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A new and rapid access to homochiral 2,3-dihydro-oxazolo[2,3-*b*]quinazolin-5-ones

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Abstract—Starting from homochiral 1,3-oxazolidine-2-thiones **1**, a two-step sequence led to homotopic 2,3-dihydro-oxazolo[2,3-*b*]quinazolin-5-one derivatives **3**. The sequence was developed and studied regarding its scope and limitations.

1. Introduction

Within the frame of our recent studies on biotechnological synthesis using vegetable sources[1] and the reactivity of homochiral 1,3-oxazolidine-2-thiones **1**,[2] we envisaged a short sequence for the efficient synthesis of the corresponding 2,3-dihydro-oxazolo[2,3-*b*]quinazolin-5-one derivatives **3a–f** (Table 1). Many papers report on cyclo-condensation reactions involving anthranilic acid derivatives together with a wide range of substrates including imidates and iminohalides[3] (Fig. 1).

Table 1. Homochiral derivatives **3a–f** produced (Fig. 2)

Entry	**1a–f**	R1; R2; R3; R4	**2a–f** (%)	**3a–f** (%)
1	OZT	H; H; H; H	55	64
2	(+)-(5*R*)-5-Vinyl-	H; H; CH=CH_2; H	93	68
3	(−)-(5*S*)-5-Vinyl-	H; H; H; CH=CH_2	85	63
4	(−)-(5*R*)-5-Phenyl-	H; H; Ph; H	73	62
5	(+)-(4*R*)-4-Methyl-	Me; H; H; H	78	82
6	(−)-(5*S*)-5-Methyl-5-ethyl-	H; H; Me; Et	94	80

We have tried to extend this type of reaction to homochiral 1,3-oxazolidine-2-thiones with a view to providing a new access to homotopic 2,3-dihydro-oxazolo[2,3-*b*]quinazolin-5-one derivatives of the type **3**. For example, such compounds have been previously synthesized as intermediates in the synthesis of analogues of ketanserin, a prototypic 5-HT_{2a} and 5-HT_{1c} serotonin antagonist.[4] In addition, it has been shown recently that chiral analogues of ketanserin enhanced the receptor affinity in the picomolar range by the introduction of an α-methyl group.[5]

In order to build up this tricyclic skeleton, compounds **1a–f** were first reacted with benzyl bromide leading to the formation of 2-benzylthio-1,3-oxazolines **2a–f**.[6] With regard to stability, the selected *S*-benzyl derivatives were shown to be the best in the preparation of intermediate oxazolines.[7] Subsequently, the cyclization

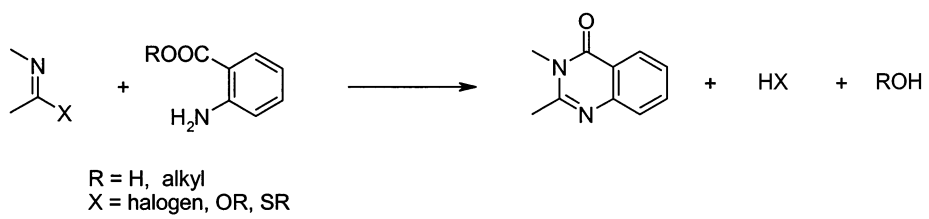

Figure 1.

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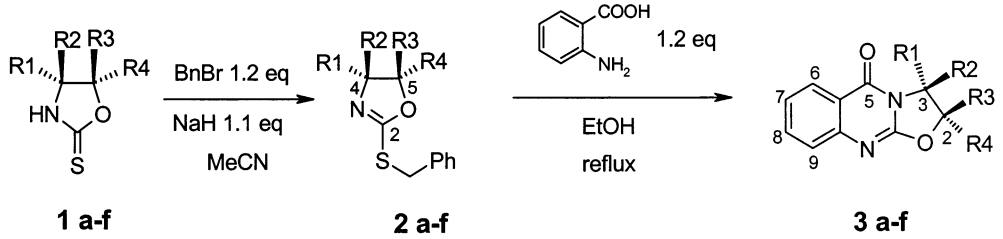


1 a-f 2 a-f 3 a-f

Figure 2.

reaction in the presence of anthranilic acid was performed in good yields.

The results obtained with the parent 1,3-oxazolidine-2-thione **1a** and homochiral derivatives **1b–f** are summarized in Table 1.

To extend the scope of the method and explore its limitations, we completed some additional trials with diverse 1,2-aromatic amino acids and oxazoline **2b** (Table 2). The results showed that the presence of an electron withdrawing aromatic system in the reagent was deleterious to the reaction. In addition, the replacement of the phenyl substituent with a pyridine ring did not allow formation of the desired compound.

In summary, a concise and practical synthesis of homochiral 2,3-dihydro-oxazolo[2,3-*b*]quinazolin-5-one derivatives has been developed starting from the corresponding 1,3-oxazolidine-2-thiones. This procedure constitutes an original extension of cyclo-condensations involving anthranilic acid.

2. Experimental

Melting points were determined with a Köfler hot-stage apparatus and are uncorrected. Specific rotations were measured at 20°C using a Perkin–Elmer polarimeter 141. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Bruker Avance DPX250 instrument operating at 250 and 62.9 MHz, respectively. The coupling constants (J) are reported in Hz and the chemical shifts (δ) in ppm downfield from tetramethylsilane as the internal standard. IR spectra were measured using a Perkin–Elmer FT Paragon 1000 PC spectrometer. Mass spectra (MS) were obtained on a Perkin–Elmer SCIEX API 300 spectrometer (Ionspray® mode).

2.1. Typical procedure for *S*-alkylation

Compounds **2** were obtained according to the procedure described by Nagao et al.[6] which was slightly modified.[2]

2.1.1. 2-Benzylthio-Δ^2-1,3-oxazoline 2a. See Ref. 6.

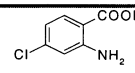
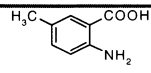
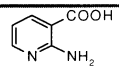
2.1.2. (5*R*)-2-Benzylthio-5-vinyl-Δ^2-1,3-oxazoline 2b. $[\alpha]_D = +9$ (*c* 1, $CHCl_3$); IR (NaCl): 1605 (C=N); ^{1}H NMR: 3.63 (dd, $J_{4b-5} = 7.7$, $J_{gem} = 13.4$, 1H, H-4b), 4.05 (t, $J_{4a-5} = 9.4$, 1H, H-4a), 4.27 (s, 2H, SCH_2), 5.04 (m, 1H, H-5), 5.24 (d, $J_{vic} = 11.5$, 1H, H-7$_Z$), 5.56 (d, $J_{vic} = 17.1$, 1H, H-7$_E$), 5.89 (m, $J_{6-5} = 7.0$, 1H, H-6), 7.26–7.49 (m, 5H, Har); ^{13}C NMR: 36.6 (SCH_2), 60.7 (C-4), 82.8 (C-5), 118.4 (=CH_2), 128.0, 129.0, 129.4, 137.0 (Car), 136.0 (=CH), 165.5 (C-2); MS: $MH^+ = 220$; HRMS calcd for $C_{12}H_{13}NOS$: 219.0718; found 219.0723.

2.1.3. (5*S*)-2-Benzylthio-5-vinyl-Δ^2-1,3-oxazoline 2c. $[\alpha]_D = -13$ (*c* 1, $CHCl_3$); HRMS calcd for $C_{12}H_{13}NOS$: 219.0718; found 219.0727.

2.1.4. (5*R*)-2-Benzylthio-5-phenyl-Δ^2-1,3-oxazoline 2d. $[\alpha]_D = +180$ (*c* 1, $CHCl_3$); mp = 120–122°C; IR (KBr): 1651 (C=N); ^{1}H NMR: 3.82 (dd, $J_{4b-5} = 7.9$, $J_{gem} = 13.5$, 1H, H-4b), 4.28 (t, $J_{4a-5} = 9.7$, 1H, H-4a), 4.30 (s, 2H, SCH_2), 5.55 (m, 1H, H-5), 7.24–7.42 (m, 10H, Har); ^{13}C RMN: 36.7 (SCH_2), 63.3 (C-4), 83.3 (C-5), 126.2, 128.0, 128.9, 129.1, 129.2, 129.4, 137.0, 140.6 (Car), 165.5 (C-2); MS: $MH^+ = 270$; HRMS calcd for $C_{16}H_{15}NOS$: 269.0874; found 269.0881.

2.1.5. (4*R*)-2-Benzylthio-4-methyl-Δ^2-1,3-oxazoline 2e. $[\alpha]_D = +8$ (*c* 0.4, $CHCl_3$); IR (NaCl): 1608 (C=N); ^{1}H NMR: 1.28 (d, $J_{vic} = 6.4$, 3H, CH_3), 3.87 (dd, $J_{4-5b} = 7.7$, $J_{gem} = 7.7$, 1H, H-5b), 4.18–4.27 (m, 1H, H-4), 4.26 (s, 2H, SCH_2), 4.43 (dd, $J_{4-5a} = 8.9$, 1H, H-5a), 7.25–7.40

Table 2. Extension to diverse heterocyclic systems

Amino acid				
Compound	**3b**	**4**	**5**	-
Yield	68 %	36 %	79 %	no reaction

(m, 5H, Har); ^{13}C NMR: 21.8 (CH_3), 36.7 (SCH_2), 62.5 (C-4), 76.0 (C-5), 128.0, 129.0, 129.4, 137.0 (Car), 165.1 (C-2); MS: $MH^+ = 208$; HRMS calcd for $C_{11}H_{13}NOS$: 207.0718; found 207.0716.

2.1.6. (5*S*)-2-Benzylthio-5-ethyl-5-methyl-Δ^2-1,3-oxazoline 2f. $[\alpha]_D = -9$ (*c* 2.9, $CHCl_3$); IR (NaCl): 1606 (C=N); ^{1}H NMR: 0.90 (t, $J_{vic} = 7.5$, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.67 (q, 2H, CH_2), 3.53 and 3.67 (2d, $J_{gem} = 13.4$, 2H, H-4), 4.23 (s, 2H, SCH_2), 7.23–7.42 (m, 5H, Har); ^{13}C NMR: 8.5 (CH_3), 25.4 (CH_3), 33.2 (CH_2), 36.4 (SCH_2), 65.0 (C-4), 89.7 (C-5), 127.9, 129.0, 129.3, 137.1 (Car), 164.5 (C-2); MS: $MH^+ = 236$; HRMS calcd for $C_{13}H_{17}NOS$: 235.1031; found 235.1023.

2.2. Typical procedure for cyclization

Compound **2b** (0.305 g, 1.39 mmol) was dissolved in ethanol (10 mL) in the presence of molecular sieves (4 Å). Anthranilic acid (0.229 g, 1.2 equiv.) was then added. The reaction mixture was refluxed for 18 h, then made neutral with aqueous sodium hydrogencarbonate and extracted with dichloromethane (3×). The combined organic phases were dried over magnesium sulfate and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/ethyl acetate 1:1) to furnish the desired compound **3b** as oil (0.202 g, 68%).

2.2.1. 2,3-Dihydro-5*H*-[1,3]oxazolo[2,3-*b*]quinazolin-5-one 3a. See Ref. 4.

2.2.2. (2*R*)-2-Vinyl-2,3-dihydro-5*H*-[1,3]oxazolo[2,3-*b*]-quinazolin-5-one 3b. $[\alpha]_D = +55$ (*c* 1.0, $CHCl_3$); IR: 1694 (C=N), 1613 (C=O); ^{1}H NMR: 4.02 (dd, 1 H, $J_{gem} = 11.3$, $J_{vic} = 7.3$, H-3b), 4.48 (dd, 1H, $J_{vic} = 8.8$, H-3a), 5.36 (m, 1H, H-2), 5.43 (d, 1H, $J = 10.5$, $=CH_{2Z}$), 5.56 (d, 1H, $J = 17.0$, $=CH_{2E}$), 6.00 (m, 1H, $J = 6.5$, =CH), 7.28 (t, 1H, $J = 7.6$, H-7), 7.47 (d, 1H, H-9), 7.63 (t, 1H, H-8), 8.11 (d, 1H, H-6); ^{13}C NMR: 47.6 (C-4), 78.8 (C-5), 118.8 (Car), 121.0 (C-7), 125.1, 126.5, 126.8 and 135.1 (CHar), 133.3 (C-6), 149.2, 155.4 and 161.1 (Car); MS: $MH^+ = 215$; HRMS calcd for $C_{12}H_{10}N_2O_2$: 214.0742; found 214.0747.

2.2.3. (2*S*)-2-Vinyl-2,3-dihydro-5*H*-[1,3]oxazolo[2,3-*b*]-quinazolin-5-one 3c. $[\alpha]_D = -60$ (*c* 1.0, $CHCl_3$); HRMS calcd for $C_{12}H_{10}N_2O_2$: 214.0742; found 214.0750.

2.2.4. (2*R*)-2-Phenyl-2,3-dihydro-5*H*-[1,3]oxazolo[2,3-*b*]-quinazolin-5-one 3d. $[\alpha]_D = +79$ (*c* 1.0, $CHCl_3$); mp = 174–176°C; IR: 1683 (C=N), 1646 (C=O); ^{1}H NMR: 4.22 (dd, $J_{vic} = 7.8$, $J_{gem} = 11.5$, 1H, H-3b), 4.74 (dd, $J_{vic} = 8.8$, 1H, H-3a), 5.93 (m, 1H, H-2), 7.32 (td, $J = 1.1$, $J = 8.0$, 1H, H-7), 7.42 (s, 5H, Har), 7.53 (dd, 1H, H-9), 7.67 (td, 1H, H-8), 8.16 (dd, 1H, H-6); ^{13}C NMR: 49.8 (C-3), 79.5 (C-2), 119.1 (C-5a), 125.2 (C-7), 126.2 (Car), 126.7 (C-9), 127.1 (C-6), 129.6 (Car), 135.3 (C-8), 137.1 (Car), 149.4 (C-9a), 155.5 (C-10a), 161.1 (C-5); MS: $MH^+ = 265$; HRMS calcd for $C_{16}H_{12}N_2O_2$: 264.0899; found 264.0908.

2.2.5. (3*R*)-3-Methyl-2,3-dihydro-5*H*-[1,3]oxazolo[2,3-*b*]-quinazolin-5-one 3e. $[\alpha]_D = -105$ (*c* 1.0, $CHCl_3$); mp = 90–92°C; IR: 1685 (C=N), 1643 (C=O); ^{1}H NMR: 1.62 (d, $J_{vic} = 6.3$, 3H, CH_3), 4.31 (dd, $J = 8.8$, $J = 4.0$, 1H, H-2b), 4.74 (dd, $J = 8.8$, 1H, H-2a), 4.90 (m, 1H, H-3), 7.31 (td, $J = 1.3$, $J = 8.0$, 1H, H-7), 7.50 (dd, 1H, H-9), 7.66 (td, 1H, H-8), 8.16 (dd, 1H, H-6); ^{13}C NMR: 19.0 (CH_3), 51.8 (C-3), 72.9 (C-2), 119.3 (C-5a), 125.1 (C-7), 126.5 (C-9), 127.0 (C-6), 135.1 (C-8), 149.4 (C-9a), 155.6 (C-10a), 161.2 (C-5); MS: $MH^+ = 203.5$; HRMS calcd for $C_{11}H_{10}N_2O_2$: 202.0742; found 202.0738.

2.2.6. (2*S*)-2-Ethyl-2-methyl-2,3-dihydro-5*H*-[1,3]oxazolo[2,3-*b*]quinazolin-5-one 3f. $[\alpha]_D = -15$ (*c* 1.0, $CHCl_3$); mp = 82–84°C; IR: 1678 (C=N), 1642 (C=O); ^{1}H NMR: 1.04 (t, $J_{vic} = 7.5$, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.90 (q, 2H, CH_2), 3.99 and 4.10 (2d, $J = 11.5$, 2H, H-3), 7.30 (td, $J = 1.1$, $J = 8.3$, 1H, H-7), 7.47 (dd, 1H, H-9), 7.64 (td, 1H, H-8), 8.17 (dd, 1H, H-6); ^{13}C NMR: 8.2 ($\mathbf{C}H_3CH_2$), 25.4 (CH_3), 33.3 (CH_2CH_3), 52.3 (C-3), 86.7 (C-2), 118.9 (C-5a), 124.7 (C-7), 126.5 (C-9), 127.0 (C-6), 135.1 (C-8), 149.7 (C-9a), 155.4 (C-10a), 161.5 (C-5); MS: $MH^+ = 231.5$; HRMS calcd for $C_{13}H_{14}N_2O_2$: 230.1055; found 230.1063.

2.2.7. (2*R*)-8-Chloro-2-vinyl-2,3-dihydro-5*H*-[1,3]oxazolo[2,3-*b*]quinazolin-5-one 4. $[\alpha]_D = +48$ (*c* 1.0, $CHCl_3$); mp = 114–116°C; IR: 1687 (C=N), 1647 (C=O); ^{1}H NMR: 4.02 (dd, $J_{vic} = 7.3$, $J_{gem} = 11.5$, 1H, H-3b), 4.49 (dd, $J_{vic} = 8.7$, 1H, H-3a), 5.39 (m, 1H, H-2), 5.47 (d, $J = 10.2$, 1H, $=CH_{2Z}$), 5.58 (d, $J = 17,1$, 1H, $=CH_{2E}$), 6.01 (m, 1H, =CH), 7.25 (dd, $J = 1.9$, $J = 8.5$, 1H, H-7), 7.47 (d, 1H, H-9), 8.04 (d, 1H, H-6); ^{13}C NMR: 47.6 (C-3), 79.1 (C-2), 117.4 (C-5a), 121.4 ($=CH_2$), 125.8 (C-7), 126.3 (C-9), 128.3 (C-6), 133.0 (=CH), 141.4 (C-8), 150.5 (C-9a), 156.2 (C-10a), 160.5 (C-5); MS: $MH^+ = 249$ and 251; HRMS calcd for $C_{12}H_9ClN_2O_2$: 248.0353 and 250.0323; found 248.0351 and 250.0319.

2.2.8. (2*R*)-7-Methyl-2-vinyl-2,3-dihydro-5*H*-[1,3]oxazolo[2,3-*b*]quinazolin-5-one 5. $[\alpha]_D = +64$ (c = 1.0, $CHCl_3$); mp = 110–112°C; IR: 1686 (C=N), 1643 (C=O); ^{1}H NMR: 2.40 (s, 3H, CH_3), 4.01 (dd, $J_{vic} = 7.2$, $J_{gem} = 11.3$, 1H, H-3b), 4.48 (dd, $J_{vic} = 8.5$, 1H, H-3a), 5.35 (m, 1H, H-2), 5.43 (d, $J = 10.5$, 1H, $=CH_{2Z}$), 5.55 (d, $J = 17.3$, 1H, $=CH_{2E}$), 6.00 (m, $J = 6.6$, 1H, CH), 7.37 (d, $J = 8.3$, 1H, H-9), 7.44 (dd, $J = 1.9$, 1H, H-8), 7.88 (sl, 1H, H-6); ^{13}C NMR: 21.4 (CH_3), 47.7 (C-3), 78.7 (C-2), 118.6 (C-5a), 121.0 ($=CH_2$), 135.1 (C-7), 126.4 (C-9 and C-6), 133.4 (=CH), 136.6 (C-8), 147.2 (C-9a), 155.0 (C-10a), 161.2 (C-5); MS: $MH^+ = 229$; HRMS calcd for $C_{13}H_{12}N_2O_2$: 228.0899; found 228.0892.

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