Reactions of 2-Methylchromones with Cyanoacetamides and Ethyl Cyanoacetate. Synthesis of 6-(2-Hydroxyaryl)-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitriles and 7-Hydroxy-6-imino-9-methyl-6H-benzo[c]chromene-8-carbonitriles

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INTRODUCTION

Chromones are naturally occurring oxygen-containing heterocyclic compounds that perform important biological functions in nature [1]. Although 2-methylchromones 1 constitute a small family of naturally occurring compounds, their synthesis and transformations into other biologically active compounds have been exploited [2,3]. It is known that the pyrone ring of 1 is susceptible to ring opening under the action of N-nucleophiles such as amines [4], hydrazines [5,6], hydroxylamine [6,7], and thiourea [8]. However, only a handful of papers describing some examples of reactions with C-nucleophiles is present in the literature. In almost all cases, the reactions with active methylene compounds proceeded without cleavage of the pyrone ring, and only 1,2-addition (Knoevenagel condensation) at the carbonyl group took place to give the corresponding methylidene derivatives [9,10], including compound 2 [10] (Scheme 1). In addition, 1,4-dianion generated from acetophenone oxime and phenyl magnesium bromide reacts with 1 at C-4 to give the spiroisoxazoline derivative [11] and 2-methyl-4-phenylchromen-4-ol [12], respectively.

On the other hand, there are only two reports on the reactions of 2-methylchromones 1 with C-nucleophiles leading to the products, which can result from the initial nucleophilic 1,4-addition. The use of methylocopper-BF3 provided 2,2-dimethylchroman-4-ones via conjugate addition to the double bond in the γ-pyrene system [13]. Recently, the reaction of 1 with malononitrile, cyanoacetamide, and ethyl cyanoacetate in the presence of sodium ethoxide, leading to isolation of 2-pyridones 3 and 2-pyrones 4, was reported [14]. Contrary to a previous report [10], the reaction proceeded via nucleophilic 1,4-addition with concomitant opening of the pyrone ring and subsequent intramolecular cyclization (Scheme 1). In view of these contradictory literature reports and our continued interest in the chemistry of chromones [15], we repeated the reaction of 2-methylchromones 1 with active methylene compounds following the literature method [10,14].

RESULTS AND DISCUSSION

Although 2-methylchromones react with cyanacetamide and N-methyl cyanoacetamide in the presence of sodium ethoxide in refluxing ethanol to produce 6-(2-hydroxyaryl)-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitriles, their reactions with ethyl cyanoacetate under the same conditions took an entirely different course and gave 7-hydroxy-6-imino-9-methyl-6H-benzo[c]chromene-8-carbonitriles.

5 proton (δ 6.30), and phenolic hydroxyl (δ 10.27). In addition, the choice between 4-Me- and 6-Me-2-pyridones was made in favor of the former on the basis of the 2D HMBC spectrum for 3b. The most informative cross-peaks are as follows: Me/C3, Me/C5, Me/CN, Me/C4. Note that in the case of 6-Me-2-pyridone, cross-peaks Me/C3 and Me/CN could not be observed.

As mentioned earlier, the previous workers [14] reported that the reaction of 1a,b with ethyl cyanoacetate leads to compounds 4 (R = H, Me), and their claim has been favorably reviewed [2]. However, the 2-pyrone ring formation was not firmly established, and in light of the known behavior of 2-(trifluoromethyl)chromones in reaction with ethyl cyanoacetate, which afforded 7-hydroxy-6-imino-9-(trifluoromethyl)-6H-benzo[c]chromene-8-carbonitriles 5 (Scheme 1) [16], it was anticipated that the process would follow a 1:2 instead of a 1:1 stoichiometry and proceed by double nucleophilic attack of the base-activated ethyl cyanoacetate to the chromone system. We therefore decided to repeat the condensation of chromones 1a–d with ethyl cyanoacetate as originally reported [14].

It was found that the reaction of 1a with ethyl cyanoacetate (2 equiv.) in the presence of sodium ethoxide in refluxing absolute ethanol gave a 61% yield of high melting solid with low solubility in solvents such as DMSO, DMF, ethanol, acetone, and toluene. This compound was described by Ibrahim et al. [14] as the α-pyrone 4 (R=H). However, in contrast with this structure, its composition corresponded to a 1:2 adduct, C15H10N2O2, which was assigned the structure 7-hydroxy-6-imino-9-methyl-6H-benzo[c]chromene-8-carbonitrile (6a) on the basis of elemental analysis, 1H NMR, 13C NMR, IR spectroscopies, and comparison of the spectroscopic data with the data reported for related systems [16]. In particular, the aromatic protons of compound 6a at δ 7.37 (H-4), 7.40 (H-2), 7.61 (H-3), and 8.26 (H-1) compare well with those of trifluoromethylated analog, 7-hydroxy-6-imino-9-(trifluoromethyl)-6H-benzo[c]chromene-8-carbonitrile (5, R=H, δ 7.41, 7.43, 7.67, and 8.38, respectively). In addition, the Me group and H-10 appeared as two singlets at δ 2.53 and 7.52 ppm; the broad signal at δ 7.70 (2H) is due to the resonances of OH and NH protons. The Ibrahim group attributed the 1H NMR aromatic signals at δ 7.37–8.29 ppm to the phenolic protons of 4 (R=H), although they are more befitting of a...
coumarin system. Consequently, structure 4 should be revisited to 6 (Scheme 2).

Similar reactions of 1b–d with ethyl cyanoacetate gave 7-hydroxy-6-imino-9-methyl-6H-benzo[c]chromene-8-carbonitriles 6b–d in 62–78% yields as the sole products after recrystallization from DMF. It should be noted that these 1:2 adducts were obtained even from the reaction of 1 with 1 equiv. of ethyl cyanoacetate, albeit in a lower yield. It was also found that formation of the tricyclic compounds 6 was encouraged by prolonged heating (12–16 h). Unfortunately, the low solubility of these 1:2 adducts was observed in the reaction of 1 with 1 equiv. of ethyl cyanoacetate, albeit in a lower yield.

Additional support for the aforementioned structures. Additional support for 6 was provided by the IR spectra, in which a highly characteristic nitrile absorption at 2208–2216 cm⁻¹ and C=N and OH bands at 1678–1698, 3321–3326, and 3420–3428 cm⁻¹ was observed.

In conclusion, we have shown that the condensation of 2-methylchromones with cyanoacetamides and ethyl cyanoacetate represents a one-pot, multistep transformation and can be employed to obtain functionalized 6H-benzo[c]chromen-6-ones.

**EXPERIMENTAL**

¹H (400 MHz) and ¹³C (100 MHz) NMR spectra were recorded on a Bruker Avance II spectrometer in DMSO-d₆ with TMS as an internal standard (only for ¹H NMR spectra). IR spectra were recorded on a Bruker Alpha FTIR instrument with the appliance of distorted total internal reflection (ZnSe crystal). Elemental analyses were performed at the Microanalysis Services of the Institute of Organic Synthesis, Ural Branch, Russian Academy of Sciences. Melting points were uncorrected. All solvents used were dried and distilled per standard procedures.

General procedure for the synthesis of 6-(2-hydroxyaryl)-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitriles (3a–h). A solution of sodium ethoxide (69 mg, 3.0 mmol sodium in 5 mL of absolute ethanol) was added with the corresponding 2-methylchromone 1 (3.0 mmol) in absolute ethanol (5 mL) and cyanoacetamide or N-methyl cyanoacetamide (3.0 mmol). The mixture was refluxed for 10 h. Then, the orange reaction mixture was poured onto dilute hydrochloric acid (2N, 25 mL), and the yellow solid so formed was filtered and washed with ethanol to give compound 3 in an analytically pure state without recrystallization.

6-(2-Hydroxyphenyl)-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (3a). Yield 55%, light-brown crystals, mp >300°C (lit. [14] mp >300°C); IR (ATR) 3182, 2222, 1654, 1597, 1531 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) 2.40 (s, 3H, Me), 6.60 (br s, 1H, H-5), 6.92 (t, 1H, H-5', J = 7.4 Hz), 6.98 (d, 1H, H-3', J = 7.8 Hz), 7.34 (dd, 1H, H-4', J = 8.2, 7.0, 1.7 Hz), 7.46 (br s, 1H, H-6'), 10.55 (br s, 1H, OH), 12.15 (br s, 1H, NH).

6-(2-Hydroxy-5-methylphenyl)-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (3b). Yield 56%, light-brown crystals, mp 260–263°C; IR (ATR) 3115, 2221, 1623, 1599, 1568, 1549 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) 2.38 (s, 3H, Me), 3.23 (s, 3H, MeN), 6.30 (s, 1H, H-5), 6.95 (d, 1H, H-5', J = 7.4, 0.8 Hz), 6.99 (d, 1H, H-3', J = 8.2 Hz), 7.23 (dd, 1H, H-6', J = 7.6, 1.7 Hz), 7.38 (dd, 1H, H-4', J = 8.2, 7.2, 1.7 Hz), 10.27 (s, 1H, OH); ¹³C NMR (100 MHz, DMSO-d₆) δ 20.8 (Me), 33.6 (Me), 100.7 (C-3), 110.7 (C-5), 116.2 (C-3'), 116.5 (CN), 119.9 (C-5'), 121.9 (C-1'), 130.1 (C-6'), 132.2 (C-4'), 152.9 (C-6), 154.8 (C-2'), 158.8 (C-4'), 160.8 (C-2). Anal. Calcd for C₁₄H₁₂N₂O₂: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.87; H, 4.91; N, 11.47.

6-(2-Hydroxy-5-methylphenyl)-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (3c). Yield 47%, light-brown crystals, mp 260–263°C; IR (ATR) 3139, 2324, 2218, 1634, 1604, 1583 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) 2.24 (s, 3H, Me), 5.20 (s, 1H, H-5), 6.56 (br s, 1H, H-5), 6.87 (d, 1H, H-3', J = 8.3 Hz), 7.15 (dd, 1H, H-4', J = 8.3, 1.7 Hz), 7.28 (br s, 1H, H-6'), 10.27 (s, 1H, OH), 12.10 (br s, 1H, NH). Anal. Calcd for C₁₃H₁₁N₂O₂: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.87; H, 4.91; N, 11.47.

6-(2-Hydroxy-5-methylphenyl)-1,4-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (3d). Yield 63%, colorless crystals, mp 283–285°C; IR (ATR) 3162, 2220, 1624, 1612, 1597, 1567, 1549, 1512 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) 2.24, 2.38 (both s, 3H, Me), 3.23 (s, 3H, MeN), 6.30 (s, 1H, H-5), 6.88 (d, 1H, H-3', J = 8.3 Hz), 7.04 (d, 1H, H-6', J = 2.0 Hz), 7.18 (dd, 1H, H-4', J = 8.3, 2.0 Hz), 10.02 (s, 1H, OH). Anal. Calcd for C₁₅H₁₃N₂O₂: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.66; H, 5.78; N, 11.13.

6-(5-Chloro-2-hydroxyphenyl)-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (3e). Yield 69%, pale-yellow crystals, mp >330°C; IR (ATR) 3153, 3108, 2390, 2221, 1638, 1616, 1585, 1540 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) 2.44 (s, 3H, Me), 6.56 (br s, 1H, H-5), 6.95 (d, 1H, H-3', J = 8.7 Hz), 7.25 (dd, 1H, H-4', J = 8.7, 2.7 Hz), 7.48 (br s, 1H, H-6'), 10.63 (br s,
1H, OH), 12.10 (br s, 1H, NH). Anal. Caled for C_{15}H_{10}N_{2}O_{2}: C, 71.99; H, 4.03; N, 8.53. Found: C, 54.74; H, 3.10; N, 8.53.

**General procedure for the synthesis of 7-hydroxy-6-imino-9-methyl-6H-benzof[chromene-8-carbonitrile (6a-d).** A solution of sodium ethoxide (69 mg, 3.0 mmol sodium in 5 ml of absolute ethanol) was added with the corresponding 2-methylchromone (0.3 mmol) in absolute ethanol (5 ml) and ethyl cyanoacetate (680 mg, 6.0 mmol). The red-orange reaction mixture was refluxed for 12–16 h, cooled, and acidified with dilute hydrochloric acid (6N, 25 ml). The solid obtained was filtered off and crystallized from DMF to give compound 6.

**7-Hydroxy-6-imino-9-methyl-6H-benzof[chromene-8-carbonitrile (6a).** Yield 61%, pale-yellow crystals, mp >300°C (lit. [14] mp 300°C; IR (ATR) 3428, 3326, 2211, 1698, 1599, 1581 cm\(^{-1}\); \(^1^H\) NMR (400 MHz, DMSO-\(d_6\)) \(2.39\) (s, 3H, Me), 3.26 (s, 3H, MeN), 6.24 (s, 1H, H-5), 6.92 (d, 1H, H-5, \(J = 8.7\) Hz), 7.34 (d, 1H, H-6, \(J = 2.6\) Hz), 7.45 (dd, 1H, H-4, \(J = 8.7, 2.6\) Hz), 10.50 (s, 1H, OH). Anal. Caled for C_{15}H_{10}N_{2}O_{2}: C, 51.96; H, 3.58; N, 8.86. Found: C, 51.69; H, 3.08; N, 8.53.

**REFERENCES AND NOTES**