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Unusual transformations of 3-thiocarbamoylchromones

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ABSTRACT

The reaction of malononitrile with 3-thiocarbamoylchromones was accompanied by rearrangement, resulting in the formation of 2,5-dihydro-1*H*-chromeno[2,3-*b*]pyridine-3-carbonitriles or 2-imino-5-oxo-1-phenyl-2,5-dihydro-1*H*-chromeno[2,3-*b*]pyridine-3-carbothioamides, depending on the nature of the substituents in the thiocarbamoyl moiety. This reaction sharply differs from the reaction of malononitrile with 3-carbamoylchromones, which gives coumarino-pyridines.

Introduction

The diverse reactivity of chromones makes them valuable substrates for the synthesis of various compounds [1–5]. Approaches based on the reactions of chromones containing electron-withdrawing substituents in position 3 with nucleophiles, which are accompanied by domino processes, are widely used to prepare various products, including heterocyclic structures [6–11]. Previously, we demonstrated that the presence of *N*-arylamide functional groups in 3-carbamoylchromones **1a-c** results in the formation of coumarino-pyridines **2a-c** upon their reaction with malononitrile according to the proposed mechanism shown below (Scheme 1) [12].

The synthetic potential of this approach could be extended by using chromones containing substituents in position 3, which have not been employed for rearrangements, in particular, with thiocarboxamides, which were not used previously in the chemistry of this heterocycle, despite their high synthetic potential. In view of more diverse reactivity of thioamide groups compared with amide groups and considering the reactions of nucleophiles with 3-carbamoylchromones described in our previous publication [12], we expected that the reactions of 3-thiocarbamoylchromones with C-nucleophiles would give other fused heterocycles, in particular, chromeno[2,3-*b*]pyridines, which are of considerable interest as biologically active compounds [13–17]. Compounds containing this motif have been studied as antiproliferative [18], anticancer [19], antitubercular, and antimicrobial agents [20], MK-2 inhibitors [21], and DNA ligase inhibitors [22]. Amlexanox, containing a chromeno-pyridine skeleton, deserves particular attention as an antiallergic and antiulcer agent, which proved to be efficient for the therapy of type 2 diabetes mellitus [23].

Previously, we have developed a novel method for the preparation of 3-carbamoylchromones **5a**, **6a** and the scarcely known 3-thiocarbamoylchromones **5b**, **6b**. The method included the reaction of *o*-hydroxyaryleneaminones **3**, **4** with isocyanates and isothiocyanates, respectively (Scheme 2) [24,25].

Our experience of studying 3-carbamoylchromones suggested that thiocarbonyl groups should also affect the ring transformations of 3-thiocarbamoylchromones, which takes place after nucleophilic attack and, hence, the structure of products.

Results and discussion

Starting materials **7a-h** were synthesized by the reaction of enaminones with aryl isothiocyanates in DMF according to the method described in our previous article (Scheme 3) [24].

The present study addresses the reactions of 3-thiocarbamoylchromones with malononitrile. These reactions were found to differ strongly from the above-described reactions which gave polyfused compounds **2a-c**. We demonstrated that malononitrile in ethanol reacts with 3-thiocarbamoylchromones **7a-c** containing electron-donating substituents on the aryl moieties in the presence

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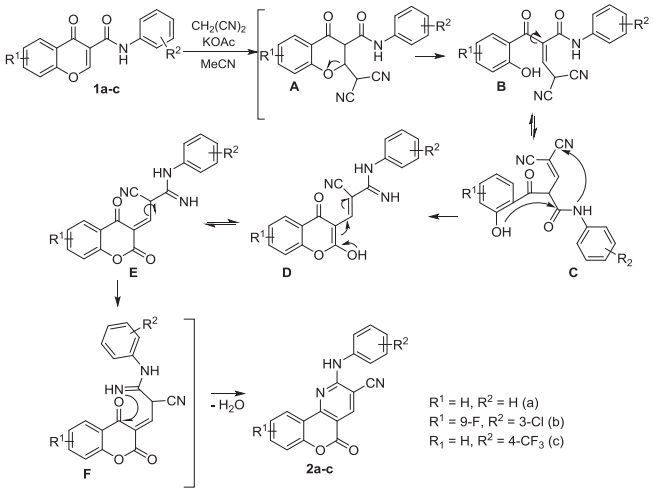
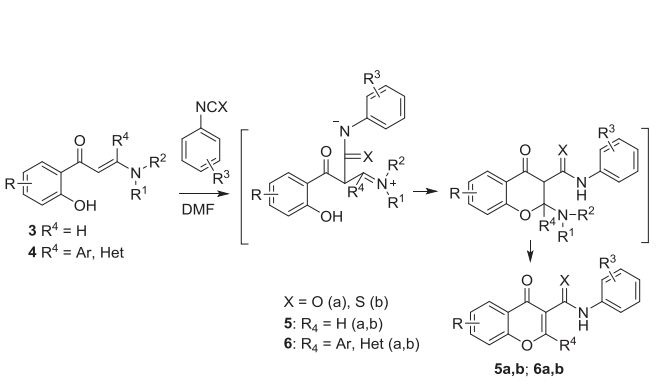
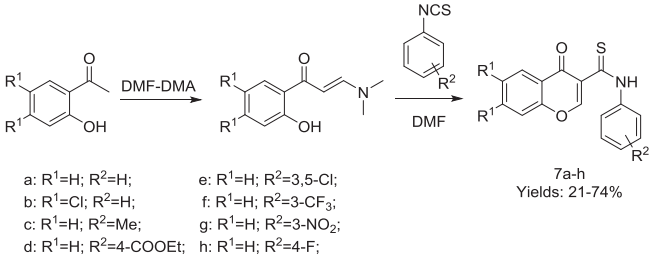


Scheme 1. Reaction of 3-carbamoylchromones with malononitrile.



Scheme 2. Synthesis of 3-carbamoyl/3-thiocarbamoyl chromones.

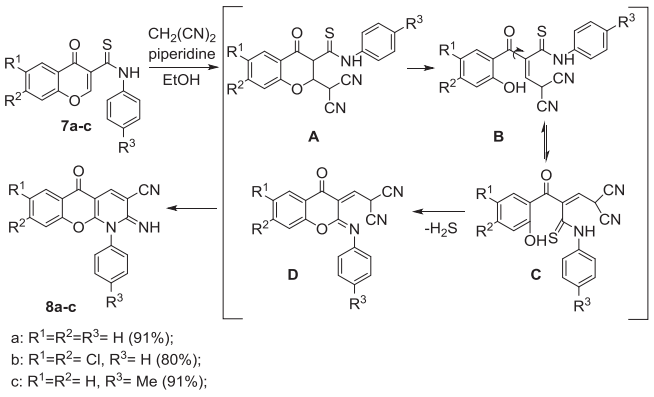


Scheme 3. Reaction of enaminones with aryl isothiocyanates.

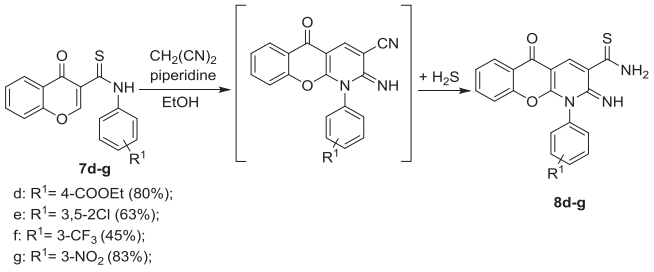
of triethylamine to give 2-imino-5-oxo-1-aryl-2,5-dihydro-1*H*-chromeno[2,3-*b*]pyridine-3-carbonitriles **8a-c** (Scheme 4).

The process presumably includes a Michael reaction involving the C-2 position of the γ-pyrone ring (**A**), which is followed by a retro-Michael reaction with γ-pyrone ring opening (**B**), rotation around the C—C bond (**C**), and cyclization involving the hydroxy group with the elimination of hydrogen sulfide yielding a new pyrone ring (**D**). The final step is heterocyclization giving chromeno[2,3-*b*]pyridines **8a-c**. In this case, the cyclization induced by the hydroxy group is directed towards the thiocarbonyl group, which is more reactive that the carbonyl group, and is not accompanied by displacement of the aniline moiety, which takes place in the reactions of *N*-substituted 3-carbamoylchromones with malononitrile.

When electron-withdrawing substituents are present in the aniline ring of **7d-g**, the hydrogen sulfide formed in the reaction



Scheme 4. Reaction of 3-thiocarbamoylchromones **7a-c** containing electron-donating substituents with malononitrile. Yields are in brackets.

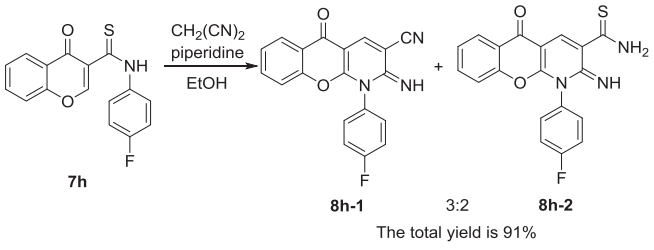


Scheme 5. Reaction of 3-thiocarbamoylchromones **7d-g** containing electron-withdrawing substituents with malononitrile. Yields are in brackets.

adds to the nitrile group of the pyridine ring to give primary thioamide **8d-g** (Scheme 5).

An intermediate situation is observed for the fluorine-substituted thiocarbamoylchromone **7h** (Scheme 6). In this case, the reaction affords a mixture of products **8h-1** and **8h-2** in a 3:2 ratio, which was established from the ratio of proton signals in the ^{1}H NMR spectrum.

The structure of compounds **8a-h** was proven by mass spectrometry and ^{1}H and ^{13}C NMR spectroscopy. For compound **8a**, two-dimensional ^{1}H ^{13}C heteronuclear correlation HSQC and HMBC spectra were recorded, which allowed the assignment of signals. The presence of a nitrile group in compounds **8a-c** was additionally confirmed by IR spectroscopy (characteristic peak at 2225 cm^{-1}). For compound **8d**, apart from the heteronuclear spectra, the ^{1}H ^{1}H COSY and NOESY spectra were recorded; the proton cross-peaks present in these spectra indicated interaction of the two protons of the thioamide group. No absorption band characteristic of a nitrile group (~2225 cm^{-1}) was present in the IR spectrum of compounds **8d-g**, and no signal of the nitrile carbon (115–117 ppm) was observed in the ^{13}C NMR spectrum.



Scheme 6. Reaction of fluorine-substituted thiocarbamoylchromone **7h** with malononitrile.

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Conclusion

We have studied for the first time the reactivity of 3-thiocarbamoylchromones, demonstrated participation of the thiocarbonyl group in the rearrangements under the action of nucleophiles and proposed a method for the synthesis of chromeno[2,3-*b*]pyridines.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152202.

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