SYNTHESIS OF NEW BENZOPYRANO[2,3-c]PYRAZoles AND 3-TRIAZOLONYLIMINOCOUMARINS FROM 3-CYANO IMINOCOUMARIN DERIVATIVES

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INTRODUCTION

Iminocoumarins derivatives have attracted intense interest in the past few decades. The growing interest is due to their chemical reactivity, biological compatibility, and number of applications associated with them. Several of these iminocoumarins derivatives exhibit exceptional biological and pharmacological activities such as antimicrobial,\textsuperscript{1} antitumor,\textsuperscript{2} and anticancer\textsuperscript{3} activities. In addition, they serve as

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inhibitors of protein-tyrosine kinase$^4$ and they are also used as dyes in laser technology.$^{5,6}$

In recent years, some works have shown that iminocoumarins functionalized at the 3-position can be used as starting materials to obtain novel heterocyclic compounds consisting of a benzopyran moiety fused with pyrazole,$^7$ naphthyridine,$^6$ quinolone,$^8$ quinoxaline,$^{9,16}$ and pyrimidine rings.$^{11–15}$ These modifications in iminocoumarin backbones could significantly increase the antimicrobial efficiency, broaden their antimicrobial spectrum, and improve their optical properties,$^{16,17}$ leading to applications in the field of fluorescent sensors$^{18,19}$ and dye-sensitized solar cells.$^{20}$

In this work, we introduce triazolonyl and pyrazole ring into iminocoumarin structure. As important aromatic nitrogen-containing heterocycles, triazole compounds have aroused special interest because of their excellent pharmacokinetic characteristics, favorable safety profile, and the latent ability for the formation of hydrogen bonds with other active molecules. A number of triazole drugs including fluconazole, itraconazole, and voriconazole have been prevalently used in anti-infective therapy.$^{21,22}$ Recently, some triazole derivatives have been reported to exhibit good anti-MRSA potency.$^{23}$ Although the extensively clinical use of triazole anti-infective agents has revolutionized the treatment of many infectious diseases, some of them are still limited by poor activities toward intractable fungi, high frequency of renal toxicity, and several adverse effects.$^{24}$

In the other hand, many previous studies have confirmed that pyrano[2,3-c]pyrazoles and their related derivatives are an important class of pharmaceutical compounds and exhibit a broad spectrum of biological activities. In particular, these compounds have been confirmed to possess antifungal, antibacterial, anticancer, anti-inflammatory, analgesic, antiplatelet, and antioxidant activities.$^{25,26}$

Over the past few years, we are particularly interested in synthesizing several new 3-cyano iminocoumarins and their N-ethoxycarbonylated derivatives followed by their transformation by N-nucleophilic reagents as amine, hydrazine, hydrazide, and hydroxylamine to obtain respectively benzopyranopyrimidines,$^{15}$ 3-triazolonyliminocoumarins,$^{27}$ benzopyranopyrazoles, and benzopyranooxazoles.$^{28}$ In continuation of our research in the synthesis of heterocyclic compounds, we describe in this article the reactivity of 3-cyano iminocoumarin with thiosemicarbazide. The second part is devoted to their N-ethoxycarbonyl derivatives with 4-phenylsemicarbazide and thiosemicarbazide as nucleophilic reagents.

RESULTS AND DISCUSSION

3-Cyano iminocoumarins (1–7) were prepared using the Knoevenagel procedure.$^{29}$ Their N-ethoxycarbonylated derivatives (8–10) were obtained in moderate yields by N-ethoxycarbonylation, as described previously.$^{29,30}$ (Scheme 1). Their structures were assigned by infrared (IR), $^1$H and $^{13}$C NMR, and elemental analysis.

To prepare a variety of benzopyranolo[2,3-c]pyrazoles derivatives, the starting 3-cyano iminocoumarins (1–7) were converted by thiosemicarbazide (a) as nucleophilic reagent. Reaction of 3-cyano iminocoumarins (1) with thiosemicarbazide (a) was selected as a model system for a thorough study aimed at optimizing the
benzopyrano[2,3-c]pyrazoles (1a) yield. Three parameters were varied in this context, namely the reaction temperature, the nature of the organic solvent, and the nature of the catalyst. The best yield of the benzopyrano[2,3-c]pyrazoles (1a) was obtained when acetic acid was utilized as a catalyst in chloroform at room temperature. The benzopyrano[2,3-c]pyrazole (1a) was isolated by simple filtration after 16 days in 85% yield with good selectivity (Scheme 2).

To explain the formation of benzopyrano[2,3-c]pyrazole (1a), we suggest in Scheme 3 a possible mechanism involving in two steps: (i) a nucleophilic attack of NH2 group on imidic carbon according to Schmidt reaction to give an amidrazone (1a') as intermediate and (ii) interaction of NH group with C14/C17 function by an intramolecular heterocyclization process leading the corresponding benzopyrano[2,3-c]pyrazole (1a).

The infrared (IR) spectra showed absence of the absorption bands characteristic of the C≡N functions and the appearance of absorption bands at 1140 and 3325 cm\(^{-1}\) corresponding to C=S and NH2 groups respectively. Moreover, the \(^1\)H NMR spectra were also in agreement with this structure. Particularly, the disappearance of original peak arising from pyranic NH at 9.25 ppm and appearance of peaks at 9.94 and 7.09 ppm corresponding of pyrazolic NH and thioamidic NH2 respectively, are clear indications that the cyclocondensation reaction had gone to completion.

Encouraged by this success, we investigate the reactivity of other 3-cyano iminocoumarins (2–7) in the same operating mode. We obtained the corresponding benzopyrano[2,3-c]pyrazoles (2a–7a) in moderate to good yields 48–87% (Table 1). The analytic spectra are in agreement with a model compound. The IR spectrum of these compounds showed in each case, absorption bands at ((cm\(^{-1}\)): 1132–1163, 1574–1618, 1642–1659, 3245–3322, and 3359–3372 corresponding to C=S, C=C, C=N, NH, and NH2 respectively. The \(^1\)H NMR spectra revealed a sharp singlet at 9.86–9.94 ppm assigned of pyrazolic NH and singlet from thioamidic NH2 at 6.98–7.09 ppm.

**Scheme 1.** Synthetic route to 3-cyano iminocoumarins (1–10).

**Scheme 2.** Synthesis of benzopyrano[2,3-c]pyrazole (1a).
We extended our study to the use of N-ethoxycarbonyl iminocoumarins (8–10) as C-electrophile reagents with thiosemicarbaside (a) or 4-phenylsemicarbazide (b). Herein we followed the same strategy. We first chose the heterocyclization reaction

Scheme 3. Proposed mechanism of benzopyranopyrazole (1a).

We extended our study to the use of N-ethoxycarbonyl iminocoumarins (8–10) as C-electrophile reagents with thiosemicarbaside (a) or 4-phenylsemicarbazide (b). Herein we followed the same strategy. We first chose the heterocyclization reaction

Table 1. Synthesis of benzopyranopyrazoles 1a–7a

| R₅ | R₆ | R₇ | R₈ | Time (days) | Yield a (%) | Mp (°C) |
|----|----|----|----|-------------|-------------|--------|
| H  | H  | H  | H  | 16          | 85          | 252    |
| H  | H  | N(Et) | H  | 2          | 62          | 220    |
| H  | H  | OH  | H  | 5          | 85          | >260   |
| H  | Cl | H  | H  | 17         | 48          | 188    |
| H  | OCH₃ | H  | H  | 18        | 70          | 194    |
| H  | H  | OCH₃ | H  | 4          | 65          | 204    |
| H  | H  | H  | OCH₃ | 3.5       | 87          | 194    |

aIsolated yield.
of iminocoumarin (8) and 4-phenylsemicarbazide (b) as a model reaction system. To optimize conditions for the reaction, a series of preliminary runs were conducted on this system modifying solvents, time, and temperature. In the final protocol, triazolonyl iminocoumarin (8b) were obtained in 76% with good selectivity by refluxing absolute methanol for 2 h.

A literature survey indicates that two mechanistic pathways that can formally be envisioned for this condensation leading the 3-triazolonyl iminocoumarin (8b) or benzopyranopyrimidine (8b') (Scheme 4).

**Table 2. Synthesis of 3-triazolonyl iminocoumarin 8a–10a and 8b–10b**

|    | R₅ | R₆ | R₇ | R₈ | X  | R  | Time (h) | Yield* (%) | Mp (°C) |
|----|----|----|----|----|----|----|----------|------------|--------|
| 8a | H  | H  | N(Et)₂ | H  | S  | H  | 24       | 74         | 230    |
| 9a | H  | H  | OCH₃  | H  | S  | H  | 3.5      | 78         | >260   |
| 10a| H  | H  | H    | OCH₃ | S  | H  | 24       | 80         | >260   |
| 8b | H  | H  | N(Et)₂ | H  | O  | Ph | 2        | 76         | >260   |
| 9b | H  | H  | OCH₃  | H  | O  | Ph | 2        | 83         | >260   |
| 10b| H  | H  | H    | OCH₃ | O  | Ph | 8        | 87         | 250    |

*Isolated yield.
The structure was defined by IR and $^1$H NMR spectral analysis involving comparison with literature data. In particular, the IR spectrum showed (i) the absence of absorption at 2214 cm$^{-1}$, which confirmed the reactivity of the cyano group, (ii) the absence of absorption at 1630 and 1640 cm$^{-1}$, and (iii) the appearance of band at 1718 cm$^{-1}$, which exclude the possibility of benzopyranopyrimidine product and confirmed the triazolonic structure.[21,22]

The application of optimized conditions, used with the model system, to various combinations gave corresponding 3-triazolonyl iminocoumarins with good yield 74–87% (Table 2). The chemical structures of the newly synthesized iminocoumarin derivatives were characterized by FTIR and $^1$H NMR spectra.

The mechanism proposed for this condensation involved three steps: (i) the nucleophilic attack of NH$_2$ on the imidic function, giving the amidine intermediate, (ii) the spontaneous cyclization between the iminocoumarin system and triazolonic heterocycle, and (iii) the formation of triazolonic heterocycle following the interaction between the carbonyl group and the carbazidic function (Scheme 5).

CONCLUSION

In conclusion, we have developed in this article a simple procedure for the synthesis of benzopyranopyrazolic and 3-triazolonyliminocoumarinic compounds...
initiated by the condensation of different iminocoumarins with thiosemicarbazide and 4-phenylsemicarbazide as nucleophilic reagents. These compounds are obtained in moderate to good yields with high selectivity.

EXPERIMENTAL

Thiosemicarbazide and 4-phenylsemicarbazide were commercially available from Aldrich. Ethanol, methanol, and chloroform (analytical grade) used for spectroscopic measurements were from VWR ProLabo and SDS, respectively. 3-Cyano iminocoumarins (1–7) and N-ethoxycarbonylated derivatives (8–10) were prepared as previously described.[29,30] The melting points were determined on an Electrothermal 9100 apparatus. Infrared spectra were registered on a Jasco FT-IR 420 spectrophotometer apparatus using a Perkin-Elmer 100 instrument. 1H NMR spectra were recorded on a Bruker WP 200 spectrometer operating at 300, in dimethylsulfoxide (DMSO-d6) or CF3CO2D with tetramethylsilane (TMS) as internal standard (chemical shifts in ppm).

General Procedure for the Synthesis of Benzopyrano[2,3-c]pyrazoles 1a–7a

A solution of 3-cyano-iminocoumarin (1–7) (5 mmol and thiosemicarbazide (a) (5 mmol) was stirred in 30 ml of chloroform. After total dissolution, a catalytic amount of glacial acetic acid was added, and the reaction mixture was stirred at room temperature during the time indicated in Table 1. After completion of the reaction, the simple benzopyrano[2,3-c]pyrazole obtained was separated by filtration and washed with chloroform.

Benzopyrano[2,3-c]pyrazole (1a)

Orange solid, IR (cm−1): ν = 1140 (C=S), 1574 (C=C), 1656 (C=N), 3255/3322 (NH), 3372 (NH2). 1H NMR (DMSO-d6): δ = 7.09 (s, 2H, NH2), 7.60 (d, J = 8.40 Hz, 1H, H8), 7.67 (t, J = 7.5 Hz, 1H, H6′), 7.80 (t, J = 7.50 Hz, 1H, H5′), 8.08 (d, J = 8.40 Hz, 1H, H5′), 8.26 (d, J = 8.40 Hz, 1H, H6′), 8.83 (d, J = 8.40 Hz, 1H, H7), 9.45 (s, 1H, H4), 9.94 (s, 1H, NH). Calculated for C15H10N4OS: C, 61.21%; H, 3.42; N, 19.04. Found: C, 61.46%; H, 3.13; N, 19.35.

General Procedure for the Synthesis of 3-Triazolonyliminocoumarin (8a–10a) and (8b–10b)

A solution of 3-cyano-N-ethoxycarbonyl iminocoumarin 8–10 (5 mmol) and 4-phenylsemicarbazid or thiosemicarbazide (5 mmol) in 30 ml of absolute methanol was refluxed during the time indicated in Table 2. After complete reaction, the simple 3-triazolonyliminocoumarin obtained was separated by filtration and washed with methanol.

3-Triazolonyliminocoumarin (8a)

Orange solid, IR (cm−1): ν = 1179 (C=S), 1592 (C=C), 1644 (C=N), 1729 (C=O), 3276 (NH). 1H NMR (CDCl3/CF3COOD): δ = 1.33 (t, J = 6.9 Hz, 6H, 2814 S. TRICHILI ET AL.
CH₃), 3.59 (q, J = 6.9 Hz, 4H, CH₂N), 6.70 (s, 1H, H₈), 6.94 (d, J = 9.3 Hz, 1H, H₆), 7.64 (d, J = 9.3 Hz, 1H, H₅), 8.05 (s, 1H, H₄), 8.69 (s, 1H, NH), 9.47 (s, 1H, NH). Calculated for C₁₆H₁₈N₆O₂S: C, 53.63%; H, 5.03; N, 23.46. Found: C, 53.59%; H, 5.08; N, 23.49.

3-Triazolonyliminocoumarin (8b)

Orange-brown solid, IR (cm⁻¹): v = 1584 (C=C), 1648 (C=N), 1718 = 1745 (C=O), 3126 (NH). ¹H NMR (CDCl₃/CF₃COOD): δ = 1.3 (t, J = 7.2 Hz, 6H, CH₃), δ = 3.6 (q, J = 7.2 Hz, 4H, CH₂N), δ = 6.75 (d, J = 2.4 Hz, 1H, H₈), 6.99 (dd, J = 2.4 Hz, J = 9.3 Hz, 1H, H₆), 7.29 (d, J = 8.1 Hz, 1H, H₅), 7.43 (t, J = 8.1 Hz, 2H, H₄), 7.52 (d, J = 8.1 Hz, 2H, H₅), 7.65 (d, J = 9.3 Hz, 1H, H₆), 8.52 (s, 1H, H₄). C₂₂H₂₂N₆O₃: C, 63.15%; H, 5.26; N, 20.09. Found: C, 63.22; H, 5.30; N, 19.99.

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SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher’s website.

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