SYNTHESIS OF NEW PYRAZOL[1,5-a]QUINAZOLINE DERIVATIVES

Dániel Kovács, Judit Molnár-Tóth, Gábor Blaskó, Imre Fejes, and Miklós Nyerges
Servier Research Institute of Medicinal Chemistry, Budapest, Hungary

GRAPHICAL ABSTRACT

Abstract The reaction of various anthranilic acid derivatives or their esters with 4-oxotetrahydrothiophene-3-carbonitrile 2, 2-oxocyclopentanecarbonitrile (9, n = 1) or 2-oxocyclohexanecarbonitrile (9, n = 2) in ethanol under reflux conditions giving rise the formation of single products isolated in each case after simple filtration. The products were characterized as pyrazolo[1,5-a]quinazolin-5-ones 4 instead of the expected pyrazol-3-amines 3. These cascade condensation–intramolecular acylation processes generated in one-step reactions from simple starting materials novel heterocyclic scaffolds ready for further functionalization. The present synthetic protocol provides acceptable yields of new tetracyclic products in high purity.

Keywords Cascade reactions; heterocycles; pyrazoles

INTRODUCTION

During one of our ongoing medicinal chemistry programs, we intended to prepare a small library of 2-aryl-4,6-dihydrothieno[3,4-c]pyrazol-3-amine derivatives (3) using the known nucleophilic addition: cyclization domino reaction between the appropriate aryl-hydrazine derivatives (1) and 4-oxotetrahydrothiophene-3-carbonitrile (2) (Scheme 1).[1] A large number of derivatives of this heterocycle are well described in the patent literature because of their interesting pharmacological

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Address correspondence to Miklós Nyerges, Servier Research Institute of Medicinal Chemistry, 7 Záhony utca., H-1031 Budapest, Hungary. E-mail: miklos.nyerges@hu.netgrs.com
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properties that allow them to function as P2X7 receptor antagonists,\textsuperscript{[2]} inhibitors of PDE4\textsuperscript{[3]} or the TrkA kinase,\textsuperscript{[4]} antivirials,\textsuperscript{[5]} or modulators of nicotinic acetylcholine receptors.\textsuperscript{[6]} However, to date there is no example described for the reaction of 2-hydrazino-benzoic acids (1, R1=COOH), or their esters (1, R1=COOR) and 4-oxotetrahydrothiophene-3-carbonitrile 2 in such processes.

**RESULTS AND DISCUSSION**

The starting 2-hydrazino-benzoic acids or their esters 1 are commercially available; however, because of their relatively high price all of them were prepared in house from the corresponding anthranilic acid derivatives according to the procedures described in the literature.\textsuperscript{[7,8]} These acids or their esters were reacted with 4-oxotetrahydrothiophene-3-carbonitrile 2 in ethanol under reflux. After 3 h heating a single product was isolated (via 6, 7 and 8) in each case after simple filtration. These products were characterized as 6,7-dihydro-5\textit{H},9\textit{H}-thieno[3',4';3,4]pyrazolo[1,5-\textit{a}] quinazolin-5-ones 4 instead of the expected thieno[3,4-\textit{c}]pyrazol-3-amines 3 on the basis of their elemental analysis as well as infrared (IR), \textsuperscript{1}H NMR, \textsuperscript{13}C NMR, and mass spectral (MS) analysis. The IR spectrum of 4 revealed the presence of a carbonyl stretching vibration band around 1680 cm\textsuperscript{-1}, for the lactam carbonyl group, and in the NMR spectra a newly formed amide was visible instead of the amine. This lactam 4 was later reduced to the corresponding amine 5, which become the key compound for further diversification of this small compound library in our medicinal
chemistry program (Scheme 2, Table 1). Among the products 5a, 5c, and 5f were successfully prepared. In other cases, a complex mixture was observed during the reduction that lacked the desired products (5b, 5d, 5e, and 5g).

The formation of the pyrazole ring in the reaction of a keto-cyanide 1 and arylhydrazine 2 is well documented in the literature. However, the intramolecular acylation of the pyrazolamine 8 usually requires more activated acid derivatives such as chloride in the presence of base (Scheme 3).

In the same way, refluxing a solution of 2-oxocyclopentanecarbonitrile (9, n = 1) or 2-oxocyclohexanecarbonitrile (9, n = 2) in ethanol with arylhydrazines 1 afforded a series of novel tetracyclic pyrazolo[1,5-a]quinazoline 10 derivatives in a single step (Scheme 4, Table 2). Then the lactam 10 was reduced to the corresponding amine 11 under the same conditions described previously. Besides the successful reactions of 11a–e, 11e, and 11f (Table 2), the products 11d, 11g, and 11h were not observed, probably due to the decomposition of the proper lactams under the applied reaction conditions.

### Table 1. The synthesized thieno[3’,4’,3,4]pyrazolo[1,5-a]quinazoline derivatives

| Entry | Hydrazine | R<sup>1</sup> | R<sup>2</sup> | R<sup>3</sup> | R<sup>4</sup> | R<sup>5</sup> | Product | Yield (%) | Product | Yield (%) |
|-------|-----------|---------------|---------------|---------------|---------------|---------------|---------|------------|---------|------------|
| 1     | 1a        | CO<sub>2</sub>H | H | H | H | 4a | 74 | 5a | 51 |
| 2     | 1b        | CO<sub>2</sub>H | H | H | CH<sub>3</sub> | 4b | 9 | 5b | — |
| 3     | 1c        | CO<sub>2</sub>H | H | CH<sub>3</sub> | H | 4c | 43 | 5c | 95 |
| 4     | 1d        | CO<sub>2</sub>H | H | H | CH<sub>3</sub> | 4d | 49 | 5d | — |
| 5     | 1e        | CO<sub>2</sub>CH<sub>3</sub> | CH<sub>3</sub> | H | H | 4e | 15 | 5e | — |
| 6     | 1f        | CO<sub>2</sub>CH<sub>3</sub> | H | OCH<sub>3</sub> | H | 4f | 56 | 5f | 85 |
| 7     | 1g        | CO<sub>2</sub>CH<sub>3</sub> | Br | H | H | 4g | 9 | 5g | — |

Scheme 3. Proposed reaction mechanism of the formation of the new thieno[3’,4’,3,4]pyrazolo[1,5-a]quinazoline derivatives.
In conclusion, we report a cascade condensation–intramolecular acylation process generated in the reaction of cyclic ketocyanides 2 and 2-hydrazino-benzoic acids or their esters 1 (R^I = CO_2H or CO_2Me accordingly) to afford novel heterocycles. The present synthetic protocol provides acceptable yields of new tetracyclic products in good purity. The bioactivity of the newly synthesized compounds will be published elsewhere.

**EXPERIMENTAL**

**Preparation of 2-Hydrazino-benzoic Acids**

The corresponding anthranilic acid (1 mmol) was suspended in hydrochloric acid (6 M, 2.4 ml) and cooled to −5°C. Sodium nitrite (1.1 mmol) was dissolved in water (0.4 ml) and added dropwise. The reaction mixture was stirred for 1 h at −5°C and then SnCl_2·2H_2O was added (0.451 g, 2 mmol dissolved in 0.6 ml of 6 M aqueous HCl). The product was precipitated, filtered, washed with water, and dried in vacuo. The product was used without any further purification (yield 64–100%).

**Reaction of Hydrazines with α-Oxo-cyanides**

The corresponding 2-hydrazino-benzoic acid or methyl-2-hydrazino-benzoate (1.1 mmol) and the α -oxo-cyano compound (1 mmol) were suspended in dry ethanol (5.5 ml) and refluxed for 3 h. After cooling, the product was precipitated, filtered, and dried in vacuo to yield (51–85%) the title products.

**Table 2. The synthesized novel tetracyclic pyrazolo[1,5-a]quinazolines**

| Entry | Hydrazine n | R^1 | R^2 | R^3 | R^4 | R^5 | Product Yield (%) | Product Yield (%) |
|-------|-------------|-----|-----|-----|-----|-----|-------------------|-------------------|
| 1     | 1           | C_3HO | H   | H   | H   |     | 10a 54           | 11a 87            |
| 2     | 1c          | C_3HO | C_3HO | H   | H   |     | 10b 44           | 11b 87            |
| 3     | 1f          | C_3HO | OCH_3 | H   | H   |     | 10c 30           | 11c 57            |
| 4     | 1g          | C_3HO | Br   | H   | H   |     | 10d 8            | 11d —             |
| 5     | 1a          | C_3HO | H   | H   | H   |     | 10e 55           | 11e 26            |
| 6     | 1c          | C_3HO | C_3HO | H   | H   |     | 10f 47           | 11f 44            |
| 7     | 1f          | C_3HO | OCH_3 | H   | H   |     | 10g 52           | 11g —             |
| 8     | 1g          | C_3HO | Br   | H   | H   |     | 10h 3            | 11h —             |
6,7-Dihydro-5H,9H-thieno[3′,4′,3,4]pyrazolo[1,5-a]quinazoline-5-one (4a)

White powder, 0.180 g (74%); 1H NMR (500 MHz, DMSO-d6): 12.28 (s, 1H, NH), 8.11 (d, 1H, J = 7.5 Hz, Ar-4'H), 7.97 (d, 1H, J = 8.0 Hz, Ar-1'H), 7.84 (t, 1H, J = 8.4 Hz, Ar-2'H), 7.45 (t, 1H, J = 7.5 Hz, Ar-3'H), 4.02 (s, 2H, H-9), 3.83 (s, 2H, H-7); 13C NMR (125 MHz, DMSO-d6): 161.3 (q), 158.8 (q), 138.5 (q), 135.6 (CH), 132.7 (q), 128.6 (CH), 125.5 (CH), 116.2 (q), 114.6 (CH), 104.7 (q), 28.9 (CH2), 26.8 (CH2); IR (KBr, cm−1): 2820, 1667. HRMS m/z calcd. for C12H9N3OS (M + H)+ 244.0546; found 244.0541.

Lactam Reduction

The corresponding indazole[2,3-a]quinazoline-5(6H)-one or pyrazolo[1,5-a]quinazoline-5-one (1 mmol) was dissolved in dry tetrahydrofurane (30 ml) and at −5°C under a nitrogen atmosphere. BH3·THF solution (1 M, 7 ml) was added dropwise. The mixture was stirred at room temperature for 4 h, and then aqueous hydrochloric acid solution (6 M, until no more gas evolved) was added. The pH was adjusted to 13 with 2 M sodium hydroxide solution, and the mixture was extracted with dichloromethane (2 × 200 ml), dried over sodium sulfate, and evaporated. The crude product was purified by column chromatography over silica (eluent: heptane–ethyl acetate 3:1) to yield (26–87%) the product.

6,7-Dihydro-5H,9H-thieno[3′,4′,3,4]pyrazolo[1,5-a]quinazoline (5a)

Yield 0.117 g (51%); white powder; 1H NMR (500 MHz, DMSO-d6): 7.45 (dm, 1H, J = 8.0 Hz, Ar-1'H), 7.29 (m, 1H, Ar-2'H), 7.23 (dm, 1H, J = 7.3 Hz, Ar-4'H), 7.09 (m, 1H, Ar-3'H), 6.75 (brs, 1H, NH), 4.34 (brs, 2H, H-5), 3.85 (brt, 2H, H-9), 3.68 (brt, 2H, H-7); 13C NMR (125 MHz, DMSO-d6): 160.3 (q), 140.8 (q), 135.9 (q), 128.7 (CH), 126.8 (CH), 124.6 (CH), 121.5 (q), 113.7 (CH), 102.5 (q), 42.8 (CH2), 28.9 (CH2), 26.7 (CH2); IR (KBr, cm−1): 3280, 2916. HRMS m/z calcd. for C12H11N3S (M + H)+ 230.0754; found 230.0741.

SUPPLEMENTAL MATERIAL

Full experimental details, assignment, the 1H and 13C NMR spectra, IR spectra, and HRMS details for this article can be accessed on the publisher’s website.

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