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Concomitant ring contraction cyclization strategy for the synthesis of novel 4-oxo-4,5-dihydro-pyrroloquinolines

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Abstract—The synthesis of novel substituted pyrroloquinolinones is described by concomitant ring contraction cyclization form 2-(2-amino-5-nitro-phenyl)-[4*H*]-1,3-thiazines, which were derived from *N*-substituted 5-nitro-anthranilonitrile. An easy access to novel 4-thiono-1,4-dihydro-1,3-quinazoline heterocycles is also mentioned.

Synthesis of naturally occurring quinoline and hydroquinoline alkaloids and their analogues have gained a lot of interest in the field of medicinal chemistry for their broad spectrum therapeutic activity as antitumor, receptor antagonist or agonist, antiarrhytmic, analgesic, enzyme inhibition, antidepressant, antiulcer, antirheumatic, immunosuppressant, antiallergic, antimalarial, and even antiviral. They are also used in agriculture as pesticides, antioxidants, corrosion inhibitors, and even in dyes as photoconductors and photosensitizers.[1]

3-, 4- or 3,4-Substituted-1,2-dihydroquinolin-2-one skeletons, in particular, have received substantial attention as they provide access to biologically potent alkaloid analogues.[2] Quinolinone intermediates are also of interest for the preparation of functionalized dihydroquinoline derivatives.[1–4]

Herein, we wish to report a short synthetic approach to novel 4,5-dihydro-pyrrolo[3,2-*c*]quinolin-4-ones, which offered multifunctional potential, by concomitant ring contraction cyclization of 2-(2-aminoaryl)-[4*H*]-1,3-thiazine intermediates derived from *N*-thioacylamidine precursors by [4+2] cycloaddition (Fig. 1).

We first investigated a model reaction to achieve the formation of 2-(2-amino-5-nitro-phenyl)-[4*H*]-1,3-thiazines **4** from 5-nitroanthranilonitrile **1** (Scheme 1). The

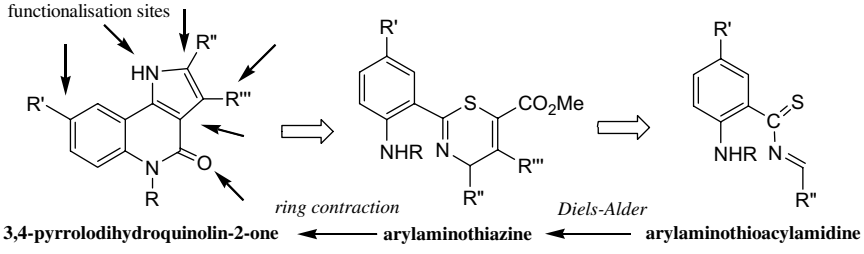

Figure 1.

Keywords: Hetero Diels–Alder reaction; Thiazines; Ring contraction; Pyrroloquinolinones.
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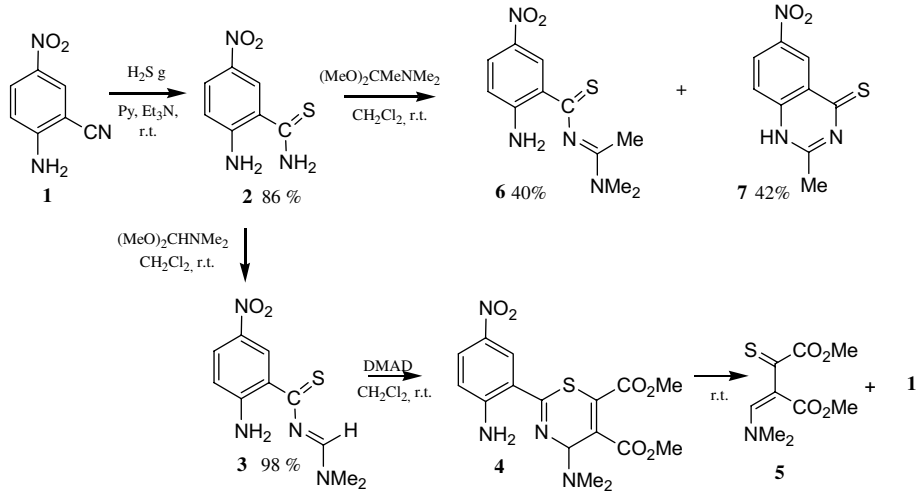


Scheme 1.

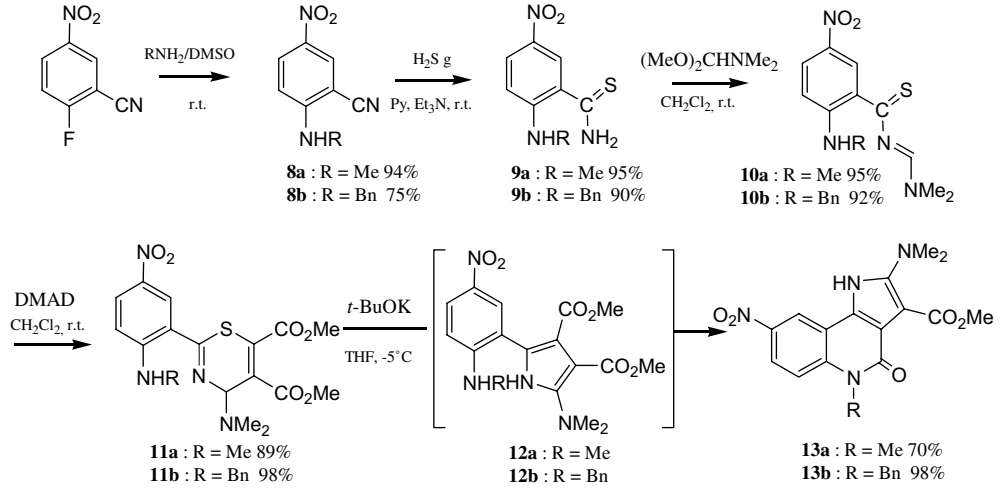
introduction of the diene moiety from nitroanthranilonitrile **1** was first carried out by usual procedure described for the preparation of *N*-thioacylamidine.[5] Thus, the sulfurization of nitrile group by treatment with gaseous hydrogen sulfide in pyridine/triethylamine led to the thioamide **2** in 86% yield. The condensation of thio-amide **2** with *N*,*N*-dimethylformamide dimethyl acetal (1 equiv) in dichloromethane gave the desired 2-(2-amino-5-nitrophenyl)thioacylamidine **3** in 98%.

Subsequent Diels–Alder reaction of the diene **3** with dimethylacetylene dicarboxylate (1 equiv), in dichloromethane at room temperature, afforded the thiazine **4** in low yield (40%) as the latter underwent a spontaneous cycloreversion to generate the thioamide vinylog **5** and nitroanthranilonitrile **1** at rt.

Earlier reports in the literature indicate that the presence of a methyl group at the 4-position of *N*-thioacylamidine retards the cycloreversion of thiazine heterocycles.[6] To overcome the problem of cycloreversion, we attempted the preparation of the corresponding 4-methyl heterodiene **6** from the thioamide **2**. In the event, when **2** was treated with *N*,*N*-dimethylacetamide dimethyl acetal, in dichloromethane at room temperature, a 1:1 mixture of *N*-thioacylamidine **6** (40%) and 1,4-dihydro-6-nitro-4-thiono-1,3-quinazoline **7** (42%) was isolated after the purification of the crude product by column chromatography. The formation of the thionoquinazoline **7**, which could be easily optimized at higher temperature (50 °C, 80%), is explained by the attack of the aromatic amino group on the electrophilic carbon bearing the dimethyl amino substituent.

In order to evaluate the influence of the aminoaryl group on the behavior of *N*-thioacylamidine, we examined the same reaction sequence with the *N*-protected nitroanthranilonitrile precursors (Scheme 2).

The preparation of the *N*-methyl and *N*-benzyl nitroanthranilonitrile **8a** and **8b** was then performed in good yields (**8a**: 94% and **8b**: 75%) by reaction of 2-fluoro-5-



Scheme 2.

nitrobenzonitrile with primary amines such as methyl- and benzylamine, respectively. Following the same two-steps procedure, **8a–b** were converted to the corresponding *N*-thioacylamidines **10a–b** (H_2S, Py/Et_3N, then $(MeO)_2CHNMe_2$, CH_2Cl_2, rt 1 h) as shown in Scheme 2.

In these cases, the condensation of *N*,*N*-dimethylformamide dimethyl acetal proceeded efficiently and the desired 2-(2-alkylamino-5-nitro)phenylthioacylamidine **10a** and **10b** could be isolated in 90% and 82% overall yield from nitrile **8**, respectively. Diels–Alder reaction of **10a** and **10b** with dimethylacetylene dicarboxylate (1 equiv), in dichloromethane at room temperature, afforded the targeted 2-(2-alkylamino-5-nitro)phenylthiazines **11a** (89%) and **11b** (98%), respectively.[7] Treatment of the *N*-substituted aminophenylthiazines **11** by potassium *tert*-butoxide in THF was applied to initiate ring contraction of thiazines into pyrrole heterocycles.[8] The rearrangement of thiazines proceeded smoothly to afford the biscarboxymethyl pyrroles **12a** and **12b**, which on concomitant attack by aromatic amino group on the methyl ester, afforded pyrroloquinolinones **13a** and **13b**, in 70% and 98% yield, respectively.[9]

To summarize, we have designed a novel synthetic pathway for the synthesis of pyrrolodihydroquinolinones from aminophenylthiazine derivatives, which were easily derived from the nitroanthranilonitrile precursors. The most important advantage of this strategy lies in the fact that it is possible to introduce various substituents at almost every step during the synthesis. For example, substituted anthraniline derivatives or various dienophiles could be used. In addition, the presence of a nitro group would allow further derivatization of the final 4,5-dihydro-[4*H*]-pyrrolo[3,2-*c*]quinolin-4-ones. We have also opened a new route to access 4-thiono-1,3-quinazoline derivatives, which are good candidates for the synthesis of original alkaloid analogues.[10] The synthesis of pyrroloquinolinone and pyrroloquinoline based NCEs (New Chemical Entities) is underway in order to study the structure activity relationship (SAR).

Acknowledgements

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7. Compound **11a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.38 (6H, s, NMe_2); 3.05 (3H, d, $J = 5.1$ Hz, Me); 3.87 (3H, s, CO_2Me); 3.90 (3H, s, CO_2Me); 5.61 (1H, s, H-4); 6.71 (1H, d, $J = 9.3$ Hz, H_{arom}); 8.20 (1H, dd, $J = 9.3$ Hz, $J = 2.2$ Hz, H_{arom}); 8.76 (1H, d, $J = 2.2$ Hz, H_{arom}); 9.74 (1H, br s, NH). Compound **11b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.12 (6H, s, NMe_2); 3.84 (3H, s, CO_2Me); 3.88 (3H, s, CO_2Me); 4.51 (2H, d, $J = 5.0$ Hz, CH_2); 5.40 (1H, s, H-4); 6.75 (1H, d, $J = 9.4$ Hz, H_{arom}); 7.26–7.37 (5H, m, Ph); 8.17 (1H, dd, $J = 9.4$ Hz, $J = 2.3$ Hz, H_{arom}); 8.81 (1H, d, $J = 2.3$ Hz, H_{arom}); 10.03 (br s, 1H, NH).
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9. 2-dimethylamino-5-methyl-8-nitro-4-oxo-4,5-dihydro-1*H*-pyrrolo[3,2-*c*]quinoline-3-carboxylic acid methyl ester **13a**: ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 2.98 (6H, s, NMe_2); 3.64 (3H, s, Me); 3.68 (3H, s, CO_2Me); 7.67 (1H, d, $J = 9.3$ Hz, H_{arom}); 8.18 (1H, dd, $J = 9.3$ Hz, $J = 2.2$ Hz, H_{arom}); 9.28 (1H, d, $J = 2.2$ Hz, H_{arom}); 11.72 (1H, br s, NH); ^{13}C NMR (50.3 MHz, DMSO-d_6) δ ppm: 29.4 (Me); 41.5 (NMe_2); 51.4 (CO_2Me); 112.6, 115.9, 117.0, 126.9, 140.1, 141.2, 147.2 (C_{arom}, C_{pyrrol}); 157.0 (CO); 166.0 (CO_2Me); Elemental Anal. Calcd for $C_{16}H_{16}N_4O_5$: C, 55.81; H, 4.68; N, 16.27. Found: C, 55.56; H, 4.35; N, 16.49. 5-Benzyl-2-dimethylamino-8-nitro-4-oxo-4,5-dihydro-1*H*-pyrrolo[3,2-*c*]quinoline-3-carboxylic acid methyl ester **13b**: ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 3.00 (6H, s, NMe_2); 3.75 (3H, s, CO_2Me); 5.57 (2H, br s, CH_2); 7.11–7.30 (5H, m, Ph); 7.47 (1H, d, $J = 9.0$ Hz, H_{arom}); 8.05 (1H, dd, $J = 9.0$ Hz, $J = 2.5$ Hz, H_{arom}); 9.30 (1H, d, $J = 2.5$ Hz, H_{arom}); 11.80 (1H, br s, NH); ^{13}C NMR (50.3 MHz, DMSO-d_6) δ ppm: 42.4 (NMe_2); 45.74 (CH_2); 52.4 (CO_2Me); 95.0, 113.9,

114.0, 117.2, 118.2, 121.8, 127.1, 127.9, 128.2, 129.5, 137.8, 140.2, 142.2, 148.3 (C_{arom}, $C_{pyrrole}$, and C_{benzyl}); 158.0 (CO); 166.9 (CO_2Me). Elemental Anal. Calcd for $C_{22}H_{20}N_4O_5$: C, 62.85; H, 4.79; N, 13.33. Found: C, 62.72; H, 4.82; N, 12.98.

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