Synthesis and characterization of new cyano-quinazolines poly-functionalized

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Abstract: Functionalized 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-aryliminioesters, 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 in several compounds of pharmacological interest having biological activity. Numerous publications state the pharmacological potential of some quinazoline derivatives. Indeed, the quinazolines are used as anti-inflammatory [3,4], anti-depressants [5], anti-microbial [6], antitumorales [7]. Pua and all. have recently unveiled an anti-arthritis [8] of a new quinazolinal derivatives by inhibiting the production of the enzyme TNF-α.

Various methods of the quinazoline synthesis are described 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-aryliminioesters by electrophile groups like ketones, ester or nitrile functions. The latter has been made ready by adopting the procedure described by Claisen [15-16].

In order to reduce the number of synthesis and purification steps to 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-aryliminioester 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-aryliminioesters.

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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 characterized. 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 iminoesters (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 comprise an asymmetrical carbon.

Table I: Functionalized N-aryliminoesters yield.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Iminoester</th>
<th>Y</th>
<th>R₁</th>
<th>R₂</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>CO₂Et</td>
<td>Me</td>
<td>Et</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>CO₂Et</td>
<td>Et</td>
<td>Me</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>CN</td>
<td>Me</td>
<td>Et</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>CN</td>
<td>Et</td>
<td>Me</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>ClPh(CO)</td>
<td>Me</td>
<td>Et</td>
<td>91</td>
</tr>
<tr>
<td>6</td>
<td>1f</td>
<td>ClPh(CO)</td>
<td>Et</td>
<td>Me</td>
<td>93</td>
</tr>
</tbody>
</table>

Table II: Quinazolines yields.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Quinazoline</th>
<th>R₁</th>
<th>R₂</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>Me</td>
<td>Et</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>Et</td>
<td>Me</td>
<td>65</td>
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<tr>
<td>3</td>
<td>2c</td>
<td>Me</td>
<td>Et</td>
<td>59</td>
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<tr>
<td>4</td>
<td>2d</td>
<td>Et</td>
<td>Me</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>2e</td>
<td>Me</td>
<td>Et</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>2f</td>
<td>Et</td>
<td>Me</td>
<td>66</td>
</tr>
</tbody>
</table>

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 (50.0 mmol, 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%. $\text{EB}_{(7.0,1mmHg)}$ 113°C; $^{1}H$ NMR $\delta$ (300 MHz, CDCl$_3$) 1.27 (t, 3H, $^{3}J_{HH} = 6.0$ Hz, CH$_3$-CH$_2$-C=O) 1.34 (t, 3H, $^{3}J_{HH} = 9.0$, CH$_3$-CH$_2$), 3.72 (q, 2H, $^{3}J_{HH} = 9.0$ Hz, CH$_2$), 4.24 (q, 2H, $^{3}J_{HH} = 9.0$ Hz, CH$_2$); 6.76 (d, 1H, $^{3}J_{HH} = 7.0$ Hz, H$_{arom}$), 7.04 (t, 1H, $^{3}J_{HH} = 7.0$ Hz, H$_{arom}$), 7.39 (t, 1H, $^{3}J_{HH} = 7.0$ Hz, H$_{arom}$), 7.89 (d, 1H, $^{3}J_{HH} = 7.0$ Hz, H$_{arom}$); $^{13}$C NMR $\delta_C$ (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)acetimidate (1b).**

Yield 92%. $\text{EB}_{(7.0,1mmHg)}$ 123°C; $^{1}H$ NMR $\delta$ (300 MHz, CDCl$_3$) 1.02 (q, 3H, $^{3}J_{HH} = 6.0$ Hz, CH$_3$-CH$_2$-C=N) 1.30 (t, 3H, $^{3}J_{HH} = 9.0$ Hz, CH$_3$-CH$_2$-O), 2.05-2.11 (m,2H, CH$_2$-CH$_2$), 3.81 (s, 3H, CH$_3$-O), 4.22-4.37 (m, 2H, CH$_2$-O), 6.54-7.90 (m, 4H, H$_{arom}$); $^{13}$C NMR $\delta_C$ (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-cyanoethyl)ethanimidate (1c).**

Yield 85%. $\text{EB}_{(7.0,1mmHg)}$ 137°C; $^{1}H$ NMR $\delta$ (300 MHz, CDCl$_3$) 1.26-1.32 (m, 3H, CH$_3$-CH$_2$-O), 1.78 (s, 3H, CH$_3$-C-N), 4.22-4.29 (m, 2H, CH$_2$-O), 6.78-7.50 (m, 4H, H$_{arom}$); $^{13}$C NMR $\delta_C$ (75.3 MHz, CDCl$_3$) 13.9, 20.0, 62.2, 105.0, 117.3, 121.7, 123.0, 132.6, 131.1, 152.4, 162.4.

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

Yield 89%. $\text{EB}_{(7.0,1mmHg)}$ 145°C; $^{1}H$ NMR $\delta$ (300 MHz, CDCl$_3$) 1.10 (t, 3H, $^{3}J_{HH} = 7.0$ Hz, CH$_3$-CH$_2$), 2.17 (q, 2H, $^{3}J_{HH} = 7.0$ Hz, CH$_2$-O), 3.27 (s, 3H, CH$_3$-O), 6.84-7.57 (m, 4H, H$_{arom}$); $^{13}$C NMR $\delta_C$ (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%. $\text{EB}_{(7.0,1mmHg)}$ 200°C; $^{1}H$ NMR $\delta$ = 1.01 (t, $^{3}J_{HH} = 9.0$ Hz, 3H, CH$_3$-CH$_2$-O); $\delta$ = 1.74 (s, 3H, CH$_3$-C=N); $\delta$ = 3.66 (q, 2H, $^{3}J_{HH} = 9.0$ Hz, CH$_3$-CH$_2$-O); $\delta$ = 6.73 - 7.56 (m, 8H, H$_{arom}$); $^{13}$C NMR $\delta_C$ (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%. $\text{EB}_{(7.0,1mmHg)}$ 209°C; $^{1}H$ NMR $\delta$ (300 MHz, CDCl$_3$) 0.98 (t,3H, $^{3}J_{HH} = 9.0$ Hz, CH$_3$-CH$_2$-C=N), 2.07 (q, $^{3}J_{HH} = 9.0$ Hz, 2H, CH$_2$), 3.23 (s, 3H, CH$_3$-O), 6.72-7.76 (m, 8H, H$_{arom}$); $^{13}$C NMR $\delta_C$ (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 diethyli ether (Et$_2$O).

2-Methyl-4-oxoquinazoline-3(4H)-carbonitrile (2a).

Yield 67%. F 221°C; $^{1}H$ NMR $\delta$ (300 MHz, CDCl$_3$) 2.54 (s, 3H, CH$_3$-O), 6.53 - 8.18 (m, 4H, H$_{arom}$); $^{13}$C NMR $\delta_C$ (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 $\delta$ (300 MHz, CDCl$_3$) 1.24 (t, $^{3}J_{HH} = 9.0$ Hz, 3H, CH$_3$-CH$_2$-O); 2.33 (q, $^{3}J_{HH} = 9.0$ Hz, 2H, CH$_2$-O), 6.96 - 7.93 (m, 4H, H$_{arom}$); $^{13}$C NMR $\delta_C$ (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 $\delta$ (300 MHz, CDCl$_3$) 2.48 (s, 3H, CH$_3$); 5.47 (s, 1H, NH); 7.53 -

![Scheme 4: Retrosynthetic synthesis of quinazolines.](image-url)
The generation of new functions during the closing cycle on quinzoline part, allows the control of the functionalization and the limitation of the side-effect reactions, which helps to increase the outcome.

REFERENCES