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Efficient synthesis of thiazoloquinazolinone derivatives

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Abstract—An original route to the rare 8*H*-thiazolo[5,4-*f*]quinazolin-9-one **1** and the novel 7*H*-thiazolo[4,5-*h*]quinazolin-6-one **2** is described. Access to the regioisomers was realized by fusion of a thiazole and a quinazoline ring via Appel's salt chemistry. Thermal reactions were carried out using a focused microwave reactor, reducing the overall time of the multi-step synthesis.

Present in many natural and synthetic products, the thiazole ring has generated interest of many groups on account of its interesting biological properties.[1,2] Thus, we recently published the synthesis of thiazoloheterocycles[3] mainly related to marine or terrestrial alkaloids (e.g. dercitine, kuanoniamine[1,2] and ellipticine[4]). Inspired by previous work describing the synthesis and the biological activity of a linear 7*H*-thiazolo[5,4-*g*]quinazolin-8-one,[5] we studied the preparation of the angular 8*H*-thiazolo[5,4-*f*]quinazolin-9-one ring **1**[6] via another route using Appel's salt[7] (4,5-dichloro-1,2,3-dithiazolium chloride) chemistry. Unfortunately, this pathway was not adapted for easy introduction of various substituents on the skeleton which was essential for its pharmaceutical evaluation. Thus, we decided to re-investigate the synthetic approach to the planar compound **1** and, in the same time, we performed the synthesis of its novel regio-isomer **2** (Fig. 1), with the aim to allow the presence of further substituents. In connection with our work on the application of microwaves in the preparation of bio-active molecules,[8] we have performed many of the reactions described in this paper using a focused microwave oven specifically designed for organic synthesis,[9] achieving short reaction times and clean reactions.

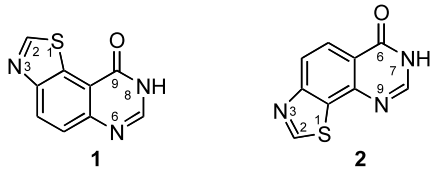

Figure 1. The 8*H*-thiazolo[5,4-*f*]quinazolin-9-one **1** and 7*H*-thiazolo[4,5-*h*]quinazolin-6-one **2**.

For the preparation of such compounds, two routes were possible. The first one was to create the thiazole ring before the quinazoline moiety, whilst the first step of the second pathway consisted of formation of the quinazoline ring. As may be predicted, the synthesis starting with the formation of the thiazole ring induced a low subsequent reactivity.

The first step of the chosen route involved preparation of 3*H*-nitroquinazolin-4-ones **3** via a traditional Niementowski condensation (Scheme 1).[10] This old reaction which consists of the fusion between anthranilic acid and formamide was recently re-investigated under microwave irradiation.[11] The quinazolin-4-ones rings were rapidly obtained and the reduction of the nitro group was realized using catalytic transfer hydrogenation in good yields. It was followed by condensation of the aromatic amines **4a**–**b** with 4,5-dichloro-1,2,3-dithiazolium chloride in order to obtain the intermediate imino-1,2,3-dithiazoles **5a**–**b**. The modest observed yields may be due to the presence of the deactivating 3*H*-quinazoline-4-one moiety. Cyclization (thermolysis in *N*-methylpyrrolidin-2-one (NMP)[3a]) of the imines **5a**–**b** into the corresponding thiazoles was unfructuous and gave the corresponding cyanoimidoyl chloride **6** or the starting amine **4b** for **5b**.

Keywords: thiazoloquinazolinones; quinazolines; 4,5-dichloro-1,2,3-dithiazolium chloride; microwave-assisted chemistry.

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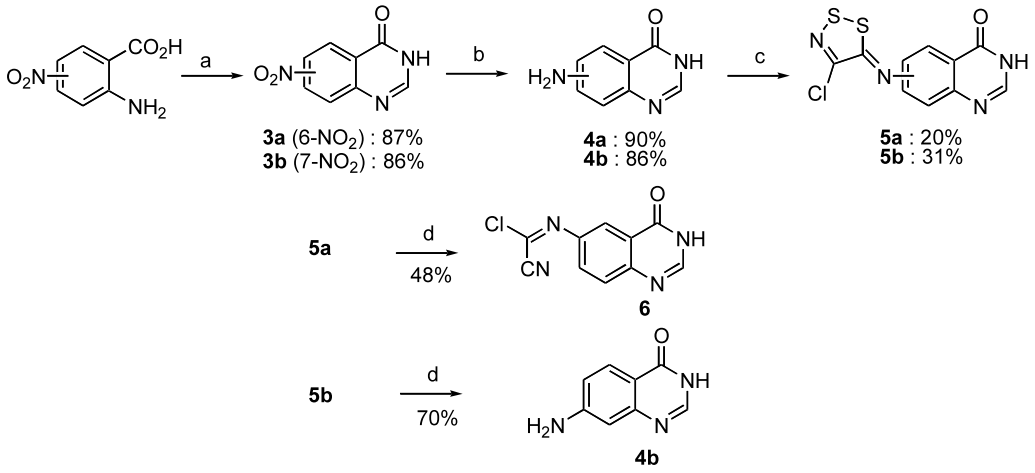
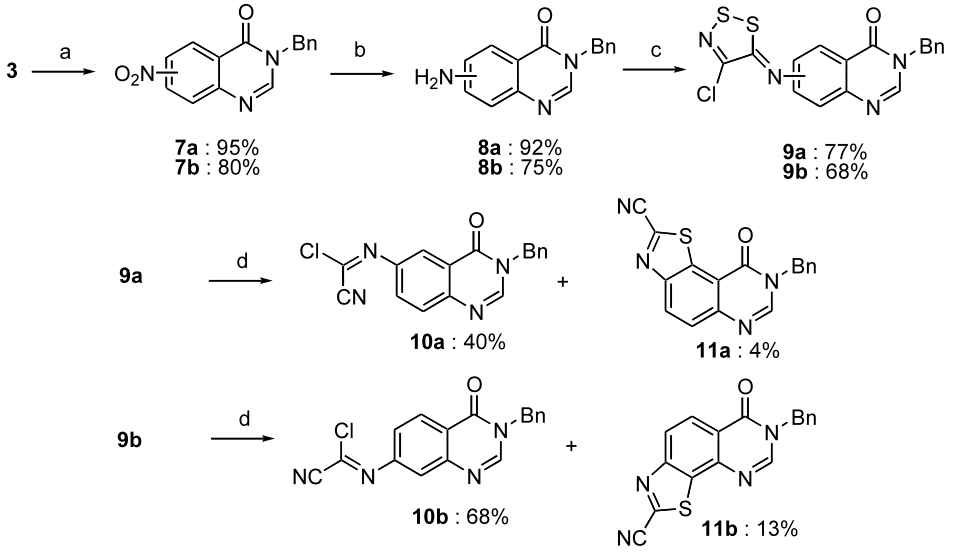


Scheme 1. *Reagents and conditions*: (a) formamide (5 equiv.), μW 150°C (P 60W), 40 min; (b) ammonium formate/Pd/C, MeOH, μW 65°C (P 60W), 10 min; (c) Appel's salt, pyridine, CH_2Cl_2, rt, 3 h; (d) NMP, μW 150°C (P 90W), 10 min.

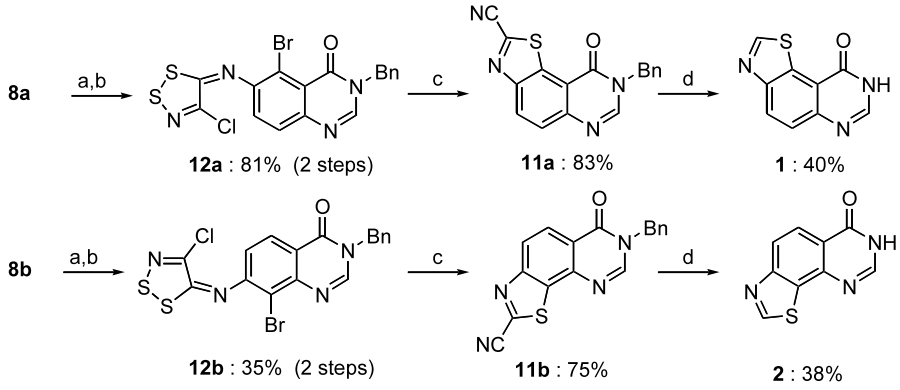
To circumvent the low yields of Appel's salt condensation, a second route starting by *N*-alkylation (benzyl group) of the nitrogen atom in position 3 of the quinazolin-4-one was investigated (Scheme 2). The protected compounds **7a**–**b** were obtained in good yields and introduced in the sequence of reactions described above. Then, reduction of the nitro group and condensation of the amine with Appel's salt gave the imino-intermediates **9a**–**b** in good yields. Again, thermolysis of the imines **9a**–**b** gave the corresponding cyanoimidoyle chlorides **10a**–**b** as major reaction products together with the desired benzothiazoles **11a**–**b** albeit in low yields.

An alternative access to the thiazole ring was then studied. Bromation of the two isomers **7a**–**b** and condensation with Appel's salt gave the iminobromoquinazolin-4-ones **12a**–**b** in quite good yields. Rapid heating in pyridine at reflux in the presence of cuprous iodide gave the expected rings **11a**–**b**.[6,8c] The resulting products possess a cyano group in position 2 (which is latent in the dithiazole ring[7]), offering many possibilities of introduction of various functions or rings. Access to the parent rings **1** and **2** were performed by heating the precursors **11a**–**b** in sulfuric acid, involving deprotection of the nitrogen group and decyanation (hydrolysis+decarboxylation) of the thiazole moiety (Scheme 3).[12]

The pharmaceutical interest of the 8*H*-thiazolo[5,4-*f*]-quinazolin-9-one skeleton **1** may be limited because of the lack of substituents, such as basic amino groups.[13] The interest of the multi-step (seven steps from the nitroanilines) synthesis described in this paper is to allow further modulations of the ring in various positions. In particular, *N*-alkylations of the nitrogene in position 8, and transformation of the cyano group present in the thiazole moiety may be studied in order to generate novel series of bio-active molecules.[14]



Scheme 2. *Reagents and conditions*: (a) BnBr, NaH, DMF, μW 70°C (P 60W), 15 min; (b) ammonium formate/Pd/C, EtOH, μW 65°C (P 60W), 10 min; (c) Appel's salt, pyridine, CH_2Cl_2, rt, 3 h; (d) *N*-methylpyrolidin-2-one, μW 150°C (P 90W), 10 min.



Scheme 3. *Reagents and conditions*: (a) Br_2, acetic acid, rt, 2 h; (b) Appel's salt, pyridine, CH_2Cl_2, rt, 3 h; (c) CuI, pyridine, μW 115°C (P 90W), 15 min; (d) conc. H_2SO_4, μW 130°C (P 80W), 15 min.

Among all the reactions performed, five were transposed with success to a focused microwave reactor. The short reaction times of these reactions (10–40 min) and the purity of the observed products compared to the purely thermal procedures allowed a quick realization of these multi-step synthesis.

In conclusion we have described a rapid and convenient multi-step access to the rare 8*H*-thiazolo[5,4-*f*]-quinazolin-9-one **1**, and, at the same time, we performed the synthesis of its novel regioisomer (7*H*-[1,3]thiazolo[4,5-*h*]quinazolin-6-one **2**) via Appel's salt chemistry. In this paper, we show the interest to combine drug discovery strategy with microwave heating allowing a rapid access to novel molecules with potential pharmacological value.

Acknowledgements

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9. Focused microwave irradiations were carried out at atmospheric pressure with a CEM *Discover*™ focused microwave reactor (300 W, monomode system) which has in situ magnetic stirrer, irradiation monitored by a PC computer, infrared measurement and continuous feedback temperature control. Equipment of the oven was completed by a condenser allowing conditions close to those involved in classical methods; it is also possible to work under dry atmosphere, in vacuo, or under pressure (0–20 bar) if necessary.
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12. Selected data for compound **11a–b**, **2**. 8-Benzyl-9-oxo-8,9-dihydrothiazolo[5,4-*f*]quinazoline-2-carbonitrile **11a**: pale yellow solid; mp (CH_2Cl_2) 190°C; IR (KBr) *v* 3064, 2230, 1665, 1588, 856, 729, 695 cm^{-1}; ^1H NMR ($CDCl_3$)

δ 5.34 (s, 2H), 7.39 (m, 5H), 8.00 (d, $J=8.8$ Hz, 1H), 8.36 (s, 1H), 8.54 (d, $J=8.8$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 50.2, 113.1, 116.3, 128.1, 128.2, 128.8, 129.3, 130.5, 132.4, 134.7, 140.2, 147.3, 148.8, 151.5, 159.4; MS (ESI, El$^+$) $m/z=319$ (MH^+); HRMS: calcd for $C_{17}H_{10}N_4OS$, 318.0575; found, 318.0566. 7-Benzyl-6-oxo-6,7-dihydrothiazolo[4,5-*h*]-quinazoline-2-carbonitrile **11b**: white solid; mp (CH_2Cl_2) 193°C; IR (KBr) ν 3078, 2235, 1688, 1600, 1455, 1369, 1350, 708 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.27 (s, 2H), 7.39 (m, 5H), 8.23 (d, $J=8.8$ Hz, 1H), 8.28 (s, 1H), 8.50 (d, $J=8.8$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 50.2, 112.6, 120.4, 123.4, 126.4, 128.2, 128.7, 129.2, 133.5, 135.0, 140.4, 144.2, 148.4, 156.0, 160.2; MS (ESI, El$^+$) $m/z=319$ (MH^+); HRMS: calcd for $C_{17}H_{10}N_4OS$, 318.0575; found, 318.0566. Thiazolo[4,5-*h*]quinazolin-6(7*H*)-one **2**: white solid, mp (EtOAc) >260°C; ^{1}H NMR (d_6-DMSO) δ 8.13 (d, $J=8.8$ Hz, 1H), 8.19 (d, $J=8.8$ Hz, 1H), 8.30 (s, 1H), 9.64 (s, 1H); ^{13}C NMR (d_6-DMSO) δ 118.9, 121.3, 123.8, 130.9, 145.1, 147.7, 156.7, 160.0, 160.8; MS (ESI, El$^+$) $m/z=204$ (MH^+); HRMS: calcd for $C_9H_5N_3OS$, 203.0153; found, 203.0145.

13. Preliminary evaluation for in vitro antiproliferative activity of the 8*H*-thiazolo[5,4-*f*]quinazolin-9-ones **1** was performed using the murine L1210 leukemia cell line as described in ref. cited below. The results have shown that the final product is considerably less active than its substituted precursors (described in Ref. 6). Léonce, S.; Pérez, V.; Casabianca-Pinède, M. R.; Anstett, M.; Bisagni, E.; Atassi, G. *Invest. New Drugs* **1996**, *14*, 169–180.
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