## AN EFFICIENT SYNTHESIS OF OPTICALLY ACTIVE 2-[4-(6-CHLORO-2-QUINOXALINYLOXY)-PHENOXY]-PROPIONAMIDE DERIVATIVES

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Abstract: An efficient synthesis of (R)-(+)-2-[4-(6-chloro-2-quinoxalinyloxy)-phenoxy]-propion-amide 4a-e is described by simple amidation of Quizalofop-methyl<sup>®</sup> [(R)-(+)-3]. The reduced susceptibility of quinoxalinyl moiety of (R)-(+)-3 toward nucleophilic reagents was discussed on the basis of QM calculation.

#### Introduction

The herbicide Fenoxaprop-ethyl<sup>®</sup> [ethyl-(R)-(+)-2-[4-(6-chloro-2-benzoxazolyloxy)-phenoxy]-propionate, (1)], a member of the 2-[aryloxy or heteroaryloxy)-phenoxy]-propionic acid chemical family, a powerful inhibitor of acetyl-CoA carboxylase (ACCase), is active on many graminaceous weed species of the genera *Avena*, *Digitaria*, *Panicum*, *Setaria*, *Sorghum* and *Echinochloa* (1-6). In the course of our study regarding the structure-activity relationship of 1, we have recently synthetized (7) its (R)-(+)-amide analogues (2a-e) whose inhibitory activity has been found to be significantly smaller than that of 1 using *Hycopersicum esculatum*, *Sinapsis alba*, *Secale cereale* and *Zea mays* as a test plant (8).



We have also recognized that (R)-(+)-2a-e could not be prepared by a simple treatment of (R)-(+)-1 with the corresponding primary amines (5a-e) at room temperature because the very rapid cleavage of its 6-chloro-2-benzoxazolyl moiety resulted quantitatively in 6a-e and (R)-(+)-7 (Scheme-1) instead of the expected amidation [(R)-(+)-1  $\rightarrow (R)$ -(+)-2a-e].



In order to study the scope and limitations of this unexpected transformation and get further information about of the structure-activity relationship concerning the herbicidal activity of 2-[4-heteroaryloxy)-phenoxy]-propionic acid derivatives, we set our sights also on the synthesis of amide analogues (4a-e) of Quizalofop-methyl<sup> $\oplus$ </sup> (3).

#### **Results and Discussions**

(R)-(+)-Methyl-2-[4-(6-chloro-2 quinoxalinyloxy)-phenoxy]-propionate (Quizalofop-methyl<sup>®</sup>, 3) was obtained from the readily available optically pure methyl-(R)-(+)-2-(4-hydroxyphenoxy)-propionate (8, ee% = 98.9) and 2,6-dichloroquinoxaline (9) prepared according to the literature (9) in the presence of potassium carbonate in dry acetonitrile at its boiling temperature in high yield (85.2%) (Scheme-2).

Then it was treated with 6 equivalents of the primary amines 5a-e using as both a solvent and reagent at the boiling temperatures of the corresponding amines. The TLC monitoring of these transformations has clearly indicated that in all cases the starting material [(R)-(+)-3] transformed only to one product whose isolation could be achieved by a simple crystallization of the crude product in good yield (76 - 97 %) (Table-1.). The structure determination of the obtained compounds was performed by <sup>1</sup>H NMR and MS confirmed the structure of this corresponding amides (R)-(+)-4a-e. Since our TLC examination has also shown that (R)-(+)-8 was not formed even in traces, it could be concluded that the nucleophilic attack of the primary amines 5a-e resulting 10a-e did not take place at the C-2 of (R)-(+)-3 at all the case of (R)-(+)-1 (7).



Scheme-2

Atom	Charge	Atom	Charge
1"	- 0.102	1'	0.091
2"	0.075	2'	- 0.177
3"	- 0.097	3'	- 0.059
4"	0.001	4'	0.022
5"	- 0.054	5'	- 0.062
6"	- 0.135	6'	- 0.126
7"	- 0.087	1	0.360
8"	- 0.065	2	0.067
		3	- 0.142

Table-2: Calculated net charges of (R)-(+)-3

Thus only the C-1 was attached in good agreement with our QM calculation (Table-2.) which clearly shows that C-1 is significantly more susceptible to nucleophilic attack than the C-2. The <sup>1</sup>H NMR measurements of (R)-(+)-4a-e in the presence of a chiral shift reagent also proved that the optical purity of (R)-(+)-3 was preserved during its amidation, as far as the accuracy of its detection by NMR measurements allows. It is noteworthy that a 3.8 Hz splitting of the doublet signal of the methyl group at C-2 by the chiral shift reagent could be also observed in the case of *rac.*-4a-e without exception.

In summary, our present results offer a simple and efficient method for the synthesis of (R)-(+)-2-[4-(6-chloro-2-quinoxalinyloxy)-phenoxy]-propionamides [(R)-(+)-4a-e] whose biological activities are under examination.

<sup>1</sup> H NMR and MS data (δ = ppm, J = Hz, e/z %)	15-0 25 (m, 2H, cyclopropyl-CH <sub>2</sub> ), 0.40-0 60 (m, 2H, cyclopropyl-CH <sub>2</sub> ), 0.85-0.95 (m, 1H, c/clopropyl-CH <sub>1</sub> , 1 65 (d, J = 7.31, 3H, CH-CH <sub>3</sub> ), 3.28 (q, J = 7.40, 2H, NH -CH <sub>2</sub> -), 4.70 (q, J = 6.60, H, CH-CH <sub>3</sub> ), 6.60 (bt, 1H, NH, 5.95-7.30 (m, 2H, H-2, H-3, H-5, H-5, H-6), 7.55-7.70 (m, 2H, H-7, -8.) 8.05 (d, J = 8.78, 1H, H-5), 8.68 (s, 1H, H-3); (n, 2H, H-3); (n, 2H, 2H, 2H, 2H, 2H, 2H, 2H, 2H, 2H, 2H	65 (d, J = 7.40 3H, CH-CH <sub>3</sub> ), 4.40 (d, J = 7.35, 2H, NH-CH <sub>2</sub> -), 4.75 (q, J = 6.80, 1H, CH-CH <sub>2</sub> ), 92 (s, 2H, O-CH <sub>2</sub> -O), 6.62-6.72 (m, 4H, NH, pyp=ron /1 H), 6.90-7 25 (m, 4H, H-2, H-3, H-5, H- ), ''.55-7.65 (m, 2H, H-7, H-8'), 8.05 (d, J = 8.60, 1H, H-5'), 8.65 (s, 1H, H-3'); 78 (M <sup>+</sup> , 100)	65 (d, J = 6.75, 3H, CH <sub>3</sub> ), 4.60 (d, J = 5.41, 2H, NH-CH <sub>2</sub> -), 4.80 (q, J = 6.80, 1H, CH-CH <sub>3</sub> ), 6.70 ss, 1H, NH), 7.00-7.30 (m, 5H, H-2, H-3, H-5, H-6, pyridyl H), 7.55-7.70 (m, 4H, H-8 <sup>°</sup> , pyridyl ;), 8.05 (d, J = 2.12, 1H, H-5 <sup>°</sup> ), 8.50-8.55 (m, 1H, H-7 <sup>°</sup> ), 8.70 (s, 1H, H-3 <sup>°</sup> )	.65 (d, J = 6.72, 3H, CH-CH <sub>3</sub> ), 4.55 (d, J = 3.23, 2H, NH -CH <sub>7</sub> -), 4.75 (q, J = 6.83, 1H, CH-CH <sub>3</sub> ), 90-7.30 (m, 6H, NH, H-2, H-3, H-5, H-6, pyridyl H), 7.50-7.70 (m, 3H, pyridyl H), 8.05 (d, J = 1.11, 1H, H-5 ), 8.50-8.55 (m, 2H, H-7 <sup>'</sup> , H-8 <sup>'</sup> ), 8.70 (s, 1H, H-3 <sup>'</sup> ); 36 (M <sup>*</sup> , 100)	.65 (d, J = 6.75, 3H, CH-CH <sub>3</sub> ), 4.50 (d, J = 5.49, 2H, NH-CH <sub>2</sub> -), 4.80 (q, J = 6.76, 1H, CH-CH <sub>3</sub> ), .90-7.30 (m, 7H, NH, H-2, H-3, H-5, H-6, pyridyl H), 7.55-7.65 (m, 2H, pyridyl H), 8.05 (d, J = .62, 1H, H-5 ), 8.50-8.55 (m, 2H, H-7, H-8 ), 8.65 (s, 1H, H-3 ); 36 (M <sup>+</sup> , 100)
$\begin{bmatrix} \alpha \end{bmatrix}_{D}^{25}$ $(c = 1 \%)$ $(solvent)$	+19.7 (CHCl <sub>3</sub> )	+51.5.) (CHCl <sub>3</sub> )	+42.90 (CHCl <sub>3</sub> )	+35.20 (CHCl <sub>3</sub> )	+23.00 (CHCl <sub>3</sub> )
 Purity % (HPLC)		6.66	8.66	8.00	6.06
M. p. (°.7) (solven:)	142 – 144 (EtOH)	163 – 165 (Hexane – acetone 2:1)	143 – 145 (Hexane – acetone 2:1)	174 – 176 (EtOH)	183 – 185 (Hexane – acetone 2:1)
Yield (%)	87	83	80	97	76
React. time (h)	e	4	14	10	L
Comp.	4a	4	5. 2	4d	46

Table-1: Characterization of Compound (R)-(+)-4a-e

### Experimental

Melting points were determined on a Büchi 535 apparatus and are not corrected. <sup>1</sup>H-NMR spectra were obtained on a Varian Gemini 200 NMR spectrometer in CDCl<sub>3</sub> with TMS as internal standard. EI-MS spectra were obtained with a VG TRIO-2 instrument. TLC was performed on Merck Kieselgel 60  $F_{254}$  pre-coated aluminium plates. The purity of the products was determined on a HP 1090 liquid-chromatograph and it has been found to be over 99.5 %. Column: Hypersil MOS (100 x 4.6 mm), solvent: (A) 0.01 N potassium dihydrogen sulphate with 0.1 % (v/v) H<sub>3</sub>PO<sub>4</sub> (99.99 %) and 10 % (v/v) methanol; (B) methanol. The gradient was increased from 10 % B to 75 % B with a flow rate of 0.5 mL / min. Optical rotation was measured with a Perkin-Elmer 241 polarimeter at the sodium – D line at the concentration of I g/100 mL. The optical purity of the compounds was determined by <sup>1</sup>H NMR (Bruker WP 200 SY) using tris[3-(trifluoromethylhydroxymethylene)-dcamphorato]europium (III) as chiral shift reagent. QM was performed by a MOPAC package (PM3 Hamiltonian) implanted the CaChe programme (10).

#### Preparation of methyl-(R)-(+)-2-[4-(6-chloro-2-quinoxalinyloxy)-phenoxy]-propanoate (3).

A mixture of (*R*)-(+)-8 (40.4 g, 0.2 mol), 2,6-dichloroquinoxaline (9) (39.8 g, 0.2 mol) and anhydrous potassium carbonate (27.6 g, 0.2 mol) was heated at reflux with stirring in dry acetonitrile (250 mL) until no starting material (8) could be detected (6 hours). The hot mixture was filtered, the residue was washed with warm acetonitrile, and the filtrate was evaporated to dryness. The residue was dissolved in toluene (1000 mL) and was extracted with water (500 mL). The organic layer was washed with water (500 mL) then dried (Na<sub>2</sub>SO<sub>4</sub>), treated with charcoal, filtered and evaporated. The crude residue was crystallized from ethanol (400 mL) to give (*R*)-(+)-3 as white crystals of mp. 114 – 115 °C (85.2 %),  $[\alpha]_D^{20} = + 37.17$  (c = 1 %, CHCl<sub>3</sub>). Lit. mp. 112 - 114 °C,  $[\alpha]_D^{31} = + 32.8$  (c = 1.20 %, CHCl<sub>3</sub>) (9).

# General procedure for the preparation of the (R)-(+)-2-[4-(6-chloro-2-quinoxalinyloxy)-phenoxy]-propionamide [(R)-(+)-4a-e].

A mixture of (R)-(+)-3 (8.97 g, 0.025 mol, ee % = 98.9) and the primary amines 4a-e (0.15 mol) was heated with stirring at the boiling temperature of the amine under nitrogen atmosphere until no starting material could be detected by TLC. Then the excess of the amines was evaporated in vacuo. The residue was dissolved in chloroform (100 mL) and subsequently washed with 5 % hydrochloric acid (2 x 50 mL), saturated sodium hydrocarbonate (2 x 20 mL) and water (3 x 20 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporation gave the crude product whose crystallization yielded solid products (see in Table-1).

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