5 mmol, 5.3 mL). After stirring for a further 5 min at the same temperature, the mixture was poured into cold 10% HCl solution, extracted with CH_2Cl_2 and washed with $NaHCO_3$ solution and water until neutral pH. The solvents were evaporated and the residual solid was purified on a silica gel column eluted with CH_2Cl_2/AcOEt in the range (v/v) 90/10 to 98/2. Compounds **4a**–**h** were obtained (Table 1). Selected data for **4d**: IR (*v*, KBr, cm^{-1}): 2225 (C≡N), 1651 (C=O). Anal. found C, 75.87; H, 5.74; N, 4.26%; calc. for $C_{21}H_{19}NO_3$ C, 75.66; H, 5.74; N, 4.20%. ^1H NMR (300 MHz, $CDCl_3$) δ 8.17



Scheme 1.

Keywords: β-bromo α-ethylthiocinnamonitrile; methyl methoxysalicylate; 2-(2-cyano-2-(ethylthio-1-arylvinyloxy))-benzoic acid methyl ester; aluminium chloride; 3-cyanoflavones; 3-formylflavones.
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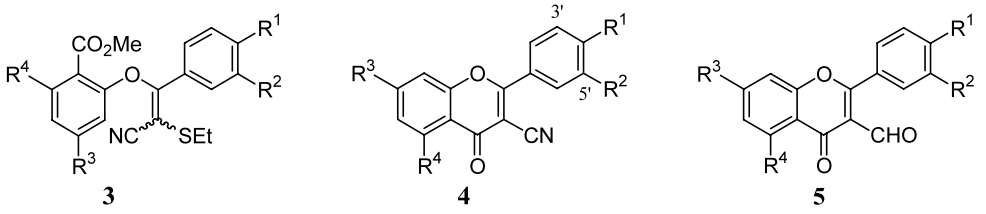
Table 1.



	R^1	R^2	R^3	R^4	**3** (Z/E mixture)		**4**		**5**	
					Yield (%)	mp (°C)	Yield (%)	mp (°C)	Yield (%)	mp (°C)
a	H	H	H	H	85	58–68	54	157–158[b]	55	151–152[d]
b	H	H	OMe	H	86	64–70	64	209–210[c]	–	–
c	Me	H	OMe	H	75	76–80	61	182–183	60	158–159
d	*t*Bu	H	OMe	H	70	128–132	60	173–174	–	–
e	Cl	H	OMe	H	70	80–94	65	221–222	–	–
f	OMe	H	OMe	H	81	90–100	63	224–225	–	–
g	OCH_2O		OMe	H	85	100–110	50	202–203	–	–
h	OMe	H	OMe	OMe	90	98–104	35[a]	269–270	–	–

[a] Cyclization occurred at 100°C and the lower yield of flavone **4h** was explained by the concomitant formation of the phenolic compound **4′h** ($R^1=R^3=$OMe, $R^2=$H, $R^4=$OH) in 15% yield. Data for **4′h**: mp = 232–233°C. EIMS: m/z found 323.0799 (M^+); calc. for $C_{18}H_{13}NO_5$: m/z 323.0794 (M^+). ^{1}H NMR (500 MHz, DMSO) δ 11.97 (1H, s, OH), 8.11 (2H, d, $J=8.7$ Hz, H-2′, 6′), 7.23 (2H, d, $J=8.7$ Hz, H-3′, 4′), 6.86 (1H, d, $J=1.75$ Hz, H-6), 6.50 (1H, d, $J=1.75$ Hz, H-8), 3.91 (3H, s, MeO), 3.89 (3H, s, MeO). ^{13}C NMR (125 MHz, DMSO) δ 178.83 (C=O), 171.25 (C-2), 166.68 (C-7), 164.00 (C-4′), 161.09 (C-5), 156.93 (C-8a), 131.50 (C-2′, 6′), 121.94 (C-1′), 115.08 (C-3′, 5′), 114.67 (C≡N), 103.44 (C-4a), 99.71 (C-6), 94.57 (C-3), 94.34 (C-8), 56.89 (MeO), 56.31 (MeO).

[b] mp (lit.[2]) = 151–152°C.

[c] mp (lit.[2]) = 202–203°C.

[d] mp (lit.[6]) = 152°C.

(1H, d, $J=8.8$ Hz, H-5), 8.07 (2H, $J=8.6$ Hz, H-2′, 6′), 7.62 (2H, d, $J=8.6$ Hz, H-3′, 5′), 7.05 (1H, dd, $J=8.8$ and 2.2 Hz, H-6), 6.97 (1H, d, $J=2.2$ Hz, H-8), 3.97 (3H, s, OMe), 1.4 (9H, s, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.43 (C=O), 170.46 (C-2), 165.18 (C-7), 157.30 (C-4′), 157.13 (C-8a), 128.51 (C-2′,6′),127.41 (C-5), 127.18 (C-1′), 126.12 (C-3′,5′), 115.68 (C-6), 115.53 (C-4a), 114.45 (C≡N), 100.76 (C-8), 97.46 (C-3), 56.15 (MeO), 35.29 (C_{qu} *t*Bu), 31.03 (CH_3). EIMS: m/z 333.1363 (M^+).

We observed that no reaction occurs without the presence of $AlCl_3$, the cyclisation is easier when electron-donating groups are in either the *ortho* or *para* position relative to the ester moiety. We suppose that the first step involves complexation of the carbonyl by $AlCl_3$ which increases the electropositivity of the carbon atom. A Mannich-type reaction of the enol ether moiety should then close the six-membered ring, releasing methoxide which could in turn assist the elimination of the ethylthio group, thereby restoring aromaticity.

Furthermore, these 3-cyanoflavones can be converted to 3-formylflavones **5**, by the reduction of the nitrile group with Raney nickel/formic acid[5] as shown for compounds **5a** and **5c** (Table 1). Selected data for **5c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.15 (1H, s, CHO), 8.20 (1H, d, $J=8.9$ Hz, H-5), 7.56 (2H, d, $J=8.1$ Hz, H-2′, 6′), 7.34 (2H, d, $J=8.1$ Hz, H-3′, 5′), 7.04 (1H, dd, $J=8.9$ and 2.3 Hz, H-6), 6.9 (1H, d, $J=2.3$ Hz, H-8), 3.92 (3H, s, MeO), 2.47 (3H, s, Me). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.02 (CHO), 175.61 (C=O), 171.86 (C-2), 164.75 (C-7), 157.4 (C-8a), 143.07 (C-4′), 129.94 (C-2′, 6′), 129.27 (C-3′, 5′), 127.92 (C-1′), 127.70 (C-5), 117.96 (C-4a), 117.30 (C-3), 115.17 (C-6), 100.69 (C-8), 55.98 (MeO), 21.70 (CH_3).

In summary, this paper describes the first simple and efficient method for the synthesis of substituted 3-cyanoflavones and a corresponding access to 3-formylflavones, which could be of interest as starting materials for preparation of novel heterocyclic systems.

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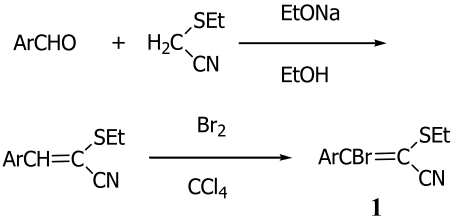
3. The bromo compounds **1** were prepared as follows:



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