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Synthesis of 3-(*N*-arylthiocarbamoyl)chromones from 2-hydroxyaryl amino enones and isothiocyanates

Dmitrii Yu. Demin,[a] Ksenia A. Myannik,[a] Pavel A. Ermolich,[b] Mikhail M. Krayushkin[a] and Vladimir N. Yarovenko*[a]

[a] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. E-mail: yarovladimir@yandex.ru*
[b] *Higher Chemical College of the Russian Academy of Sciences, D. I. Mendeleev University of Chemical Technology of Russia, 125047 Moscow, Russian Federation*

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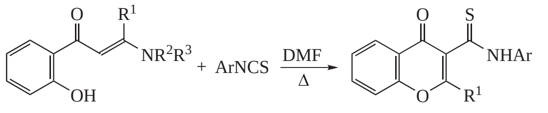
New both 2-unsubstituted and 2-substituted 3-(*N*-arylthiocarbamoyl)chromones were obtained by the reaction between 3-dimethylamino-1-(2-hydroxyaryl)prop-2-en-1-ones and aryl isothiocyanates.

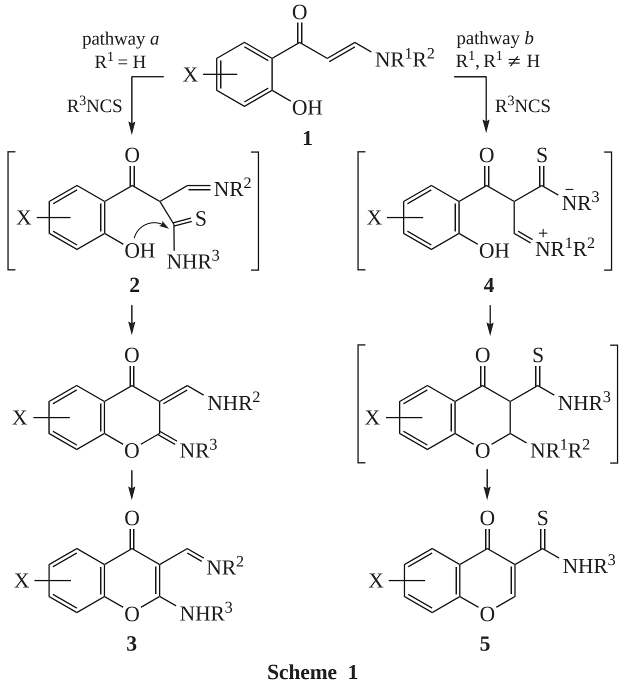


14 examples, 21–75%

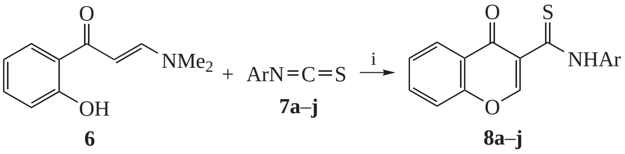
Chromones are the subject of increasing interest due to a wide use of these heterocyclic compounds as structural building blocks for the design of various promising pharmacological agents[1–5] and components for super-high capacity optical archive storage systems.[6] Chromones with thiocarbamoyl substituents are not studied sufficiently. To the best of our knowledge, only two reports[7,8] are available for the synthesis of 3-thiocarbamoylchromones providing a small number of compounds of limited diversity. Derivatives having substituents on the benzene ring of the thioamide group, containing heterocyclic fragments or bearing substituents on the 2-position of the chromene moiety have not been described.

The goal of this work was to develop a new general method for the synthesis of 3-(*N*-arylthiocarbamoyl)chromones including 2-substituted ones containing various aryl substituents at the thioamide group. We hypothesized that the reactions 3-amino-1-(2-hydroxyaryl)prop-2-en-1-ones **1** with isothiocyanates as cyclizing reagents should bring about 3-thiocarbamoylchromones (Scheme 1). It can be assumed that after addition of isothiocyanate at the enamine moiety of substrate **1**, the reaction can occur *via* one of two pathways. When R^1 = H in reactant **1**, neutral intermediate **2** should be formed whose cyclization would occur with H_2S elimination giving finally amino imino chromone **3** (pathway *a*). In the case of tertiary amino reactants (R^1, R^2 ≠ H), the intermediate should be zwitterion **4** (pathway *b*). Its heterocyclization would supposedly proceed with retention of sulfur and elimination of amine HNR^{1}R^2 leading thus to thiocarbamoylchromones **5** (see Scheme 1). It should be noted that isothiocyanates were not previously used as cyclizing reagents in the chemistry of chromones.

We studied the conditions for the reaction of 3-dimethylamino-1-(2-hydroxyphenyl)prop-2-en-1-one **6** with isothiocyanates **7a**–**j** aiming to access thiocarbamoylchromone **8a**–**j** (Scheme 2). In a model reaction with phenyl isothiocyanate **7a**, we varied the solvents, reaction temperature, and reaction time (Table 1) and



Scheme 1



a Ar = Ph, 68%
b Ar = 4-BrC_6H_4, 53%
c Ar = 3-MeC_6H_4, 42%
d Ar = 4-FC_6H_4, 21%
e Ar = 2,4-$Cl_2C_6H_3$, 61%
f Ar = 3,5-$Cl_2C_6H_3$, 63%
g Ar = 2-$MeOC_6H_4$, 49%
h Ar = 4-$O_2NC_6H_4$, 75%
i Ar = 4-$EtO_2CC_6H_4$, 74%
j Ar = 3-$F_3CC_6H_4$, 70%

Scheme 2 *Reagents and conditions:* i, DMF, Δ.

Table 1 Influence of the reaction conditions on the yield of thiocarbamoylchromone **8a**.[a]

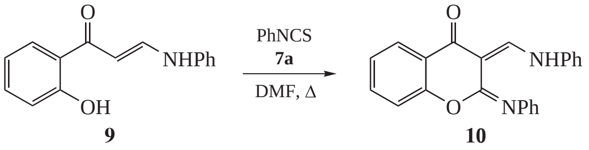
Entry	Solvent	*T*/°C	Yield of **8a** (%)
1	nitromethane	reflux	11
2	THF	reflux	24
3	dioxane	reflux	trace
4	toluene	reflux	43
5	DMF	120	68
6	solvent free	120	38

[a] From **6** (1 mmol), **7a** (2.2 mmol), solvent (2 ml).

found that the heating in DMF provided the highest yield of thiocarbamoylchromone **8a** (entry 5).

This procedure turned to be rather general and allowed us to synthesize thiocarbamoylchromones **8a–j** with various substituents (see Scheme 2).[†] Substituents on isothiocyanates proved to have a considerable effect on the yield of product **8**, with electron-withdrawing substituents facilitating the reaction.

The reaction of phenyl isothiocyanate **7a** with amino enone **9** bearing a secondary amino group[9] gave sulfur-free chroman-4-one **10**, which meant that the thiocarbamoyl moiety was involved in the cyclization (Scheme 3).



Scheme 3

Obviously, amino enones containing a tertiary nitrogen atom should be used in the synthesis of thiocarbamoylchromones. The structure of compound **10** was confirmed by ^{1}H and ^{13}C NMR spectroscopy; the complete assignment of all signals in the ^{1}H and ^{13}C NMR spectra was made using 2D ^{1}H–^{1}H COSY, ^{1}H–^{13}C HSQC, and ^{1}H–^{13}C HMBC homo- and heteronuclear correlation techniques. The solution concentrations and the acquisition time of the 1D experiments were chosen according to the recommendations.[10] A further analysis revealed that compound **10** can exist in solution in two tautomeric forms **A** and **B**, which interconvert *via* the proton transfer between nitrogen atoms (Figure 1).

To explain the experimentally observed prevalence of form **B**, we performed the quantum chemical modeling of the tautomeric equilibrium in the isolated molecule approximation by the density functional theory including dispersion corrections (PBE1PBE/def2SVP GD3BJ). Both tautomeric forms are characterized by the presence of an intramolecular NH–N hydrogen bond. Calculations of total energy and Gibbs energy changes for the tautomeric equilibrium demonstrated that the equilibrium is shifted toward form **B**, which has a lower total energy ($\Delta E = -1.0$ kcal mol^{-1}) and a lower Gibbs energy ($\Delta G = -0.8$ kcal mol^{-1}), thus accounting for the experimental results.

It should be noted that the approach based on the reaction of 2-hydroxyaryl amino enones with isothiocyanates can also be applied to synthesize 3-carbamoylchromones containing substituents in the 2-position. For this purpose, the appropriate substituent R should be introduced into the amino enone moiety. Previously,[11] we demonstrated that reaction of benzylamine with 3-acyl-2-(het)arylchromones **11a**,**b** or 2-(het)arylchromones **11c**,**d** in ethanol afforded amino hydroxyl chalcones **12a**,**b** (Scheme 4). Their treatment with aryl isocyanates resulted in 2-substituted carbamoylchromones **13a–d** (see Scheme 4).[†]

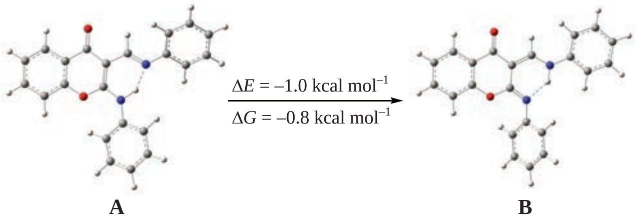
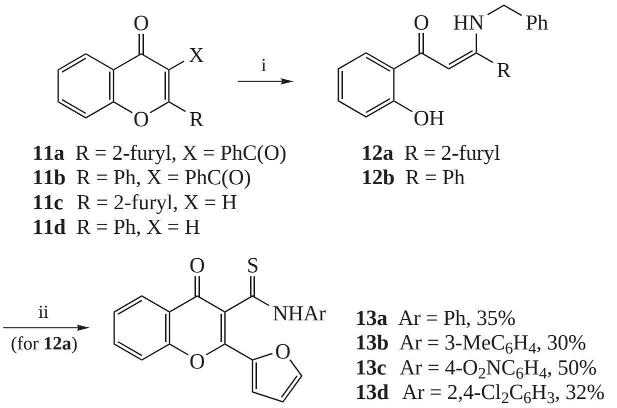


Figure 1 Fully optimized (PBE1PBE/def2SVP GD3BJ) tautomeric forms of compound **10**.



Scheme 4 *Reagents and conditions:* i, $PhCH_2NH_2$, EtOH; ii, ArNCS (**7a**,**c**,**e**,**h**), DMF, Δ.

To summarize, we accessed both 2-unsubstituted and 2-substituted 3-thiocarbamoylchromones from readily available compounds. The products seem promising for further study as carbamoylchromone analogues which showed high biological activity and obvious synthetic potential.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.09.010.

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[†] *General procedure for the synthesis of 3-thiocarbamoylchromones* **8a–j**, **13a–d**. A mixture of amino enone (1 mmol) and aryl isothiocyanate (2.2 mmol) in dry DMF (2 ml) was heated at 120 °C for 4–16 h (TLC control). The precipitate formed was filtered off and washed with mixture CH_2Cl_2–hexane (1 : 10), and the crude material was purified by column chromatography (CH_2Cl_2–hexane, 2 : 1, as an eluent).