Synthesis and characterization of new cyano-quinazolines poly-functionalized

Tarak Saïed, Nourchaine Jelaiel, Mohamed Lotfi Efrit*

Université de Tunis El Manar
Laboratoire de Synthèse Organique et Hétérocyclique, Département de Chimie
Faculté des Sciences de Tunis, 2092-Tunis-Tunisie

(Received: 19 February 2016, accepted: 03 June 2016)

Abstract: Fonctionalized N-aryliminoesters are obtained from the conversion of different aromatic amines by action on orthoesters. The closing cycle or cyclisation of latter is developed by nucleophile attack through one of the two electrophile centre of the iminoesters followed by a second intermolecular development of binucleophile which is the cyanamid. A scale of generated products is functionalized cyano-quinazolines.

Keywords: aromatic amines, N-aryliminoesters, cyanamide, cyano-quinazoline.

INTRODUCTION

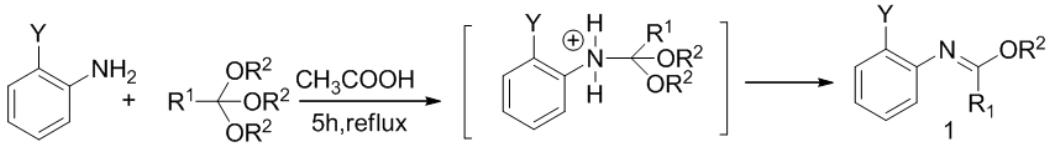
The heterocycles form the structural units of several ligands, cryptants or pharmacophores. Among many families of biologically active molecules, the condensed aromatic bicycles like the quinazolines are more and more frequently found. In this general context, these molecules have drawn our attention. Quinazolines are the essential moities inseveral compounds of pharmacological interest having biological activity. Numerous publications state the pharmological potential of some quinazoline derivatives. Indeed, the quinazolines are used as anti-inflammatory [3,4], anti-depressants [5], anti-microbial [6], anti-tumeroles [7]. Pua and all. have recently unveiled an anti-arthritis [8] of a new qunazolinial derivatives by inhibiting the production of the enzyme TNF-α.

Various methods of the quinazoline synthesis are descrided in literature [9]. Nevertheless, these methods show a drawback either by using catalysts [10] and costly products [11], multi steps [12-14]. So, we've undertaken a new, simple and concise way allowing us to get access to quinazolines with outcomes superior or equal to those described in literature using less expensive products.

RESULTS AND DISCUSSION

To have access to compounds **1**, we resort to the action of cyanamid on functionalized ortho-N-aryliminoesters by electrophile groups like ketones, ester or nitrile functions. The latter has been made ready by adopting the procedure describded by Claisen [15-16].

In order to reduce the number of synthesis and purification stepsto ensure a fast and effective access to targeted quinazolines, we have imagined a sequence "one-pot", in which the intermediaries wouldn't be isolated, leading directly to the expected closing cycle. Compiled with the anticipated strategy the N-aryliminoester previously synthetized (**1a-f**) are set the reflux of ethanol with some drop of acitic acid as catalyst thus leading to forming the expected products. Once the



Scheme 1 : Synthesis of functionalized N-aryliminoesters.

* Corresponding author, e-mail address : medlotfi.efrit@gmail.com
tarak.saied@gmail.com ; nourchaine.jelaiel@gmail.com

Table I : Functionalized N-aryliminoesters yield.

Entry	Iminoester	Y	R^1	R^2	Yield(%)
1	1a	CO_2Et	Me	Et	84
2	1b	CO_2Et	Et	Me	92
3	1c	CN	Me	Et	85
4	1d	CN	Et	Me	89
5	1[e]	ClPh(CO)	Me	Et	91
6	1f	ClPh(CO)	Et	Me	93

solvent is evaporated, the product is precipitated in the ether petroleum and washed with diethyl ether.
The sequence that we developed is carried out in one-pot and the different synthesis intermediaries are not isolated and character-rized. Nevertheless, the next mechanism may be reasonably moved forward in the formation of quinazolines (**2a-d**) this away calls out first the attack of the amine on the iminoester (**1a-d**), leading to the formation of the intermediary.
The cyclocondensation intervenes to generate an imine or amide which are converted to the corresponding of quinazolines (**2a-d**). (Scheme 2).
Particularly, we have noticed the use of imino-esters (**1e-f**) as basic substratum while taking up the same synthesis strategy previously described which has allowed us to separate the following quinazoline (**2e-f**). The latter has a specific detail to compire an asymmetrical carbon.

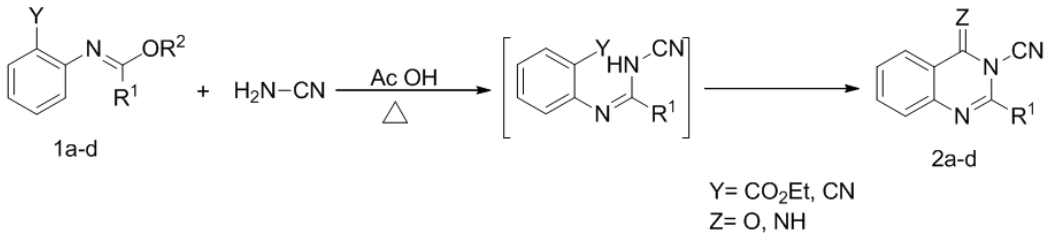
Table II: Quinazolines yields.

Entry	Quinazoline	R^1	R^2	Yield (%)
1	2a	Me	Et	67
2	2b	Et	Me	65
3	2c	Me	Et	59
4	2d	Et	Me	60
5	2e	Me	Et	70
6	2f	Et	Me	66

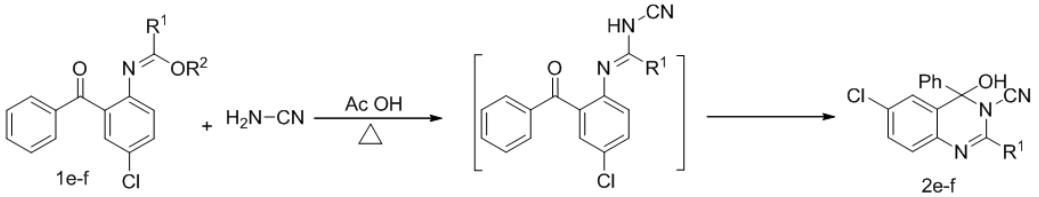
EXPERIMENTAL SECTION

*General procedure for the synthesis of iminoesters(**1a-f**)*

To a solution of selected arylamine (30 mmol, 1.0 equiv.) and appropriate orthoester (50.0mmol, 1.7 equiv.) were added few drops of acetic acid.



Scheme 2 : 4-imino-2-methylquinazoline-3(4H)-carbonitrile



Scheme 3: 6-chloro-4-hydroxy-2-alkyl-4-phenylquinazoline-3(4H)-carbonitrile.

The resulting mixture was then stirred at reflux for 5h. Reaction was monitored by TLC (Ethyl acetate/ cyclohexane 1/9). Purification by reduced pressure distillation (0.1 mmHg) afforded the expected compounds as oils.

*Ethyl N-(2-carbethoxyphenyl)acetimidate(**1a**).*

Yield **84%**.$Eb_{(0,1mmHg)}$ 113°C;^{1}H NMR δ_H(300 MHz, $CDCl_3$)1.27 (t, 3H, $^3J_{HH}$ = 6.0 Hz, $\underline{CH_3}$-CH_2-C=O) 1.34 (t, 3H, $^3J_{HH}$ = 9.0, $\underline{CH_3}CH_2$), 3.72 (q, 2H,$^3J_{HH}$ = 9.0 Hz, CH_2), 4.24 (q ,2H, $^3J_{HH}$ = 9.0 Hz, CH_2); 6.76 (d, 1H, $^3J_{HH}$ = 7Hz, H_{arom}), 7.04 (t, 1H, $^3J_{HH}$ = 7Hz, H_{arom}), 7.39 (t, 1H, $^3J_{HH}$ = 7Hz, H_{arom}), 7.89 (d, 1H, $^3J_{HH}$ = 7Hz, H_{arom}) ;^{13}C NMR δ_C(75.3 MHz, $CDCl_3$)14.2, 15.2, 16.7, 18.3, 57.3, 60.5, 121.9, 122.6, 131.1, 132.8, 150.1, 160.6, 166.6.

*Methyl N-(2-carbethoxyphenyl)propionimidate(**1b**).*

Yield **92%**.$Eb_{(0,1mmHg)}$ 123°C;^{1}H NMR δ_H(300 MHz, $CDCl_3$) 1.02 (q,3H,$^3J_{HH}$ = 6.0 Hz, $\underline{CH_3}$-CH_2-C=N), 1.30 (t,3H, $^3J_{HH}$ = 9.0 Hz, $\underline{CH_3}CH_2O$), 2.05-2.11 (m,2H, $\underline{CH_2}CH_3$), 3.81 (s, 3H, CH_3O), 4.22-4.37 (m, 2H, CH_2O), 6.54–7.90 (m, 4H, H_{arom});^{13}C NMR δ_C(75.3 MHz, $CDCl_3$) 10.1, 14.1, 23.8, 53.2, 60.3, 115.8, 124.3, 127.1, 127.8, 133.6, 134.1, 144.2, 166.3, 168.0.

*Ethyl N-(2-cyanophenyl)ethanimidate (**1c**).*

Yield 85%.$Eb_{(0,1mmHg)}$ 137°C;^{1}H NMR δ_H(300 MHz, $CDCl_3$) 1.26-1.32 (m, 3H, $\underline{CH_3}CH_2O$), 1.78 (s, 3H, $\underline{CH_3}$-C=N), 4.22-4.29 (m, 2H, $\underline{CH_2}$-O), 6.78 -7.50 (m, 4H, H_{arom}); ^{13}C NMR δ_C(75.3 MHz, $CDCl_3$) 13.9, 20.0, 62.2, 105.0, 117.3, 121.7, 123.0, 132.6, 133.1, 152.4, 162.4.

*Methyl N-(2-cyanophenyl)propionimidate (**1d**).*

Yield **89%**.$Eb_{(0,1mmHg)}$ 145°C;^{1}H NMR δ_H(300 MHz, $CDCl_3$) 1.10 (t, 3H, $^3J_{HH}$ = 7.0 Hz, $\underline{CH_3}CH_2$), 2.17 (q, 2H, $^3J_{HH}$ = 7.0 Hz, CH_2), 3.82 (s, 3H, CH_3O), 6.84–7.57 (m, 4H, H_{arom});^{13}C NMR δ_C (75.3 MHz, $CDCl_3$) 10.2, 23.1, 53.2, 104.9, 110.6, 115.9, 122.6, 133.7, 150.6, 163.7, 166.5, 167.9.

*Ethyl N-(2-benzoyl-4-chlorophenyl)acetimidate (**1e**).*

Yield **86%**.$Eb_{(0,1mmHg)}$ 200°C; ^{1}H NMR : δ = 1,01 (t, $^3J_{HH}$ = 9,0 Hz, 3H, $\underline{CH_3}$-CH_2-O); δ = 1,74 (s, 3H, $\underline{CH_3}$-C=N); δ = 3,66 (q, 2H, $^3J_{HH}$ = 9,0 Hz, CH_3-$\underline{CH_2}$-O); δ = 6,73 - 7,56 (m, 8H, H_{arom}));^{13}C NMR δ_C (75.3 MHz, $CDCl_3$) 10.17, 23.8, 53.2, 115.8, 118.2, 128.0, 128.2, 128.9, 129.1, 129.5, 131.4, 132.6, 133.6, 138.4, 145.9, 165.6, 197.1.

*Methyl N-(2-benzoyl-4-chlorophenyl)propionimidate (**1f**).*

Yield **93%**.$Eb_{(0,1mmHg)}$ 209°C;^{1}H NMR δ_H (300 MHz, $CDCl_3$) 0.98 (t,3H, $^3J_{HH}$ = 9.0 Hz, $\underline{CH_3}CH_2C$=N), 2.07 (q, $^3J_{HH}$ = 9.0 Hz, 2H, CH_2),3.23 (s, 3H, CH_3O), 6.72-7.776 (m, 8H, H_{arom});^{13}C NMR δ_C (75.3 MHz, $CDCl_3$) 10.3, 23.7, 53.1, 118.5, 123.3, 128.0, 128.3, 128.9, 129.0, 129.6, 131.3, 132.8, 134.0, 137.3, 145.8, 165.4, 196.0.

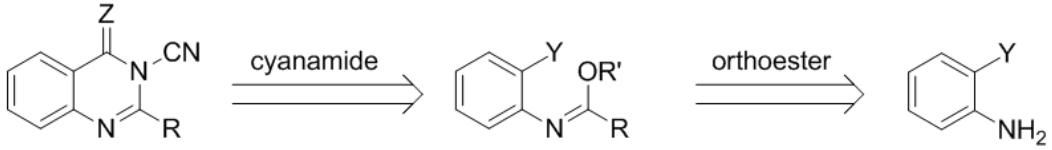
*General procedure for the synthesis of quinazoline (**2a-f**).*

To a solution of selected appropriate iminoester (10.0mmol, 1.0 equiv.) and cyanamid (16.0mmol, 1.6 equiv.) were added few drops of acetic acid in the ethanol. The resulting mixture was then stirred at reflux for 24h. Reaction was monitored by TLC (Ethyl acetate/ cyclohexane 7/3). Purification by reduced pressure distillation (0.1 mmHg) afforded the expected compounds as oils. After solvent evaporation, crude product was obtained by precipitation in petroleum ether and then purification was carried out by successive washings with diethyl ether (Et_2O).

2-Methyl-4-oxoquinazoline-3(4H)-carbonitrile (**2a**). Yield 67%. F 221°C; ^{1}H NMR δ_H (300 MHz, $CDCl_3$) 2.54 (s, 3H, CH_3,); 6.53 – 8.18 (m, 4H, H_{arom}) ;^{13}C NMR δ_C (75.3 MHz, $CDCl_3$) 24.7, 114.4, 115.3, 120.6, 123.3, 123.7, 132.6, 150.4, 162.9, 167.0.

2-Ethyl-4-oxoquinazoline-3(4H)-carbonitrile (**2b**). Yield 65%. F 203°C; ^{1}H NMR δ_H (300 MHz, $CDCl_3$) 1.24 (t, $^3J_{HH}$ = 9.0 Hz, 3H, $\underline{CH_3}$-CH_2,); 2.33 (q, $^3J_{HH}$ = 9.0 Hz, 2H, CH_3-$\underline{CH_2}$); 6.96 – 7.93 (m, 4H, H_{arom});^{13}C NMR δ_C (75.3 MHz, $CDCl_3$) 11.2, 29.5, 115.0, 118.5, 121.8, 125.8, 126.1, 133.5, 150.6, 160.0, 162.8.

4-Imino-2-methylquinazoline-3(4H)-carbonitrile (**2c**). Yield 59%. F 227°C; ^{1}H NMR δ_H (300 MHz, $CDCl_3$) 2.48 (s, 3H, CH_3); 5.47 (s, 1H, NH); 7.53 -



Scheme 4 : Retrosynthetic synthesis of quinazolines.

8.42 (m, 4H, H_{arom});^{13}C NMR δ_C (75.3 MHz, $CDCl_3$) 24.6, 115.0, 116.8, 125.6, 127.1, 135.6, 135.9, 150.6, 159.3, 161.2.

2-Ethyl-4-iminoquinazoline-3(4H)-carbonitrile (**2d**).

Yield 60%. F 148°C; ^{1}H NMR δ_H (300 MHz, $CDCl_3$) 1.33 (t, $^3J_{HH}$ = 9.0 Hz, 3H, $\underline{CH_3}$-CH_2); 2.74 (q, $^3J_{HH}$ = 9.0 Hz, 2H, CH_3-$\underline{CH_2}$); 3.64 (s, 1H, NH); 7.49 - 8.27 (m, 4H, H_{arom});^{13}C NMR δ_C (75.3 MHz, $CDCl_3$) 11.3, 29.5, 109.7, 111.9, 128.6, 129.2, 133.5, 135.9, 166.5, 168.4, 177.3.

4-Hydroxy-2-methyl-4-phenylquinazoline-3(4H)-carbonitrile (**2e**).

Yield 70%. F 257°C; ^{1}H NMR δ_H (300 MHz, $CDCl_3$) 2.48 (s, 3H, CH_3,) ; 5.53 (s, 1H, OH) ; 6.63 - 7.87 (m,9H, H_{arom});^{13}C NMR δ_C (75.3 MHz, $CDCl_3$) 24.6, 114.0, 114.5, 117.7 126.8 (2C), 128.4 (2C), 132.5, 133.3, 135.9, 140.8, 142.1, 142.5, 146.3, 174.0.

2-Ethyl-4-hydroxy-4-phenylquinazoline-3(4H)-carbonitrile (**2f**).

Yield 66%. F 112°C; ^{1}H NMR δ_H (300 MHz, $CDCl_3$) 1.02 (t, $^3J_{HH}$ = 9.0 Hz, 3H, $\underline{CH_3}$-CH_2,); 1.83 (q, $^3J_{HH}$ = 9.0 Hz, 2H, CH_3-$\underline{CH_2}$); 3.59 (s, 1H, OH); 7.06 - 7.91 (m,9H, H_{arom}; ^{13}C NMR δ_C (75.3 MHz, $CDCl_3$) 14.7, 22.4, 114.5, 114.9, 116.4 127.1 (2C), 129.6 (2C), 133.8, 134.3, 135.7, 141.0, 142.1, 142.5, 146.3, 174.6.

CONCLUSION

As far as the synthesis and functionalization of quinazolines, the literature results are abundant. However, obtaining functionalized quinazolines requires long sequences, synthesis and/or comprising restrictive stages. Besides on these results, it's interesting for us to develop a new approach for the formation of functionalized quinazolines, by a sequence of introduced groups. The strategy that we have anticipated is made according two main stages (Scheme 4). The functionalities have already been present on the arylic skeleton during the iminoester synthesis. The generation of new functions during the closing cycle on quinazoline part, allows thecontrol of the functionalization and the limitation of the side-effect reactions, which helps to increase the outcome.

REFERENCES

[1] A. J. Kochanowska-Karamyan, M. T. Hamann, *Chem. Rev.* **2010**, *110*, 4489-4497.

[2] P. Pahari, J. Rohr, *J. Org. Chem.* **2009**, *74*, 2750-2754.

[3] J. P. Michael, *Nat. Prod. Rep*. **2005**, *22*, 627-646.

[4] M. C. Tsengy, Y. H. Chu, *Tetrahedron*. **2008**, 64, 9515–9520.

[5] A. I. Sánchez, V. Martínez-Barrasaa, C. Burgos, J. J. Vaqueroa ,J. Alvarez-Buillaa, E. Terricabras, V. Segarra. *Bioorganic&MedicinalChemistry*. **2013**, *21*, 2370–2378.

[6] J. Chevaliera, A. Mahamouda, M. Baitiche, E. Adama, M. Viveirosb, A. Smarandached, A. Militarub, M. L. Pascub, L. Amaralb, J. M. Pagès. *International Journal of Antimicrobial Agents*. **2010**, *36*, 164–168.

[7] S. Jantova L. Cipa, D. Slamen˘ova, V. Horva´tha, P. Raukob. *Toxicology in Vitro.***2003**, *17*, 457-463.

[8] Y. Pua, D. Caoa, C. Xieb, H. Peia, D. Lia, M. Tanga, L. Chen. *Biochemical and Biophysical Research Communications*,**2015**, *462*, 288–293.

[9] S.T. Oswald, V. P. Ghanshyam, *J. Org. Chem*. **1976**, *41*, 838-845.

[10] P. Thanigaimalai, P. Lee, K. C. Bang, S. C. Lee, J. H.; Yun, C. Y. Roh, E. Hwang, B. Y. Kim, Y. Jung, S. H. Bioorg. *Med. Chem*. **2010**, *18*, 1555.

[11] B.Z. Schoenowsky, B. Sachse, A. Naturforsh, *J. Org. Chem.***1982**, *37*, 907.

[12] A. Chilin, G. Marzaro, S. Zanatta, V. Barbieri, G. Pastorini, P. Manzini, A. Guiotto. *Tetrahedron***2006**, *62*, 12351–12356.

[13] P. Yin, W. B. Ma, Y. Chen, W. C. Huang, Y. Deng, L. He, Org. Lett., **2009**, *11*, 5482-5485.

[14] M. Kosugi, T. Ogata, T. Tamura, H. Sano, H. Migita, *T. Chem. Lett*. **1986**, 1197–1200.

[15] L. CLAISEN, Ann. **1895**. *287*, 360.

[16] R. Roger, D. G. Neilson, *Chem. Rev.*, **1961**, *61,* 179-211.