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Synthesis of Benzoxazines, 3,4-Dihydroquinazolines and Quinazolinethiones

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SYNTHESIS OF BENZOXAZINES, 3,4-DIHYDROQUINAZOLINES AND QUINAZOLINETHIONES.

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Abstract: *Reaction of aldehydes, ketones, imines and isothiocyanates with N-(2-bromophenyl) ethylimidates* ***1a*** *in presence of lithium, is considered as an original route to 4H-3,1-benzoxazines, 3,4-dihydroquinazolines and 4(3H)-quinazolinethiones.*

In previous works, and within our ongoing research on the use of iminoesters as intermediates in heterocyclic synthesis, we reported results of the reaction of a variety of organometallic reagents with imidates possessing CN, COR and CO_2R in β and γ positions and involving the formation of oxazolic[1], oxazolinic[2], benzoxazinic[3], dioxazinic[4] and quinolic[5] derivatives.

In the present work, we report a new route to benzoxazines, quinazolines and quinazolinethiones based on the reaction of lithiated N-(2-bromophenyl) imidates **1a** with some carbonyl derivatives, imines and isothiocyanates. The titled compounds have been synthesized using many methods starting from different substrates[6-9] and have exhibited highly interesting features in biomedical[10-16] and agricultural industry[17-18]. The new method, described in this paper, is general and efficient.

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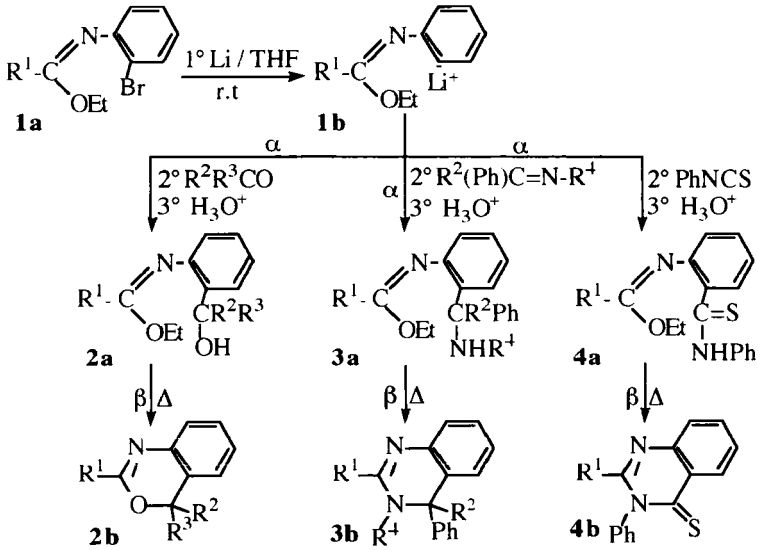

2 a1, 2 b1: R1 = Me, R2 = H, R3 = Me; **3 a1, 3 b1**: R1 = Et, R2 = H, R4 = iBu; **4 a1, 4 b1**: R1 = Me

2 a2, 2 b2: R1 = Et, R2 = Me, R3 = Ph; **3 a2, 3 b2**: R1 = Ph, R2 = H, R4 = Ph; **4 a2, 4 b2**: R1 = Et

2 a3, 2 b3: R1 = Ph, R2 = R3 = Me; **3 a3, 3 b3**: R1 = Me, R2 = Me, R4 = Ph; **4 a3, 4 b3**: R1 = Ph

2 a4, 2 b4: R1 = Me, R2 = Me, R3 = Ph;

Scheme 1

Since iminoester carbon presents a low reactivity towards organometallic reagents[19], it is possible to obtain a variety of lithiated iminoester in common conditions. Such imidates are highly interesting intermediates. They may be used to functionnalize the imidic groupment.

Treatment of N-(2-bromophenyl) imidates **1a** with lithium at room temperature yields the corresponding lithiated compounds **1b**. Reaction of these intermediates with carbonyl derivatives (aldehyds and ketones), imines and isothiocyanates leads to hydroxyimidates **2a**, aminoimidates **3a** and thioamidoimidates **4a** via hydrolysis (Scheme-1- step α).

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In contrast to lithiated species **1b** which are thermally stable, hydroxyimidates, aminoimidates and thioamidoimidates cyclize at a fairly short time when heated in refluxing chlorobenzene to afford 4H-3,1-benzoxazines **2b**, 3,4-dihydroquinazolines **3b** and 4(3H)-quinazoline-thiones **4b** respectively (Scheme-1- step β) in moderate yield (50%).

The second step leading to the formation of compounds **2b**, **3b** and **4b** is relatively faster than the first and the third.

The rate of formation of lithiated intermediate (complete disappearance of Li) seems to depend on the nature of R^1 group, the solvent and the temperature.

Lithiation is faster when the reaction is carried out in THF rather than diethylether at room temperature and not at 0°C. Moreover the lithiated species formation is considerably faster when R^1=Ph than when R^1= Me or Et. As a matter of fact, the transformation of iminoester **1a** (R^1=Ph) into its corresponding lithiated form **1b** requires only 30 minutes when R^1=Ph, however it takes 12 hours in the case of R^1= Me or Et.

The heating time required by the functionalized imidates **2a**, **3a** and **4a** to cyclize into benzoxazines **2b**, or quinazolines **3b** and **4b** respectively, depends on the temperature and the nature of the introduced functions (alkohol, amine or thioamide) in the second step β. The higher the solvent boiling point, the faster the reaction is. For the same solvent, the reaction time for cyclization increases in this order: aminoimidate first, then hydroxyimidate and finally thioamidoimidate. In chlorobenzene, the reaction time is 12 hours, 24 hours and 36 hours respectively.

EXPERIMENTAL SECTION

Infrared spectra were obtained on a Perkin Elmer 681 spectrometer in $CHCl_3$. Proton NMR spectra were recorded on a Jeol C-HL60 instrument at 60MHz using $CDCl_3$ solution with TMS as the internal standard.

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Elemental analysis was carried out at the Elemental Analysis Center of Paul Sabatier University of Toulouse, France.

Uncorrected melting points were obtained using a Büchi melting point apparatus.

Synthesis of alkohols 2a, amines 3a and thioamides 4a.

The method is general. The procedure for the synthesis of compound **2a$_1$** is given as an example.

10 mmol (2,42g) of N-(2-bromophenyl) ethylacetimidate were added to 20 mmol (0,14g) of lithium in THF (30ml) at 20°C under nitrogen atmosphere. The solution obtained was cooled at 0°C and 10 mmol (0,44g) of acetaldehyde dissolved in 15 ml of THF were added. The reaction mixture was brought to room temperature, stirred for 3 hours and hydrolised with a saturated aqueous solution of NH_4Cl. The product was extracted with ether and the organic layer was dried over $MgSO_4$. The mixture was concentrated and distilled under reduced pressure. We obtained 1,76g (Rdt = 85%) of alkohol imidate **2a$_1$**.

2 a$_1$:Eb_1= 70; Rdt= 85%; IR: ν_{OH} = 3600-3400; $\nu_{C=N}$ = 1665; ^1H NMR: 7.6-6.6 (m, 4H); 4.25(q, 2H); 3.45(m, 1H); 1.8(s, 3H); 1.5 (q, 1H); 1.4(d, 3H); 1.3 (t, 3H). Anal. %($C_{12}H_{17}NO_2$) . Cal.: C 69.56 ; H 8.21 ; N 6.76.Tr. : C 69.09; H 8.17 ; N 6.83.

2a$_2$:$Eb_{0.6}$= 83; Rdt= 69%; IR: ν_{OH} = 3600-3395; $\nu_{C=N}$ = 1665; ^1H NMR: 7.6- 6.7(m, 9H); 4.25(q, 2H); 2.8(m, 1H); 2.2(q, 2H); 1.55(s, 3H); 1.3(t, 3H); 1.05 (t, 3H). Anal. %($C_{19}H_{23}NO_2$). Cal.: C 76.76 ; H 7.74 ; N 4.71. Tr. : C 75.92 ; H 7.58 ; N 4.64.

2a$_3$:$Eb_{0.6}$= 49; Rdt= 72%; IR: ν_{OH} = 3600-3400; $\nu_{C=N}$ = 1655. ^1H NMR: 7.35-6.6 (m, 4H); 4.25(q, 2H); 2.2(m, 1H);1.8(s, 3H); 1.35(s, 3H); 1.3(s, 6H). Anal.% ($C_{18}H_{21}NO_2$): Cal.: C 76.33 ; H 7.42; N 4.95. Tr.: C 75.98 ; H 7.37 ; N 4.92.

2a$_4$:$Eb_{0.8}$=109; Rdt= 60%; IR: ν_{OH} =3600-3400; $\nu_{C=N}$ =1660. ^1H NMR: 7.5-6.75(m, 9H); 4.25(q, 2H); 2.55(m, 1H); 1.8(s, 3H); 1.35(t, 3H); 1.3(s, 3H).

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3a$_1$:Eb$_{1.5}$ =78; Rdt 63%; IR: ν_{NH} =3320, $\nu_{C=N}$ =1660. ^{1}H NMR: 7.8-6.7(m, 9H); 4.30(q, 2H); 3.45(d, 2H); 3.95(m, 1H); 2.6(s, 1H); 2.05(q, 2H); 2.0(m, 1H);1.35(t, 3H); 1.1(t, 3H); 0.95(d, 6H). Anal.% ($C_{22}H_{30}N_2O$): Cal.:C 78.11; H 8.87 ; N 8.28. Tr. :C 77.56; H 8.59 ; N 8.24.

3a$_2$:Eb$_1$ =118; Rdt = 60%; IR: ν_{NH} =3320, $\nu_{C=N}$=1660. ^{1}H NMR:8.0-6.5(m,19H); 4.45(q, 2H); 3.95(m, 1H); 2.70(s, 1H); 1.45(t, 3H).

3a$_3$:Eb$_{1.5}$ =92; Rdt =59%; IR: ν_{NH} =3320, $\nu_{C=N}$ =1660. ^{1}H NMR: 8.0- 6,5 (m, 14H); 4.20(q, 2H); 3.75(m, 1H); 2.20(s, 3H);1.75(s, 3H);1,35(t, 3H).

4a$_1$:Eb$_{2.5}$ =102; Rdt = 74%; IR: ν_{NH} =3400 and 3385, $\nu_{C=N}$ =1665, $\nu_{C=S}$ =1100. ^{1}H NMR: 8.25(m, 1H); 7.3-6.55(m, 9H); 4.6(q, 2H);1.75(s, 3H); 1.35(t, 3H).

4a$_2$:Eb$_2$ = 90; Rdt = 70%; IR: ν_{NH} =3410 and 3385,$\nu_{C=N}$ =1665, $\nu_{C=S}$ =1100. ^{1}H NMR: 8(m, 1H); 7.6-6.7(m, 9H); 4.35(q, 2H); 2.15(q, 2H); 1.40(t, 3H); 1.1(t, 3H).

4a$_3$:Eb$_2$ = 110; Rdt = 67%; IR: ν_{NH} =3410, $\nu_{C=N}$ =1655, $\nu_{C=S}$ =1100. ^{1}H NMR: 8.10(m, 1H); 7.6-6.5(m, 14H); 4.5(q, 2H); 1.50(t, 3H).

Synthesis of benzoxazines 2b, quinazolines 3b and quinazolinethiones 4b.

The procedure described is general.

10 mmol of alkohol imidate **2a**, aminoimidate **3a** or thioamidoimidate **4a** was refluxed in chlorobenzene for 24 hours, 12 hours and 36 hours respectively. Then, the solvent was removed by evaporation and the oil residue was, either distilled at reduced pressure, when the product is liquid, or filtered and recrystallized in ethanol when the product is solid. The end of cyclisation was determined using Thin Layer Chromatography (Merck F 254).

2b$_1$:F=58; Rdt=90%; IR: $\nu_{C=N}$ =1645. ^{1}H NMR: 7.9-7.1(m, 4H); 5.05(q, 1H); 2.6(s, 3H); 2(d, 3H). Anal. % ($C_{10}H_{11}NO$): Cal.: C 74.53 ; H 6.83 ; N 8.69. Tr. : C 74.87; H 6.80 ; N 8.72.

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2b$_2$:Eb$_2$=164; Rdt=65%; IR: $\nu_{C=N}$ =1635. ^{1}H NMR: 7.4-7 (m, 9H); 2.40 (q, 2H); 1.95(s, 3H); 1.35(t, 3H). Anal. %($C_{17}H_{17}NO$): Cal.: C 81.27; H 6.77; N 5.58. Tr.: C 80.83 ; H 6.71 ; N 5.54.

2b$_3$:Eb$_{0.3}$=119; Rdt=75%; IR:$\nu_{C=N}$ =1630. ^{1}H NMR:7.4-6.95 (m, 9H);1.6 (s, 3H); 0.9(t, 3H). Anal. %($C_{16}H_{15}NO$): Cal.:C 81.01 ; H 6.33 ; N 5.91. Tr.: C 80.56; H 6.26 ; N 6.47.

2b$_4$:Eb$_{1.5}$=148; Rdt=80%; IR:$\nu_{C=N}$ =1640. ^{1}H NMR: 7.3-6.9(m, 9H); 2.10(s, 3H); 1.95(s, 3H). Anal. %($C_{16}H_{15}NO$): Cal.: C 81.01 ; H 6.33 ; N 5.91. Tr.: C 80.89 ; H 6.35 ; N 5.86.

3b$_1$:F=142; Rdt=80%; IR: $\nu_{C=N}$=1640. ^{1}H NMR: 7.8-6.55(m, 9H); 5.60(s, 1H); 3.35(d, 2H); 2.40(q, 2H); 2(m, 1H); 1.10 (t, 3H); 0.95(d, 6H). Anal. % ($C_{20}H_{24}N_2O$):Cal.:C 82.19 ; H 8.22 ; N 9.59. Tr.: C 81.85 ; H 8.16; N 9.44.

3b$_2$:F=214; Rdt=80%;IR:$\nu_{C=N}$=1640.^{1}H NMR: 7.4-6.5(m, 19H); 5.6(s, 1H).

3b$_3$:F=167; Rdt=80%; IR: $\nu_{C=N}$ =1650. ^{1}H NMR: 7.8-6.5(m, 14H); 2.45 (s, 3H); 1.90(s, 3H).

4b$_1$:F=185; Rdt=80%; IR: $\nu_{C=N}$=1660, $\nu_{C=S}$=1360. ^{1}H NMR: 7.9-6,7(m, 9H); 2.45(s, 3H).

4b$_2$:F=122; Rdt=68%; IR: $\nu_{C=N}$=1650, $\nu_{C=S}$=1360. ^{1}H NMR: 7.9-6.7 (m, 9H); 2.95(q, 2H); 1.4(t, 3H).

4b$_3$:F=207; Rdt=65%; IR: $\nu_{C=N}$=1660, $\nu_{C=S}$=1360. ^{1}H NMR: 8-6.6(m, 14H).

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