Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 7657–7659

Microwave-assisted regioselective N-alkylation of cyclic amidines

Maria de Fatima Pereira, Valérie Thiéry and Thierry Besson*

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

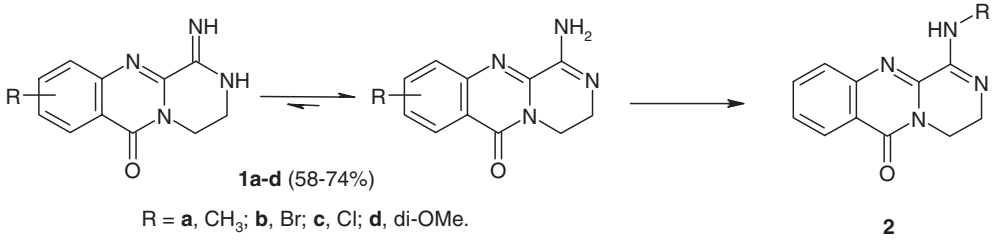
Received 27 June 2007; revised 1 August 2007; accepted 28 August 2007
Available online 31 August 2007

Abstract—A simple and efficient methodology for regioselective alkylation of exocyclic nitrogen of cyclic amidines was developed by microwave-assisted heating in the presence of amines. Novel N-alkylated 3,4-dihydropyrazino[2,1-*b*]quinazolin-6-ones were prepared in good yields. The reaction occurred via a transamination (addition–elimination) process involving a first attack of the amine on the electrophilic carbon of the amidine function.

The occurrence of the cyclic amidine function in various natural and synthetic products has generated interest of many research groups in medicinal chemistry because of their useful biological properties.[1–3] As a part of our ongoing research program dealing with the preparation and pharmacological evaluation of some original quinazoline derivatives, we unambiguously established the 3D structure of novel 3,4-dihydropyrazino[2,1-*b*]quinazolin-6-ones (**1a**–**d** in Scheme 1) and we confirmed their amidine isomerization in the solid state by X-ray crystallography.[4,5]

Recent biological screening of these novel molecules suggested that it might possess significant antimicrobial activity.[6] Considering these results, we focused our efforts on the synthesis of various N-substituted amidines (e.g., **2** in Scheme 1) in which the substituent will be present specifically on the exogenic nitrogen atom. The recent results of Bourguignon and his co-workers[3] on the synthesis of amidines trust us to publish this preliminary work in which we describe a rapid and simple method for the preparation of N-alkylated cyclic amidines via a mechanism of transamination. This work is connected to our study on the development of environmentally convenient microwave-assisted methods in organic and medicinal chemistry.

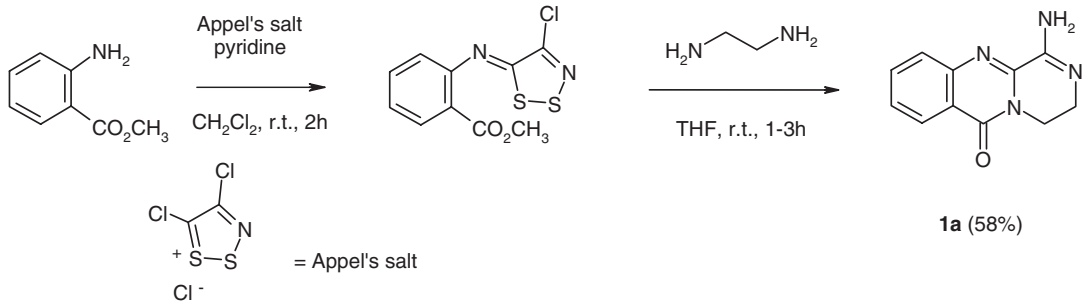
The synthesis of 2,3-condensed (3*H*)-quinazolin-4-one precursor **1a** was performed from methyl *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-anthranilate itself obtained by condensation of 4,5-dichloro-1,2,3-dithiazolium chloride (Appel's salt[7]) and methyl anthranilate (Scheme 2). Stirring of a solution of the intermediate imine and ethylenediamine at room temperature in tetrahydrofuran, for 1 or 2 h, gave a 58% yield of 1-amino-3,4-dihydropyrazino[2,1-*b*]quinazolin-6-one **1a** (Scheme 2).



Scheme 1.

Keywords: Cyclic amidines; Regioselective N-alkylation; Microwave heating.
* Corresponding author at present address: UMR CNRS 6014, Laboratoire de Chimie Pharmaceutique, UFR Médecine-Pharmacie, Université de Rouen, 22 Boulevard Gambetta, 76183 Rouen cedex 1, France. Tel.: +33 0235148399; fax: +33 0235148423; e-mail: thierry.besson@univ-rouen.fr

0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2007.08.100



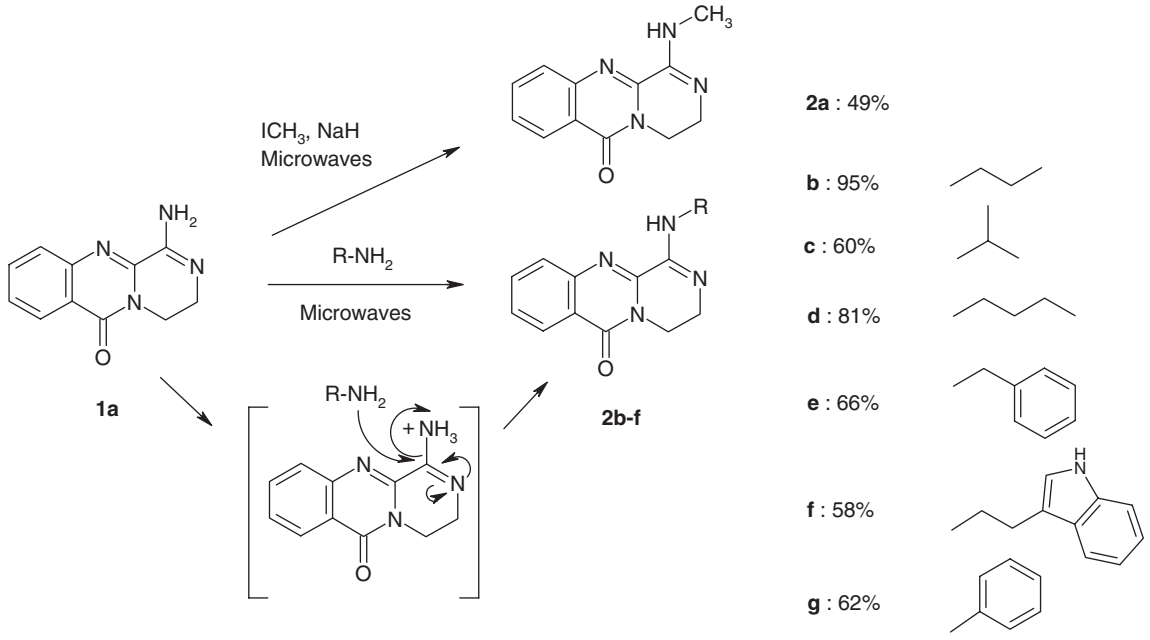
Scheme 2. Synthesis of **1a** from methyl anthranilate.

The second step of the synthesis is an alkylation of the heterocyclic amidine present on the studied molecule. The usual methods for alkylation of this 1,3-dinucleophile usually afforded mixtures of both the N-endosubstituted and the N-exosubstituted products.[8,9] For example, microwave heating of **1a** with methyl iodide in THF in the presence of sodium hydride gave a mixture of N-endo (6%) and N-exomethylated 3,4-dihydropyrazino[2,1-*b*]quinazolin-6-one **2a** (49%). Our method consists in microwave heating[10] of a mixture of **1a** and aliphatic amines in tetrahydrofuran (THF), in the presence of 1.1 equiv of *para*-toluenesulfonic acid (PTSA), in a sealed tube. The expected N-alkylated 3,4-dihydropyrazino[2,1-*b*]quinazolin-6-ones (**2**) were obtained in good yields. The suggested mechanism of this reaction is a transamination (addition–elimination) process in which the primary amine will first attack the carbon of the amidine function, and then, eliminate ammonia (Scheme 3).

In order to confirm the utility of microwave-assisted heating in this reaction, a traditional heating (oil bath) of **1a** and propylamine was realized under similar conditions (temperature, quantities and sealed tube). Only 58% of the attempted product (**2b**) were isolated after 30 h of experiment.

Applying the conditions described above to an aromatic amine (e.g., aniline in Scheme 3) led to different results. The low nucleophilicity of the amine can explain that the synthesis of the expected product needed a more intense heating (220 °C) of the starting reactants in the presence of *N*-methylpyrrolidinone (NMP), a solvent which is particularly well adapted for microwave experiments (Scheme 3).

In conclusion, we developed a simple and efficient methodology for regioselective alkylation of exocyclic nitrogen of cyclic amidines via a transamination process. These results confirm that microwave-assisted heating is helped by the capacity of reactants to heat under the microwave field. This phenomenon was combined with pressure to allow very short reaction times and clean conditions for work-up (no by-products).



Scheme 3. Reagents and conditions: THF, MW, reflux, 20 min (for **2a**); PTSA (1.1 equiv), THF, MW, 150 °C, 5 min (for **2b–f**); NMP, MW, 220 °C, 15 min (for **2f**).

Acknowledgments

We thank the *Comités de Charente* (16) and *Charente-Maritime* (17) *de la Ligue Nationale contre le cancer* for financial support and for a PhD grant (M.-F.P.). This work is also supported by the *Canceropôle Grand-Ouest* program 'Modulators of apoptosis'. We also thank Biotage for multiform support on microwave experiments.

References and notes

1. Simone, M.; Erba, E.; Damia, G.; Vikhanskaya, F.; Di Francesco, A. M.; Riccardi, R.; Bailly, C.; Cuevas, C.; Fernandez Souza-Faro, J. M.; D'Incalci, M. *Eur. J. Cancer* **2005**, *41*, 2366–2377.
2. Mizuno, T.; Iwai, T.; Ishino, Y. *Tetrahedron Lett.* **2004**, *45*, 7073–7075.
3. Hellal, M.; Bihel, F.; Mongeot, A.; Bourguigon, J.-J. *Org. Biomol. Chem.* **2006**, *4*, 3142–3146.
4. Pereira, M.-F.; Alexandre, F. R.; Thiéry, V.; Besson, T. *Tetrahedron Lett.* **2004**, *45*, 3097–3099.
5. Pereira, M.-F.; Picot, L.; Guillon, J.; Léger, J.-M.; Jarry, C.; Thiéry, V.; Besson, T. *Tetrahedron Lett.* **2005**, *46*, 3445–3447.
6. Pereira, M.-F., PhD thesis, Université de La Rochelle, France, 2006.
7. (a) Appel, R.; Janssen, H.; Siray, M.; Knoch, F. *Chem. Ber.* **1985**, *118*, 1632–1643; For a review on the chemistry of Appel's salt derivatives see: (b) Kim, K. *Sulfur Reports* **1998**, *21*, 147–207.
8. Abarghaz, M.; Kerbal, A.; Bourguignon, J.-J. *Tetrahedron Lett.* **1995**, *36*, 6463–6466.
9. Fossey, J.; Loupy, A.; Strezelecka, H. *Tetrahedron* **1981**, *37*, 1935–1941.
10. Focused microwave irradiations were carried out with a Smith-Synthetizer™ (personal chemistry, AB) focused microwave reactor (300 W, 2450 MHz, monomode system). The Smith-Synthetizer™ (personal chemistry, AB) is a single mode cavity, producing controlled irradiation at 2450 MHz. Reaction temperature and pressure were determined using the built-in, on-line IR, and pressure sensors. Microwave-assisted reactions were performed in sealed Smith process vials (0.5–5 mL, total volume 10 mL) under air with magnetic stirring. The microwave output power was regulated by the software algorithm so that the selected maximum temperature was maintained for the desired reaction/irradiation time. After the irradiation period, the reaction vessel was cooled rapidly to ambient temperature by compressed air (gas-jet cooling). The minimal reaction times were determined by performing sequential series of identical reactions at constant temperature and with continuous heating, but with different irradiation times. Completion of the reaction was estimated by T.L.C. after each individual heating period.). Technical description of this microwave reactor with integrated robotics was recently published: Schanche, J. S. *Mol. Diversity* **2003**, *7*, 293–300.