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Synthesis of Carbamate Derivatives of Coumarin and Chromene

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Abstract—Condensation of methyl (3-hydroxyphenyl)carbamate with ethyl acetoacetate and ethyl benzoylacetate at room temperature, as well as with L-2-hydroxysuccinic acid on heating, in the presence of concentrated sulfuric acid gave the corresponding methyl (4-R-2-oxo-2*H*-chromen-7-yl)carbamates (R = Me, Ph, H). Condensation of methyl (3-hydroxyphenyl)carbamate with benzylidenemalononitrile or with aromatic aldehydes and malononitrile on heating in propan-2-ol in the presence of piperidine led to the formation of the corresponding methyl (4-aryl-2-amino-3-cyano-4*H*-chromen-7-yl)carbamates.

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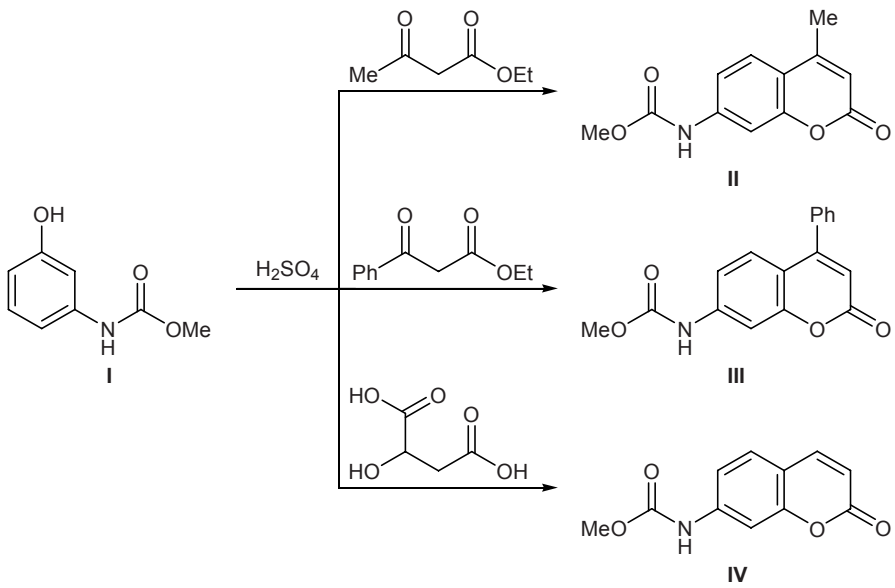
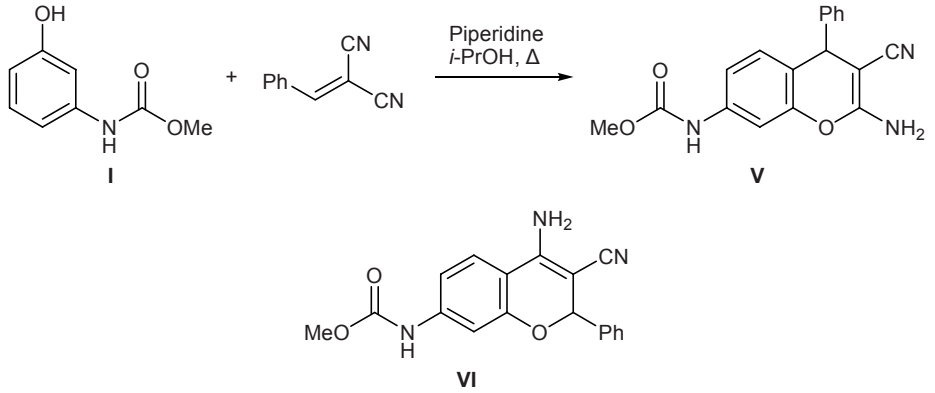
It is well known that phenols are capable of reacting with various carbonyl compounds and that electron-rich phenols and naphthols react with α,β-unsaturated nitriles. Among these transformations, the most interesting are those leading to oxygen-containing heterocyclic compounds, in particular coumarins and 2-amino-4*H*-chromenes which are potential biologically active substances. Some their derivatives exhibit a strong antiproliferative activity, while others were recommended for the treatment of immune disorders, atrophic arthritis, atherosclerosis, cirrhosis, and cancer [1]. Therefore, it seemed important to study the behavior in analogous reactions of phenylcarbamates whose chemical properties in many cases resemble those of phenols and phenol ethers [2].

We examined the condensation of methyl phenylcarbamates having a hydroxy group in the aromatic ring with ethyl acetoacetate and ethyl benzoylacetate in the presence of concentrated sulfuric acid at room temperature, as well as with L-2-hydroxysuccinic acid at 110°C. We found that methyl (2-hydroxyphenyl)carbamate does not react with the above carbonyl-containing compounds and that the corresponding *para* isomer gives rise to carbamate coumarin derivatives in a very poor yield (10–15%). On the other hand, the condensation of methyl (3-hydroxyphenyl)carbamate

Scheme 1.



Scheme 2.



(**I**) with the same compounds gave the corresponding 4-substituted 7-methoxycarbonylaminocoumarins **II**–**IV** in 23–87% yield (Scheme 1).

The structure of coumarin derivatives **II**–**IV** was confirmed by IR and ^{1}H NMR spectroscopy. The ^{1}H NMR spectra of **II** and **III** contained a singlet from the 3-H proton at δ 6.22–6.24 ppm. In the spectrum of **IV** the 3-H proton resonated as a doublet at δ 6.20 ppm (J = 9.5 Hz), while the 4-H signal was overlapped by signals from protons in the benzene ring. Unlike initial carbamate **I**, the IR spectra of coumarins **II**–**IV** lacked broad absorption band at 3385 cm^{-1}, typical of phenolic hydroxy group, stretching vibrations of the NH group gave rise to absorption in the region 3280–3287 cm^{-1}, and absorption bands due to the carbamate and lactone carbonyl groups were located at 1730 and 1690–1695 cm^{-1}, respectively.

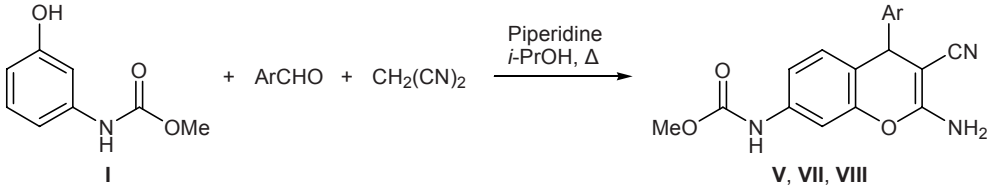
The condensation of methyl (3-hydroxyphenyl)carbamate (**I**) with benzylidenemalononitrile on heating in boiling isopropyl alcohol in the presence of piperidine (reaction time 8 h) resulted in the formation of methyl (2-amino-3-cyano-4-phenyl-4*H*-chromen-7-yl)carbamate (**V**) in 78% yield (Scheme 2). The structure of chromene **V** was confirmed by the IR and ^{1}H NMR spectra and elemental analysis. Theoretically, this reaction could give rise to 4*H*- and 2*H*-chromene derivatives **V** and **VI**. The latter can be formed via attack by the phenolic oxygen atom on the electron-deficient double bond of benzylidenemalononitrile to give isomeric Michael adduct and subsequent cyclization as a result of electrophilic attack by the cyano carbon atom on the carbon atom in the *ortho*-position with respect to the oxygen atom.

The product structure as 4*H*-chromene derivative **V** was identified on the basis of the ^{1}H NMR data. The ^{1}H NMR spectrum contained a singlet at δ 4.67 ppm from the 4-H proton linked to sp^3-hybridized carbon atom. It is well known that signals in the region δ 4.5–5.0 ppm are typical of 4*H*-pyrans, 4*H*-thiopyrans, and related structures [3, 4]. If the product were 2*H*-chromene, the 2-H signal would appear in a stronger field.

We also examined the possibility for synthesizing carbamate chromene derivatives by three-component condensation of carbamate **I** with aromatic aldehydes and malononitrile. Aromatic aldehydes should react with malononitrile in isopropyl alcohol in the presence of piperidine to give the corresponding arylmethylidenemalononitriles. In fact, we succeeded in obtaining methyl (4-aryl-2-amino-3-cyano-4*H*-chromen-7-yl)-carbamates **V**, **VII**, and **VIII** in good yield according to one-pot procedure (Scheme 3). However, unlike resorcinol, α- and β-naphthols, and some other substituted phenols [5], these one-pot syntheses required more severe conditions (8 h under reflux).

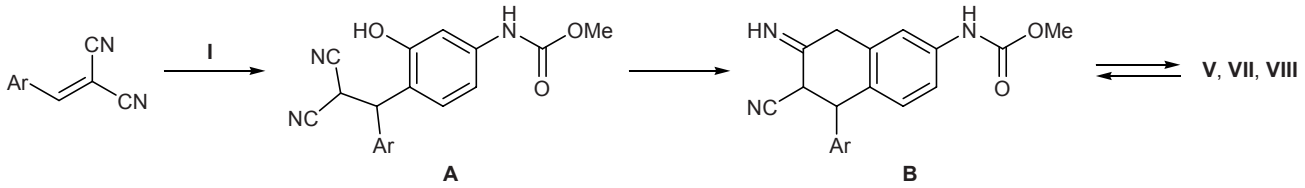
Chromenes **V**, **VII**, and **VIII** are likely to be formed via nucleophilic addition of hydroxyphenyl-

Scheme 3.



V, Ar = Ph; **VII**, Ar = 4-MeOC$_6$H$_4$; **VIII**, Ar = 3,4-(MeO)$_2$C$_6$H$_3$.

Scheme 4.



carbamate **I** at the electron-deficient carbon atom of arylmethylidenemalononitrile. The subsequent intramolecular cyclization of Michael adduct **A** gives intermediate iminochromene **B**, and tautomerization of the latter yields the final aminochromene (Scheme 4). The structure of methyl (4-aryl-2-amino-3-cyano-4*H*-chromen-7-yl)carbamates **V**, **VII**, and **VIII** obtained by the three-component condensation was confirmed by the IR and ^{1}H NMR data. In addition, ^{13}C NMR and mass spectra were recorded for compound **V**. Compounds **V**, **VII**, and **VIII** displayed in the IR spectra absorption bands at 2200 and 3220–3210 cm^{-1} due to stretching vibrations of the C≡N and NH_2 groups, respectively; absorption bands at 1715 and 3410 cm^{-1} were assigned to stretching vibrations of the carbonyl and NH groups in the carbamate moiety. The 4-H proton resonated in the ^{1}H NMR spectra of **V**, **VII**, and **VIII** at δ 4.67–4.52 ppm.

According to [5], analogous condensations with resorcinol, naphthalene-1,5-diol and α- and β-naphthols were complete in 0.5–1 h; in our case, more severe conditions are related to weaker electron-donating power the methoxycarbonylamino group as compared to phenolic hydroxy group. Our attempts to involve in analogous condensation arenecarbaldehydes having electron-withdrawing substituents were unsuccessful. Even after heating for 10 h under reflux, we isolated from the reaction mixtures only the corresponding arylmethylidenemalononitriles and initial carbamate **I**.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on VXR-400 (400.13 MHz) and Bruker DRX 500 (500.13 MHz) spectrometers using DMSO-d_6 as solvent and TMS as internal reference. The ^{13}C NMR spectrum was measured with complete decoupling from protons on a Bruker DRX 500 instrument at 126 MHz using DMSO-d_6 as solvent. The IR spectra were recorded in the spectral range from 4000 to 400 cm^{-1} on a Specord M82 spectrometer from samples prepared as KBr pellets. The mass spectrum (electron impact, 70 eV) was obtained on a Kratos MS-30 instrument. The purity of the isolated compounds was checked by TLC on Silufol UV-254 plates. Methyl (3-hydroxyphenyl)carbamate was synthesized according to the procedure reported in [6], mp 94–95°C (from benzene); published data [7]: mp 94.5–95.5°C.

Methyl (4-methyl-2-oxo-2*H*-chromen-7-yl)carbamate (II). A solution of 0.7 g (4 mmol) of methyl (3-hydroxyphenyl)carbamate (**I**) in 0.55 ml (4 mmol) of ethyl acetoacetate was added dropwise under stirring to 4 ml of concentrated sulfuric acid cooled to 5°C (the temperature of the reaction mixture should not exceed 10°C). The mixture was left to stand for 24 h at room temperature and poured into 50 ml of ice water. The precipitate was filtered off, washed with 100 ml of water on a filter, dried over concentrated sulfuric acid, and recrystallized from ethanol. Yield 0.85 g (87%), colorless crystals, mp 256–257°C. IR spectrum, ν, cm^{-1}: 3280 (NH); 1730, 1692 (C=O); 1620, 1584, 1536, 1512 (C=C, C–C_{arom}). ^{1}H NMR spectrum (500.13 MHz), δ, ppm: 2.38 s (3H, Me), 3.73 s (3H, OMe), 6.22 s (1H, 3-H), 7.38 d.d (1H, 6-H, J = 2.0, 8.4 Hz), 7.54 s (1H, 8-H), 7.69 d (1H, 5-H, J = 8.4 Hz), 10.15 (1H, NH). Found, %: C 61.67; H 4.51; N 5.58. $C_{12}H_{11}NO_4$. Calculated, %: C 61.80; H 4.72; N 6.01.

Methyl (4-phenyl-2-oxo-2*H*-chromen-7-yl)carbamate (III) was synthesized in a similar way from 0.7 g (4 mmol) of carbamate **I** and 0.69 ml (4 mmol) of ethyl benzoylacetate. Yield 0.28 g (23%), colorless crystals, mp 205–206°C (decomp.). IR spectrum, ν, cm^{-1}: 3287 (NH); 1730, 1695 (C=O); 1620, 1575, 1535 (C=C, C–C_{arom}). ^{1}H NMR spectrum (400.13 MHz), δ, ppm: 3.73 s (3H, OMe), 6.24 s (1H, 3-H), 7.12–7.23 m (2H, H_{arom}), 7.43–7.64 m (6H, H_{arom}), 9.65 (1H, NH). Found, %: C 68.94; H 4.37; N 4.59. $C_{17}H_{13}NO_4$. Calculated, %: C 69.15; H 4.41; N 4.75.

Methyl (2-oxo-2*H*-chromen-7-yl)carbamate (IV). A solution of 0.58 g (4.3 mmol) of L-2-hydroxysuccinic acid in 4 ml of concentrated sulfuric acid was cooled to 15°C, 0.7 g (4.2 mmol) of carbamate **I** was added, and the mixture was kept for 0.5 h at room

temperature and was then heated for 0.5 h at 110°C. The mixture was cooled and poured into 50 ml of ice water, and the precipitate was filtered off, washed with water (2×50 ml), dried in air, and recrystallized from ethanol. Yield 0.72 g (78%), colorless crystals, mp 165–167°C (decomp.). IR spectrum, ν, cm^{-1}: 3280 (NH); 1730, 1690 (C=O); 1620, 1578, 1535 (C=C, C–C_{arom}). ^{1}H NMR spectrum (400.13 MHz), δ, ppm: 3.73 s (3H, OMe), 6.20 d (1H, 3-H, J = 9.5 Hz), 7.45 d (1H, 6-H, J = 7.9 Hz), 7.56–7.62 m (3H, 4-H, 5-H, 8-H), 9.51 (1H, NH). Found, %: C 60.18; H 3.87; N 6.18. $C_{11}H_9NO_4$. Calculated, %: C 60.27; H 4.11; N 6.39.

Methyl (2-amino-3-cyano-4-phenyl-4*H*-chromen-7-yl)carbamate (V). *a*. A mixture of 1.67 g (0.01 mol) of carbamate **I**, 0.67 g (0.01 mol) of benzylidenemalononitrile, and 1 ml of piperidine in 30 ml of propan-2-ol was heated for 8 h under reflux. The mixture was cooled, and the precipitate was filtered off, dried in air, and recrystallized from ethanol. Yield 2.5 g (78%), light yellow crystals, mp 240–241°C.

b. Freshly distilled piperidine, 1 ml, was added to a mixture of 0.01 mol of benzaldehyde, 0.01 mol of carbamate **I**, and 0.01 mol of malononitrile in 30 ml of propan-2-ol. The mixture was heated for 8 h under reflux and cooled, and the precipitate was filtered off, washed with 5 ml of ethanol on a filter, dried in air, and recrystallized from ethanol. Yield 2.2 g (67%), mp 240–241°C. IR spectrum, ν, cm^{-1}: 3410, 3220 (NH, NH_2); 2200 (CN); 1715 (C=O); 1620, 1578, 1535 (C=C, C–C_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 38.24 (C^4), 51.79 (OCH_3), 56.16 (C^3), 105.13 (C^8), 114.60 (CN), 117.18 (C^6), 120.59 (C^{10}), 126.78 (C^5), 127.44 (C^o), 128.68 (C^m), 129.47 (C^o, C^p), 139.04 (C^7), 146.10 (C^i), 148.44 (C^2), 153.93 (C=O), 160.33 (C^9). Mass spectrum, m/z (I_{rel}, %): $[M]^+$ 321 (10), 288 (5), 244 (100), 212 (70), 185 (15), 158 (12), 77 (25), 59 (57), 51 (35). Found, %: C 67.14; H 4.53; N 12.94. $C_{18}H_{15}N_3O_3$. Calculated, %: C 67.29; H 4.67; N 13.08.

Compounds **VII** and **VIII** were synthesized in a similar way according to method *b*.

Methyl [2-amino-3-cyano-4-(4-methoxyphenyl)-4*H*-chromen-7-yl]carbamate (VII). Yield 2.95 g (84%), light yellow crystals, mp 235–238°C. IR spectrum, ν, cm^{-1}: 3410, 3210 (NH, NH_2); 2200 (CN); 1715 (C=O); 1620, 1575, 1535 (C=C, C–C_{arom}). ^{1}H NMR spectrum (400.13 MHz), δ, ppm: 3.62 s (3H, OMe), 3.73 s (3H, CO_2CH_3), 4.52 s (1H, 4-H), 6.52 d (2H, 3′-H, 5′-H, J = 7.7 Hz), 6.61 s (2H, NH_2), 6.75 d (1H, 6-H, J = 7.9 Hz), 7.52–7.61 m (4H, 5-H, 8-H, 2′-H, 6′-H), 8.52 (1H, NH). Found, %: C 65.02; H 4.62; N 12.14. $C_{19}H_{17}N_3O_4$. Calculated, %: C 64.96; N 4.84; N 11.97.

Methyl [2-amino-3-cyano-4-(3,4-dimethoxyphenyl)-4*H*-chromen-7-yl]carbamate (VIII). Yield 3.09 g (81%), light yellow crystals, mp 243–245°C. IR spectrum, ν, cm^{-1}: 3410, 3220 (NH, NH_2); 2200 (CN); 1715 (C=O); 1620, 1570, 1535 (C=C, C–C_{arom}). ^{1}H NMR spectrum (400.13 MHz), δ, ppm: 3.65 s (6H, OMe), 3.71 s (3H, CO_2CH_3), 4.42 s (1H, 4-H), 6.59 s (2H, NH_2), 6.75–6.78 m (2H, 6-H, 5′-H), 7.26–7.29 m (2H, 2′-H, 6′-H), 7.52–7.62 m (2H, 5-H, 8-H), 8.51 (1H, NH). Found, %: C 62.82; H 5.02; N 10.87. $C_{20}H_{19}N_3O_5$. Calculated, %: C 62.99; H 4.99; N 11.02.

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