

One-pot Syntheses of Fused Quinazolines by Reaction of *N*-(2-Cyanophenyl)chloromethanimidoyl Chloride. I. A New Synthesis of 1,3-Oxazolo- and 1,3-Oxazino[2,3-*b*]quinazolines

Hana Divišová, Helena Havlišová, Petr Borek, and Pavel Pazdera*

Department of Organic Chemistry, Faculty of Science, Masaryk University, CZ-611 37 Brno, Czech Republic. Tel.: +420 5 41129 305, Fax: +420 5 412 112 14.

*Author to whom correspondence should be addressed; E-mail: pazdera@chemi.muni.cz

Received: 14 Aug 2000; in revised form 13 Sep 2000 / Accepted: 19 Sep 2000 / Published: 31 Oct 2000

Abstract: 12*H*-Benzo[1,3]oxazolo[2,3-*b*]quinazolin-12-imine (**5a**), 9-chloro-12*H*-benzo[1,3]oxazolo[2,3-*b*]quinazolin-12-imine (**5b**), 2,3-dihydro-5*H*-[1,3]oxazolo[2,3-*b*]quinazolin-5-imine (**5c**), 2,3-dihydro-3,3-dimethyl-5*H*-[1,3]oxazolo[2,3-*b*]quinazolin-5-imine (**5d**) and 3,4--dihydro-2*H*,6*H*-[1,3]oxazino[2,3-*b*]quinazolin-6-imine (**5e**) were synthesized in a *one-pot* reaction of *N*-(2-cyanophenyl)chloromethanimidoyl chloride (**1**) with 2-aminophenols, 2-aminoethanol, and 3-aminopropanol in the presence of a base. The course of the reaction was controlled by the temperature and the amount of base used. *N*-(2-Cyanophenyl)-(2-hydroxyanilino)methanimidoyl chloride (**3a**), 2-chloro-3-(2-hydroxyphenyl)-3,4-dihydroquinazolin-4-imine (**4a**) and 6-imino-2*H*, 3*H*, 4*H*, 6*H*, 11*H*-1,3-oxazino[2,3-*b*]-5-quinazolinium chloride (**6**) were identified as intermediates of the *one-pot* process.

Keywords: *N*-(2-cyanophenyl)chloromethanimidoyl chloride, 1,3-oxazolo[2,3-*b*]quinazoline, 1,3-oxazino[2,3-*b*]quinazoline, methanimidoyl chloride, fused quinazolines, *one-pot* synthesis

Introduction

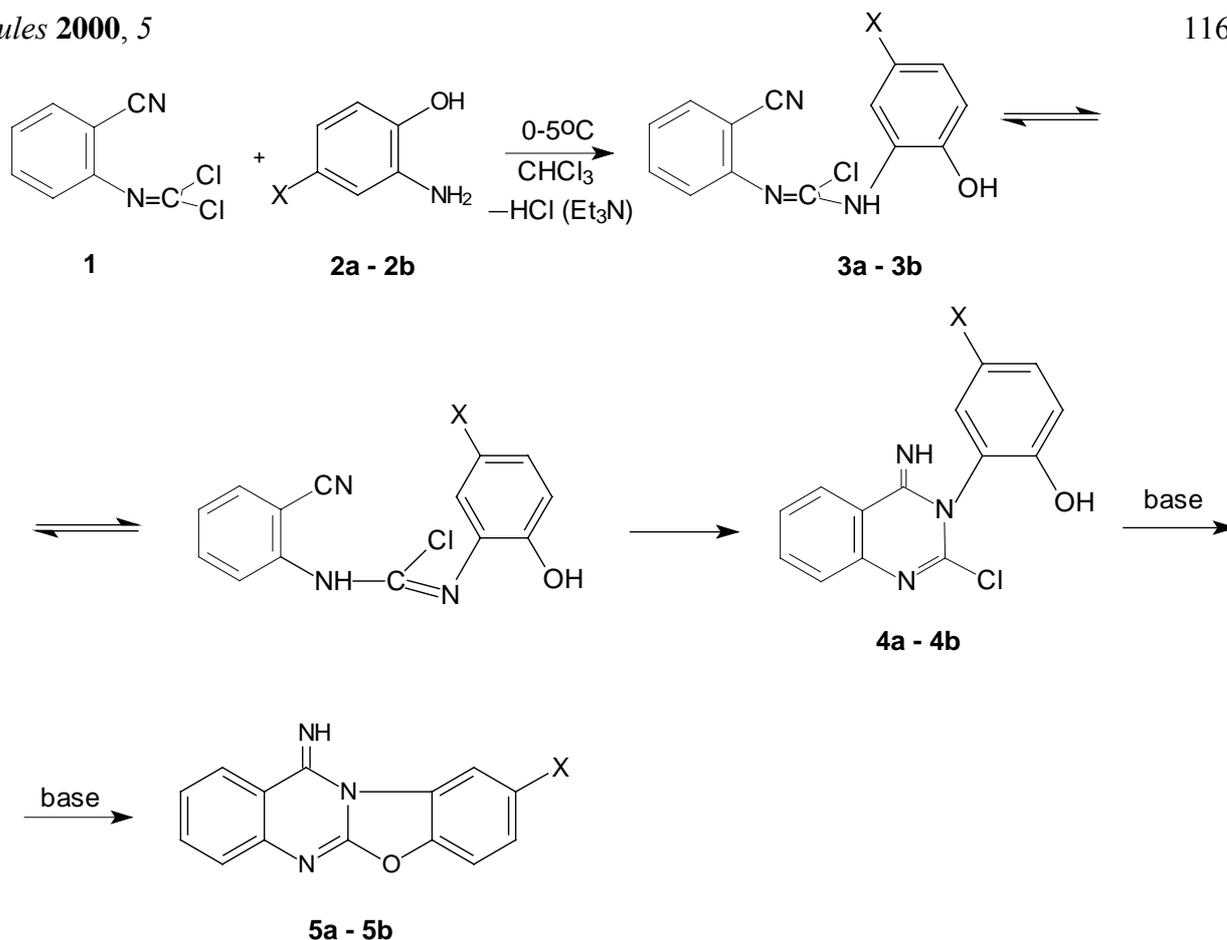
In the search for economic and environmentally friendly synthetic methods, *one-pot* syntheses could offer a significant step ahead. N-(2-Cyanophenyl)chloromethanimidoyl chloride (**1**) [1] has been used already as a trifunctional electrophilic reagent in the *one-pot* syntheses of 3-substituted 4-imino-1,2,3,4-tetrahydroquinazolin-2-thiones and their 2-selenoxo analogues [2, 3].

A wide spectrum of biological effects is reported for compounds containing the quinazoline ring system [4-6]. A literature search showed that 1,3-oxazolo[2,3-b]quinazoline skeletons can be prepared by: the ring closure at 3-(2-hydroxyethyl)-2-methylthio-4-phenyl-3,4-dihydroquinazoline [7]; the coupling of anthranilamide with 2-chloroethyl isocyanate [8]; the reaction of anthranilonitrile with allyl isocyanate [9]; treatment of aziridine, 2,2-dimethylaziridine, 2-aminoethanol or 2-amino-2-methyl-1-propanol with 2-methoxycarbonylphenyl isocyanate [10] and the cyclocondensation of anthranilic esters with 2-chloro-2-bromalkylisocyanate [11]. 1,3-Oxazino[2,3-b]quinazolines were prepared by cyclization of 3-(3-hydroxypropyl)-2-methylthio-4-phenyl-3,4-dihydroquinazoline [7] or *via* coupling of anthranilamide with 3-chloropropyl isocyanate [8]. However, the *one-pot* syntheses of 1,3-oxazolo- and 1,3-oxazino[2,3-b]quinazolines using N-(2-cyanophenyl)chloromethanimidoyl chloride (**1**) and 2-aminophenols, 2-aminoethanols and 3-aminoalcohols **2**, respectively, have not been reported yet.

Results and Discussion

Our goal was to prepare 1,3-oxazolo- and 1,3-oxazino[2,3-b]quinazoline syntheses by a *one-pot* reaction of N-(2-cyanophenyl)chloromethanimidoyl chloride (**1**) with the aforementioned *N,O*-bifunctional nucleophiles. The starting compound **1** can act as a trifunctional electrophilic reagent – it can be attacked by two nucleophilic reagents on the carbon atom of the chloromethanimidoyl chloride group or on the carbon of the cyano group. We expected that attack of the *N,O*-bifunctional nucleophiles would be initiated on the primary amino group, which is more nucleophilic than the hydroxy group.

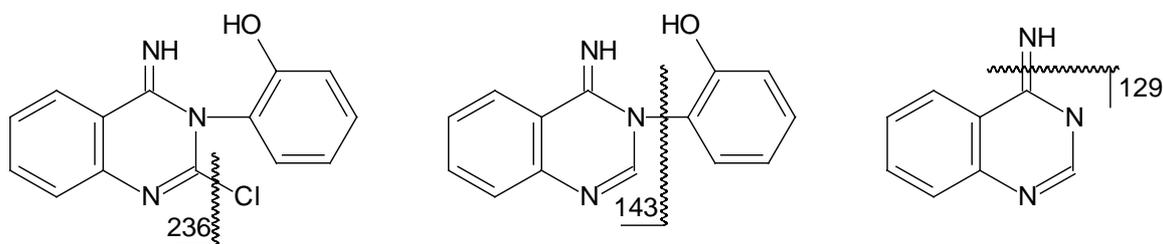
First we studied the room temperature reaction of **1** with 2-aminophenol **2a** in the presence of one equivalent of triethylamine as a base (Scheme 1) because the phenolic hydroxyl is less nucleophilic than the alcoholic one, we expected that consecutive attacks would be suppressed under those conditions and we would be able to investigate the intermediate(s) of this reaction. After the reaction was finished 2-chloro-3-(2-hydroxyphenyl)-3,4-dihydroquinazolin-4-imine (**4a**) was separated and identified as the main product.



2a - 5a: X = H, NaH (DMF)
 2b - 5b: X = Cl, Et₃N

Scheme 1. Reaction of 1 with 2a, 2b

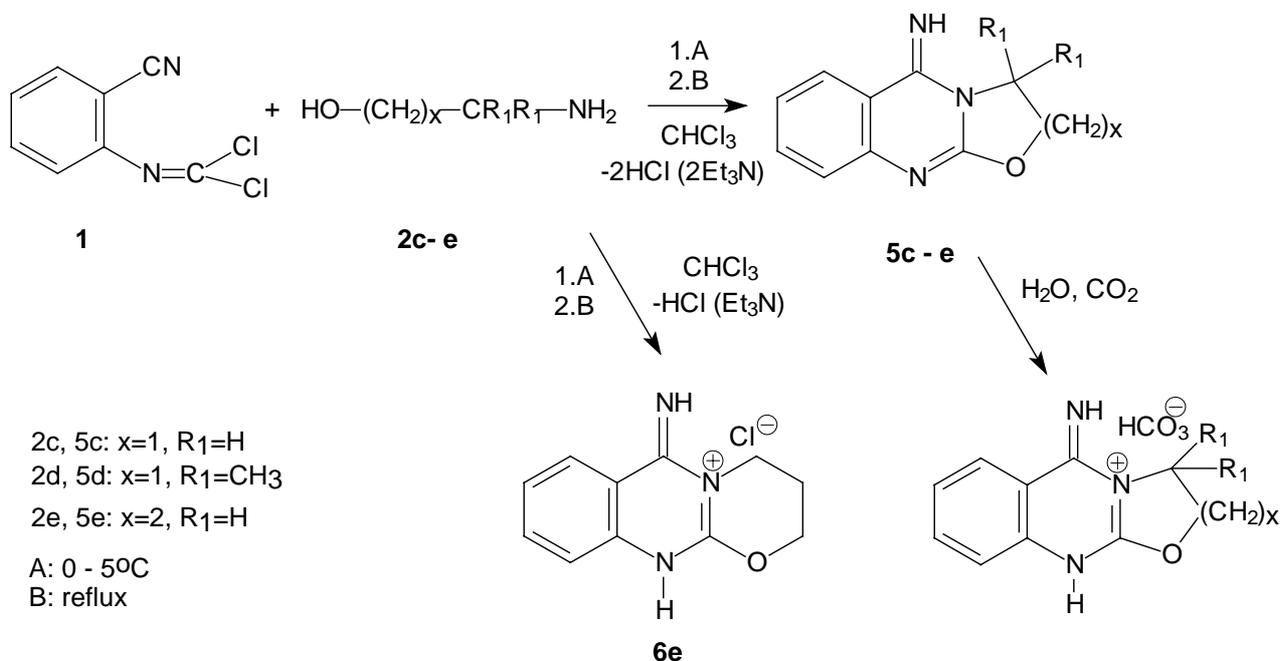
Since we did not obtain an acyclic intermediate **3a** in the studied reaction we carried out the same reaction at a temperature of 0° to -5°C. Thus we successfully obtained *N*-(2-cyanophenyl)-(2-hydroxyanilino)methanimidoyl chloride (**3a**) in this case. The identity of both intermediates **3a**, **4a** was supported by the elementary analysis, FTIR, ¹H- (both tautomers of **3a**) and ¹³C-NMR spectroscopy and in the case of **4a**, by mass spectroscopy (Scheme 2).



Scheme 2. MS fragmentations of 4a

In the next step of the synthesis we attempted to cyclize **4a** to the fused quinazoline **5a** by heating in a chloroform solution in the presence of the second equivalent of triethylamine but the reaction was unsuccessful. The resulting **5a** was obtained only by using sodium hydride as a base in dimethylformamide solution at room temperature. On the other hand, the analogous compound **5b** was prepared in a *one-pot* synthesis using 2 equivalents of triethylamine in chloroform solution. This finding may be explained by a higher acidity of the phenolic proton of the intermediate **4b** than **4a** (Scheme 1).

Our attempt to detect intermediates of the reactions between **1** and 1,2- or 1,3-aminoalcohols **2c-2e** described in Scheme 3 was not successful. Using one equivalent of triethylamine, cooling, room temperature and heating, respectively, mixtures of **1**, final fused quinazoline **5** and some other products were obtained. However, they undergo degradation in the course of their separation and highly polar products were formed. The trapping of the reaction intermediates was unsuccessful at lower temperature ($-25\text{ }^{\circ}\text{C}$), regardless of the base used, amount, and duration of the reaction. 6-Imino-2*H*, 3*H*, 4*H*, 6*H*, 11*H*-1,3-oxazino[2,3-*b*]-5-quinazolinium chloride (**6e**) was isolated only in the case of the reaction of **1** with **2e**.

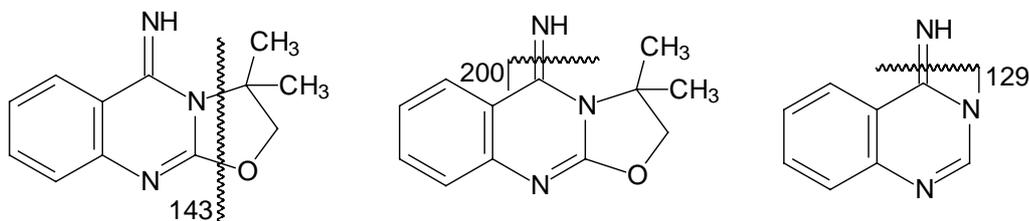


Scheme 3. Reaction of **1** with **2c – 2e**

We have found that these conditions are optimal for a two- step *one-pot* synthesis: the first exothermic step was carried out with one equivalent of triethylamine at $0 - 5^{\circ}\text{C}$ and the next step with the second equivalent of a base. The reaction stopped after the first step, unless *N*-(2-cyanophenyl)-chloromethanimidoyl chloride (**1**) was present in the reaction mixture. The reaction of amino alcohols can proceed *via* the quinazoline intermediate formation or by formation of oxazolane/oxazinane imine

intermediates, similar to reactions between amino alcohols and chloromethanimidoyl chlorides described in the literature [12].

The identities of the products **5c** – **5e** and **6e** were confirmed by elemental analysis, FTIR, ^1H - and ^{13}C NMR spectroscopy and in the case of **5d**, by mass spectroscopy (Scheme 4).



Scheme 4. MS fragmentations of **5d**

The corresponding vibration bands of the COC and C=N groups were found in the FTIR spectra of **5c** – **5d**. In the NMR spectra of **5c-5e** and **6e** the signals of aliphatic groups were observed. The salt **6e** was identified as the 1,3-oxazino[2,3-b]-5-quinazolinium cation in accordance with the FTIR spectrum, in which $\text{N}^+\text{-H}$ valence vibrational bands and the isouronium moiety (absence of the band about 1650 cm^{-1}) were not present. Furthermore, we have found that these imines **5c-5e** form very stable hydrogen carbonates by action of atmospheric carbon dioxide and water. They were insoluble in water, dimethylsulfoxide, organic, inorganic acids and other solvents. But they afforded FTIR spectra with the same characteristics as in case of **6e**. We expect that these hydrogen carbonates contained the corresponding 1,3-oxazolo[2,3-b]quinazoline-4-ium or 1,3-oxazino[2,3-b]-5-quinazolinium cation, respectively.

Conclusions

Optimal conditions for the *one-pot* synthesis of 1,3-oxazolo- and 1,3-oxazino[2,3-b]quinazolines **5a-5e** via reaction of *N*-(2-cyanophenyl)chloromethanimidoyl chloride (**1**) and 2-aminoethanols, 2-aminoethanols and 3-aminopropanol are highly diluted solution of the adducts, a temperature range of 0 to $-5\text{ }^\circ\text{C}$ and the presence of one equivalent of a base in the first reaction step. Use of a second equivalent of the base and higher temperatures is optimal for the next step of the sequence.

Acknowledgements

This work was supported by the Grants of the Ministry of Education of the Czech Republic (Grant No. 393/1999 and CEZ:J07/98:143100011). We would like to thank Analytical Department of Lachema

Co., Brno, Czech Republic for elemental analysis and Advanced Chemistry Development, Inc., Toronto, Canada for the free on-line simulation of ^1H - and ^{13}C -NMR spectra.

Experimental

General

Melting points of the compounds prepared were measured on a Boetius Rapido PHMK 79/2106 (Wägetechnik) instrument and are not corrected. TLC was carried out on Silufol UV 254 plates (Kavalier, Votice) and the detection with Fluotest Universal (Quarzlampen, Hanau) or by iodine vapors. Chloroform and diethyl ether were used as eluents. Purity of all compounds was determined by C, H, N elemental analysis on an Erba 1102 instrument. FTIR spectra were taken on a Genesis (UNICAM) spectrometer in potassium bromide pellets. NMR spectra were measured on a Bruker Avance DRX-500 spectrometer in deuteriochloroform or deuterodimethyl sulfoxide. The ^1H and ^{13}C spectra were referenced to tetramethylsilane as the internal standard or to the solvent signal (deuteriochloroform, hexadeuterodimethylsulfoxide). The measured ^{13}C and ^1H -NMR spectra were correlated with those obtained by on-line simulation (Advanced Chemistry Development, Inc., Toronto, Canada). Gas chromatography was accomplished on a Shimadzu GC – 17A apparatus and on a TRIO 1000 GC/MS system (FISONS Instruments). The electron impact method was used for ionization (70eV).

General procedure – Reactions of **1** with *N,O*-bifunctional nucleophiles **2**

Part 1. A triethylamine (0.5 g, 5 mmol) solution in chloroform (10 mL) was added dropwise with stirring at 0 to -5°C to mixture of *N*-(2-cyanophenyl)chloromethanimidoyl chloride (**1**) (1.0 g, 5 mmol) and the corresponding 2-aminophenol, 2-aminoethanol or 3-aminopropanol **2** (5 mmol) in chloroform (75 ml).

Part 2. The second equivalent of triethylamine was added after 3 hours of stirring. The solution was refluxed for 20 hours. The reaction mixture was cooled and washed with water and then dried with sodium sulfate. The filtrate was concentrated *in vacuo*. The residue was crystallized.

N-(2-cyanophenyl)-(2-hydroxyanilino)methanimidoyl chloride (**3a**)

2-Aminophenol (**2a**) (0.53 g, 5 mmol) and 1 equivalent of triethylamine were used in accord with the above described general procedure – Part 1. Yield 0.87 g (65 %); M.p. 142-144°C (benzene – cyclohexane); For $\text{C}_{14}\text{H}_{10}\text{ClN}_3\text{O}$ (271.21) calculated 61.97 % C, 3.72 % H, 15.49 % N; found 62.10 % C, 4.12 % H, 15.11 % N; FTIR, $\tilde{\nu}/\text{cm}^{-1}$: 3305 (NH), 2226 (CN), 1650 (C=N), 1237 (CO), 770 (CCl); ^1H -

NMR (CDCl₃) δ : 9.12 (0.5H, bs, NH), 8.64 (1H, bs, OH), 8.40 (0.5H, bs, NH), 7.82 – 7.64 (1H, m, ArH), 7.58 – 7.28 (4H, m, ArH), 7.09 – 6.93 (2H, m, ArH), 6.72– 6.54 (1H, m, ArH); ¹³C NMR (CDCl₃) δ : 148.05 (C_q), 145.41 (C_q), 142.44 (C_q), 135.89 (CH_{Ar}), 134.22 (CH_{Ar}), 127.58 (C_q), 125.56 (CH_{Ar}), 123.44 (CH_{Ar}), 122.89 (CH_{Ar}), 122.13 (C_q), 119.68 (CH_{Ar}), 118.34 (CH_{Ar}), 117.94 (CH_{Ar}), 114.22 (C_q).

2-(3-Hydroxyphenyl)-2-chloro-3,4-dihydroquinazolin-4-imine (4a)

From 2-aminophenol (**2a**) (0.53 g, 5 mmol) and 2 equivalent of triethylamine. Yield 0,2 g (49%); M.p. 213-215° (acetone); For C₁₄H₁₀ClN₃O (271.21) calculated 61.97 % C, 3.72 % H, 15.49 % N; found 61.68 % C, 3.34 % H, 15.70 % N; FTIR, $\tilde{\nu}$ /cm⁻¹: 3450 (OH), 3300 (NH), 1660 (C=N), 1238 (CO), 655 (CCl); ¹H-NMR (DMSO-d₆) δ : 9.73 (1H, s, NH), 8.37 – 7.40 (8H, m, ArH), 4.22 (1H, s, OH); ¹³C NMR (DMSO) δ : 148.06 (C_q), 138.71 (C_q), 138.53 (C_q), 129.66 (C_q), 127.21 (CH_{Ar}), 122.03(C_q), 120.68 (CH_{Ar}), 119.57 (CH_{Ar}), 119.51 (CH_{Ar}), 118.86 (CH_{Ar}), 118.64 (CH_{Ar}), 111.83 (C_q), 110.35 (CH_{Ar}), 104.36 (CH_{Ar}); MS, m/z (I_r/%) : 270 (39), 236 (39), 179 (15), 145 (2), 129 (29).

12H-Benzo[1,3]oxazolo[2,3-b]quinazolin-12-imine (5a)

To solution of **4a** (1,0 g, 3 mmol) in dimethylformamide (1 mL) was added sodium hydride (0.2 g, 8 mmol). After 48 hours of stirring product **5a** was precipitated by addition of water. Yield 0.7g (80 %); M.p. 236-237°C (dimethylformamide-water); For C₁₄H₉N₃O (235.24) calculated: 71.48 % C, 3.86 % H, 17.85 % N; found: 71.85 % C, 3.76 % H, 17.54 % N; FTIR, $\tilde{\nu}$ /cm⁻¹: 3210 (NH), 1620 (C=N), 1230, 1070 (COC); ¹H-NMR (DMSO-d₆) δ : 9.62 (1H, s, NH), 8.67 – 7.35 (8H, m, ArH), ¹³C NMR (DMSO) δ : 153.61(C_q), 153.45 (C_q), 144.26 (C_q), 144.07 (C_q), 132.76 (CH_{Ar}), 127.58 (C_q), 126.22 (CH_{Ar}), 125.11 (CH_{Ar}), 125.06 (CH_{Ar}), 124.40 (CH_{Ar}), 117.37 (C_q), 115.90 (CH_{Ar}), 109.91 (CH_{Ar}).

9-Chloro-12H-benzo[1,3]oxazolo[2,3-b]quinazolin-12-imine (5b)

From 4-chloro-2-aminophenol (**2b**) (0.7 g, 5 mmol) and 2 equivalents of triethylamine. Yield 0.9 g (69 %); M.p. 264-266°C (acetone); For C₁₄H₈ClN₃O (269.69) calculated: 62.35 % C, 3.00 % H, 15.57 % N; found: 62,71 % C, 3.32 % H, 15.24 % N; FTIR, $\tilde{\nu}$ /cm⁻¹: 3290 (NH), 1630 (C=N), 1245, 1085 (COC); ¹H-NMR (DMSO-d₆) δ : 9.57 (1H, s, NH), 8.51 – 7.40 (7H, m, ArH); ¹³C NMR (DMSO) δ : 153.50 (C_q), 152.43 (C_q), 143.86 (C_q), 143.27 (C_q), 135.11 (C_q), 132.93 (CH_{Ar}), 128.75 (C_q), 128.06 (CH_{Ar}), 126.35 (CH_{Ar}), 125.17 (CH_{Ar}), 124.66 (CH_{Ar}), 117.30 (CH_{Ar}), 115.51 (C_q), 111.20 (CH_{Ar}).

2,3-Dihydro-5H-[1,3]oxazolo[2,3-b]quinazolin-5-imine (5c)

From 2-aminoethanol (**2c**) (0.3 g, 5 mmol) and 2 equivalents of triethylamine. Yield 0.6 g (65 %); M.p. 210–211°C (dimethylformamide); For C₁₀H₉N₃O (187.20) calculated: 64.16 % C, 4.86 % H, 22.44 % N; found: 64.55 % C, 4.61 % H, 22.78 % N; FTIR, $\tilde{\nu}$ /cm⁻¹: 3300 (NH), 3030, 2980, 2890 (CH), 1620, 1650 (C=N), 1235, 1060 (COC); ¹H-NMR (DMSO-d₆) δ : 11.79 (1H, bs, NH), 7.47 – 7.38 (1H, m, ArH), 8.09 – 7.54 (3H, m, ArH), 4.49 – 4.15 (4H, m, CH₂); ¹³C NMR (DMSO) δ : 160.20 (C_q), 156.84 (C_q), 148.64 (C_q), 135.53 (CH), 126.76 (CH), 125.28 (CH), 124.60 (CH_{ar}), 115.82 (C_q), 66.34 (CH₂), 48.03 (CH₂).

2,3-Dihydro-5H-3,3-dimethyl-5H-[1,3]oxazolo[2,3-b]quinazolin-5-imine (5d)

From 2-amino-2-methylpropan-1-ol (**2d**) (0.45 g, 5 mmol) and 2 equivalents of triethylamine. Yield 0.85 g (70 %); M.p. 116–119°C (2-methoxyethanol); For C₁₂H₁₃N₃O (215.25) calculated: 66.95 % C, 6.10 % H, 19.51 % N; found: 67.13 % C, 6.37 % H, 19.21 % N; FTIR, $\tilde{\nu}$ /cm⁻¹: 3478, 3444 (NH), 3025, 2975, 2929 (CH), 1646 (C=N), 1216, 1054 (COC); ¹H-NMR (DMSO-d₆) δ : 8.76 – 7.53 (4H, m, ArH), 4.56 (2H, s, CH₂), 1.84 (s, 6H, CH₃); ¹³C NMR (DMSO) δ : 155.32 (C_q), 153.56 (C_q), 148.51 (C_q), 137.20 (CH_{ar}), 126.24 (CH_{ar}), 125.92 (CH_{ar}), 125.65 (CH_{ar}), 112.86 (C_q), 79.04 (CH₂), 65.32 (C_q), 22.67 (CH₃); MS, m/z (I_r/%) : 215 (54), 200 (80), 186 (18), 157 (9), 143 (6), 129 (18).

3,4-Dihydro-2H,6H-[1,3]oxazino[2,3-b]quinazolin-6-imine (5e)

From 3-aminopropanol (**2e**) (0.41 g, 5 mmol) and 2 equivalents of triethylamine. Yield 0.60g (63 %); M.p. 128–130°C (ethanol); For C₁₁H₁₁N₃O (201.23) calculated: 65.65 % C, 5.52 % H, 20.87 % N; found: 66.0 % C, 5.71 % H, 20.47 % N; FTIR, $\tilde{\nu}$ /cm⁻¹: 3369, 3245 (NH), 1656 (C=N), 1256, 1055 (COC); ¹H-NMR (DMSO-d₆) δ : 12.20 (0.3H, bs, NH), 11.52 (0.7H, bs, NH), 8.54 – 8.52 (1H, m, ArH), 7.82 – 7.79 (1H, m, ArH), 7.38 – 7.33 (1H, m, ArH), 3.99 – 3.97 (2H, m, OCH₂), 3.60 – 3.58 (2H, m, NCH₂), 2.12 – 2.10 (2H, m, CH₂); ¹³C NMR (DMSO) δ : 175.54 (C_q), 159.74 (C_q), 139.50 (C_q), 135.84 (CH_{ar}), 127.72 (CH_{ar}), 124.90 (CH_{ar}), 116.02 (CH_{ar}), 115.95 (C_q), 59.40 (CH₂O), 44.18 (CH₂N), 30.38 (CH₂).

6-Imino-2H, 3H, 4H, 6H, 11H-1,3-oxazino[2,3-b]quinazolin-5-ium chloride (6)

From 3-aminopropanol (**2e**) (0.41 g, 5 mmol) and 1 equivalent of triethylamine, as described in the general procedure – Part 1. Yield 0.71 g (60 %); M.p. 183–185°C (ethanol); For C₁₁H₁₂ClN₃O (237.68) calculated: 55.58 % C, 5.10 % H, 17.67 % N; found: 55.95 % C, 5.42 % H, 17.50 % N; FTIR, $\tilde{\nu}$ /cm⁻¹: 3240, 3280 (NH), 2960 (CH), 1620 (C=N), 1250, 1055 (COC); ¹H-NMR (DMSO-d₆) δ : 12.10 (1H, s, NH), 9.35 (1H, s, NH), 8.10 – 7.21 (4H, m, ArH), 4.62 – 4.60 (2H, m, OCH₂), 3.46 – 3.42 (2H, m, N⁺CH₂), 1.90 – 1.87 (2H, m, CH₂); ¹³C NMR (DMSO) δ : 174.42 (C_q), 154.14 (C_{11a}), 135.70 (C_q),

133.23 (CH), 126.07 (CH_{ar}), 124.05 (CH_{ar}), 115.66 (CH_{ar}), 114.62 (C_q), 58.76 (OCH₂), 44.70 (N⁺CH₂), 29.52 (CH₂).

References and Notes

1. Pazdera P.; Divišová H.; Havlišová H; Borek P., *Molecules* **2000**, *5*, 189.
2. Pfeiffer W.-D.; Pazdera P.; Hetzheim A.; Mücke J., *Pharmazie* **1995**, *50*, 21.
3. Pfeiffer W.-D.; Hetzheim A.; Pazdera P.; Bodtke A.; Mücke J., *J. Heterocyclic Chem.* **1999**, *36*, 1327.
4. Dictionary of Natural Products, Buckingham J., ed., Chapman and Hall, London (1994).
5. John S., *Pharmazie* **1981**, *36*, 583;
6. Waisser K., Dostál H., Kubíková L., and Kolář K., *Čes. a Slov. Farm.* **2000**, *49*, 113.
5. Kosasayama A.; Higashi K.; Ishikawa F., *Chem. Pharm. Bull.* **1979**, *27*, 880.
6. Chern J. W.; Shish F. J.; Chang C. D., Chan C. H.; and Liu K. C., *J. Heterocyclic. Chem.* **1988**, *27*, 1103.
7. Shiau C. H.; Chern J. W.; Liu K. - C.; Chan C. H.; Yen M. H., *J. Heterocyclic. Chem.* **1990**, *27*, 1467.
8. Peet N. P.; Anzeveno P. B., *J. Heterocyclic. Chem.* **1979**, *16*, 877.
9. Kampe K. D., *Synthesis* **1976**, *7*, 469.
10. Kühle E.; Anders B.; Klauke E.; Tarnow H.; Zumach G., *Angew. Chem.* **1962**, *74*, 861.

Sample Availability: Available from the authors.

© 2000 by MDPI (<http://www.mdpi.org>). Reproduction is permitted for noncommercial purposes.