Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 45 (2004) 3097–3099

A rapid and convenient synthesis of novel 1-imino-2,3-dihydro-1*H*-pyrazino[2,1,-*b*]quinazolin-5-ones

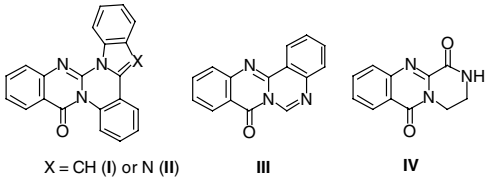
Maria de Fatima Pereira, François René Alexandre, Valérie Thiéry and Thierry Besson*

Laboratoire de Biotechnologie et Chimie Bioorganique, CNRS FRE-2766, UFR Sciences Fondamentales et Sciences pour l'Ingénieur, Bâtiment Marie Curie, Université de la Rochelle, F-17042 La Rochelle cedex 1, France

Received 14 January 2004; revised 17 February 2004; accepted 18 February 2004

Abstract—Exploring original approaches for the synthesis of therapeutic agents having a quinazoline part, we discovered that novel 3,4-dihydro-2*H*-pyrazino[2,1,-*b*]quinazolines (**3**) may be rapidly and easily obtained via the chemistry of 4,5-dichloro-1,2,3-dithiazolium chloride (**1**). Our synthetic approach of this reaction is described with the aim of obtaining a well-controlled access to this very rarely described pyrazino[2,1,-*b*]quinazoline skeleton.

The quinazoline skeleton, when selectively functionalized, is a building block for the preparation of numerous alkaloids and substances with pronounced biological activities.[1] The main activity of our group consists in the synthesis of heterocyclic structures with potential pharmaceutical value. Our molecular targets are inspired by natural marine (e.g., hinkdentine, dercitine and kuanoniamines) or terrestrial (e.g., rutaecarpine and luotonine) alkaloids for which interesting biological activity was detected. We recently described the synthesis of novel heterocycles in which the quinazoline ring is fused with indole (**I**), benzimidazole (**II**) or quinazoline rings (**III**) (Scheme 1)[2] and concentrated our work on the synthesis of 2,3-condensed (3*H*)-quinazolin-4-one derivatives (**IV** in Scheme 1), which can be employed as intermediates in the synthesis of expected bioactive compounds. Although a wide range of 2,3-condensed (3*H*)-quinazolin-4-ones occurs in different families of plants and micro-organisms, only a few papers describe the synthesis and the reactivity of such ring systems.[3]



Scheme 1.

Studying the chemistry of 4,5-dichloro-1,2,3-dithiazolium chloride[4] (**1**) and its derivatives,[5] we discovered that novel 3,4-dihydro-2*H*-pyrazino[2,1,-*b*]quinazolines may be rapidly and easily obtained from methyl *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-anthranilates, accompanied by the known 2,3-dihydro-1*H*-imidazo[2,1,-*b*]quinazolin-5-ones. In this paper, we describe our synthetic approach using this reaction with the aim of obtaining a well-controlled access to the very rarely described pyrazino[2,1,-*b*]quinazoline skeleton. Increasing the range of methyl anthranilate derivatives that condense with the salt **1**, we successfully varied the substituents on the aromatic moiety of the new polycyclic products.

It is now well known that reaction of 4,5-dichloro-1,2,3-dithiazolium chloride **1** with primary aromatic amines in dichloromethane at room temperature allows access to stable *N*-arylimino-4-chloro-5*H*-1,2,3-dithiazoles (e.g., **2**).[4] These compounds have proved to be highly versatile intermediates in heterocyclic synthesis, undergoing a variety of reactions initiated by inter- or intra-molecular nucleophilic attack at S-1, S-2 or C-5 of the dithiazole ring.[5]

Following the usual methods, treatment of methyl anthranilates with 4,5-dichloro-1,2,3-dithiazolium

Keywords: Quinazolin-4-ones; 4,5-dichloro-1,2,3-dithiazolium chloride; Pyrazino[2,1,-*b*]quinazolines; Imidazo[2,1,-*b*]quinazolin-5-ones; Anthranilate derivatives.
* Corresponding author. Tel.: +33-05-4645-8276; fax: +33-05-4645-8247; e-mail: tbesson@univ-lr.fr

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.02.095

chloride **1** in dichloromethane at room temperature gave the corresponding methyl *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-anthranilates **2a–d** in quantitative yield. Stirring of a solution of these imines and ethylenediamine at room temperature in tetrahydrofuran, gave a mixture of two compounds, which could be easily separated by column chromatography and isolated in reasonable yields. The products then obtained were identified as the novel 1-imino-2,3-dihydro-1*H*-pyrazino[2,1,-*b*]quinazolin-5-ones (**3**) (only one example of a similar heterocyclic skeleton was given in literature from isatoic anhydride via a 2-chloroformyl-4*H*-3,1-benzoxazin-4-one[6]) accompanied by a small amount of the known 2,3-dihydro-1*H*-imidazo[2,1,-*b*]quinazolin-5-one (**4**) derivatives[7] (see Table 1).

A possible mechanism for the reaction is shown in Scheme 2. Opening of the dithiazole ring by the aliphatic amine is presumably initiated by attack at C-5 and generation of the cyano group, which is latent in the iminodithiazole ring (e.g., **5**). The following intramolecular cyclization by nucleophilic attack of the secondary amino group to the ester carbonyl carbon would give the intermediate N-substituted quinazolines (e.g., **6**).[10] In a second step, the formation of the imidazopyrazine ring on the quinazoline skeleton would occur by final nucleophilic attack of the primary amino group on the carbonitrile carbon to generate the cyclic amidines **3**, whilst the nucleophilic substitution of the cyano group leads to the five-membered derivatives **4**.

Table 1. Synthesis of **3** and **4** from anthranilic esters.[a,8,9]

Starting ester (R)	Diamine equiv	Yield of **2** (%)	Yield of **3** (%)	Yield of **4** (%)
a (H)	1	98	54	8[b]
a (H)	3	—	56	18
b (5-Br)	1	98	74	17[b,c]
b (5-Br)	3	—	4	28
c (4-Cl)	1	71	61	22
c (4-Cl)	3	—	8	57
d (4,5-diOMe)	1	99	—	—
d (4,5-diOMe)	3	—	62	—

[a] Conditions and reagents: ethylene diamine (1 or 3 equiv), tetrahydrofurane (THF), rt.

[b] The same reaction (same quantities of reactants and solvent) was performed at 0 or −20 °C. The yields obtained are similar to those observed at room temperature.

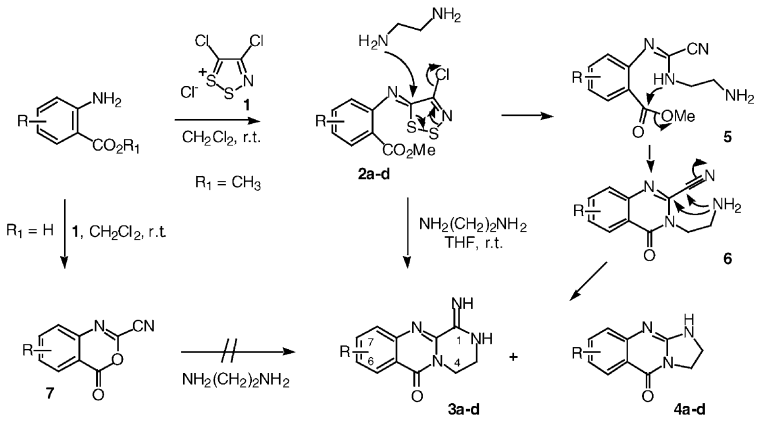
[c] Under these conditions (1 equiv of diamine), heating at reflux (oil bath or microwaves) caused a decrease in the amount of **3b** (40%) in favour of **4b** (41%).

Studying various experimental conditions we varied the amount of the diamine (1 or 3 equiv). The results show that a large quantity of ethylenediamine is favourable to the imidazoquinazolines **4a–c**, reducing considerably the amount of isolated six-membered pyrazino[2,1,-*b*]-quinazolines (**3a–c**) (Table 1). Surprisingly, methyl 4,5-dimethoxyanthranilate gave the expected product **3d** only in the presence of 3 equiv of the diamine (see Table 1), in contrast to other anthranilates. Whichever method was used (1 or 3 equiv of diamine, heating or not) no trace of the five-membered product **4d** was detected.

Exploring possible alternative routes to this rarely described ring, we tried to condense ethylene diamine with a 2-cyano-4*H*-3,1-benzoxazin-4-one **7**, itself obtain by condensation of anthranilic acid $R_1 = H$ in Scheme 1 with salt **1**, in the presence of a base.[11] In this case, and whatever condition were experimented, no trace of the expected pyrazino[2,1,-*b*]quinazoline **3a** was detected.

In connection with our work on the utility of microwaves in organic synthesis, we also decided to investigate the microwave-assisted heating of the reaction mixture. Conventional heating was experimented under the same conditions of reactants. Whichever method was used, the cyclized products were obtained in lower yield than at room temperature. Here again the main products were the five-membered derivatives (**4**) and, curiously, in the case of compound **2a**, starting methyl-anthranilate was recovered in modest yield (less than 10%), showing a possible hydrolysis of the intermediate imino-1,2,3-dithiazoles **2a**.

Hydrochloric acid hydrolysis (refluxing HCl for 2 h or more) of the novel 1-imino-2,3-dihydro-1*H*-pyrazino[2,1,-*b*]quinazolin-5-ones **3a** and **3b** was also experimented. Unfortunately, no trace of the corresponding amides was detected and the starting material was completely recovered.



Scheme 2. Suggested mechanism and alternative route for the generation of **3** and **4**.

In conclusion, we describe here the rapid synthesis of novel 1-imino-2,3-dihydro-1*H*-pyrazino[2,1,-*b*]quinazolin-5-ones (**3**) via the intermediate methyl *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-anthranilates (**2**). This work is a further example of the applicability of 4,5-dichloro-1,2,3-dithiazolium chloride (Appel's salt) in the preparation to novel polyheterocyclic systems. The high solubility of such compounds and their chemical stability open the door to promising pharmaceutical applications. Investigations are currently under way and will be published later.

Acknowledgements

We thank the Comité de Charente-Maritime de la Ligue Nationale contre le Cancer for financial support.

References and notes

1. (a) Johne, S. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Tamm, Ch., Eds.; Spinger, Wien, 1984; p 159–229 (b) Johne, S. In *The Alkaloids, Chemistry and Pharmacology*; Brossi, A., Ed.; Academic: New York, 1986; Vol. 29, pp 99–140.
2. (a) Alexandre, F.-R.; Berecibar, A.; Wrigglesworth, R.; Besson, T. *Tetrahedron* **2003**, *59*, 1413–1419; (b) Domon, L.; Le Coeur, C.; Grelard, A.; Thiéry, V.; Besson, T. *Tetrahedron Lett.* **2001**, *42*, 6671–6674; (c) Soukri, M.; Guillaumet, G.; Besson, T.; Aziane, D.; Aadil, M.; Essassi, El M.; Akssira, M. *Tetrahedron Lett.* **2000**, *41*, 5857–5860; (d) Frère, S.; Thiéry, V.; Bailly, C.; Besson, T. *Tetrahedron* **2003**, *59*, 773–779.
3. (a) Armarego, W. L. F. *Adv. Heterocycl. Chem.* **1979**, *24*, 1–62; (b) *Comprehensive Heterocyclic Chemistry II*; Katrizky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1996.
4. Appel, R.; Janssen, H.; Siray, M.; Knoch, F. *Chem. Ber.* **1985**, *118*, 1632–1643.
5. For reviews on the chemistry of Appel's salt derivatives see: (a) Kim, K. *Sulfur Reports* **1998**, *21*, 147–207; (b) Rees, C. W. *J. Heterocycl. Chem.* **1992**, *29*, 639–651.
6. Motohiro, T.; Motome, H. *Heterocycles* **1984**, *21*, 706, This paper (only one page) is an abstract of a congress, there is no description of the physical data of the compound cited.
7. (a) Dean, W. D.; Papadopoulos, E. P. *J. Heterocycl. Chem.* **1982**, 1117–1124; (b) Jen, T.; Dienel, B.; Bowman, H.; Helt, A.; Loev, B. *J. Med. Chem.* **1972**, *15*, 727–731.
8. Typical procedure for the synthesis of 1-imino-2,3-dihydro-1*H*-pyrazino[2,1,-*b*]quinazoline-5-ones **4** (1-imino-1,2,3,4-tetrahydro-2,4a,9-triaza-anthracen-10-ones): A solution of ethylene diamine (0.083 g, 1.38 mmol) in tetrahydrofuran (10 mL) was added slowly to a solution of *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-yliden)-methyl-5-bromobenzoate (0.504 g, 1.38 mmol) in tetrahydrofuran (10 mL). The mixture was stirred under argon at room temperature, for 2 h. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (dichloromethane/methanol, 95:5) to furnish **3** and **4** as colourless solids.
9. All compounds were fully characterized by spectroscopic and elemental analysis. Spectral data for compounds **2** and **4** are consistent with structures published (in Ref. 5 and references cited for **2** and Ref. 7 for **4a**,**c** and **8**).
Selected data for new compounds **3a**–**d** and **4b** (R = Br).
1-Imino-1,2,3,4-tetrahydro-2,4a,9-triaza-anthracen-10-one (**3a**), white solid; mp 208 °C; IR (KBr) ν 3474, 3098, 2332, 2060, 1734, 1669, 1602, 1293, 1174, 783 cm^{-1}; ^{1}H NMR (d_6-DMSO+D_2O) δ 8.18 (dd, $J = 8.0$ Hz and $J = 2.0$ Hz, 1H), 7.88 (td, $J = 8.0$ Hz and $J = 2.0$ Hz, 1H), 7.77 (d, $J = 8.0$ Hz, 1H), 7.62 (td, $J = 8.0$ Hz and $J = 2.0$ Hz, 1H), 4.03 (t, $J = 6.0$ Hz, 2H), 3.61 (t, $J = 6.0$ Hz, 2H); ^{13}C NMR (d_6-DMSO+D_2O) δ 159.57, 152.00, 145.65, 139.98, 134.79, 129.71, 128.34, 127.82, 126.25, 121.42, 41.12; MS (EI) $m/z = 214$ (M^+); HRMS: calcd for $C_{11}H_{10}N_{14}O$, 214.0855; found, 214.0852.
6-Bromo-1-imino-1,2,3,4-tetrahydro-2,4a,9-triaza-anthracen-10-one (**3b**), white solid; mp>260 °C decomp.; IR (KBr) ν 3438, 3076, 2950, 1684, 1594, 1470, 828 cm^{-1}; ^{1}H NMR (d_6-DMSO+D_2O) δ 8.26 (d, $J = 1.6$ Hz, 1H), 8.03 (dd, $J = 8.8$ Hz and $J = 1.6$ Hz, 1H), 7.74 (d, $J = 8.8$ Hz, 1H), 4.03 (t, $J = 6.4$ Hz, 2H), 3.62–3.56 (m, 2H); ^{13}C NMR (d_6-DMSO+D_2O) δ 158.61, 151.08, 144.92, 140.66, 137.34, 129.98, 128.94, 122.94, 120.19, 42.54, 38.48; MS (EI) $m/z = 292$ (M^+); HRMS: calcd for $C_{11}H_9N_{14}OBr$, 291.9956; found, 291.9969.
7-Chloro-1-imino-1,2,3,4-tetrahydro-2,4a,9-triaza-anthracen-10-one (**3c**), white solid; mp 188 °C (dec); IR (KBr) ν 3472, 3093, 1678, 1586, 1366, 782 cm^{-1}; ^{1}H NMR (d_6-DMSO+D_2O) δ 8.14 (d, $J = 8.8$ Hz, 1H), 7.60 (dd, $J = 8.8$ Hz and $J = 2.0$ Hz, 1H), 7.80 (d, $J = 2.0$ Hz, 1H), 3.97 (t, $J = 6.4$ Hz, 2H), 3.55 (t, $J = 6.4$ Hz, 2H); ^{13}C NMR (d_6-DMSO+D_2O) δ 159.80, 151.78, 147.67, 141.86, 139.71, 128.85, 128.65, 127.33, 120.78, 42.82, 38.94; MS (EI) $m/z = 248$ (M^+); HRMS: calcd for $C_{11}H_9N_{14}OCl$, 248.0465; found, 248.0449.
6,7-Dimethoxy-1-imino-1,2,3,4-tetrahydro-2,4a,9-triaza-anthracen-10-one (**3d**), white solid; mp>260 °C; IR (KBr) ν 3440, 3008, 2960, 2832, 1740, 1643, 1354, 1002, 782, 603 cm^{-1}; ^{1}H NMR (d_6-DMSO+D_2O) δ 7.48 (s, 1H), 7.23 (s, 1H), 4.10 (t, $J = 6.0$ Hz, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 3.65–3.60 (m, 2H); ^{13}C NMR (d_6-DMSO+D_2O) δ 158.62, 154.78, 152.30, 150.00, 141.62, 138.66, 115.05, 108.35, 105.46, 56.03, 55.93, 41.05, 38.29; MS (EI) $m/z = 274$ (M^+); HRMS: calcd for $C_{13}H_{14}N_{14}O_3$, 274.1066; found, 274.1074.
7-Bromo-2,3-dihydro-1*H*-imidazo[2,1-*b*]quinazolin-5one (**4b**), white solide; mp>260 °C ; IR (KBr) ν 3046, 2884, 1706, 1654, 1469, 1278, 822, 674 cm^{-1}; ^{1}H NMR (d_6-DMSO+D_2O) δ 7.97 (d, $J = 2.4$ Hz, 1H), 7.66 (dd, $J = 8.8$ Hz and $J = 2.4$ Hz, 1H), 7.18 (d, $J = 8.8$ Hz, 1H), 4.12 (t, $J = 8.8$ Hz, 2H), 3.64 (t, $J = 8.8$ Hz, 2H); ^{13}C NMR (d_6-DMSO+D_2O) δ 158.98, 154.90, 150.31, 136.41, 127.64, 126.57, 118.82, 113.01, 12.21; MS (EI) $m/z = 265$ (M^+); HRMS: calcd for $C_{10}H_8N_3OBr$, 264.9851; found, 264.9853.
10. Opening of the dithiazole ring by aliphatic amines has also been described by Kim and co-workers to be synthetically useful for the synthesis of 3-alkyl-2-cyanoquinazolin-4-ones Lee, H. S.; Chang, Y.-G.; Kim, K. *J. Heterocycl. Chem.* **1998**, *35*, 659–668, In our group the same quinazoline ring was also isolated after nucleophilic attack of alkylated and aromatic polyamines: Pereira, M. de F. unpublished results.
11. Besson, T.; Kumaraswamy, E.; Rees, C. W. *J. Chem. Soc., Perkin. Trans. 1* **1995**, 2097–2102.