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PRELIMINARY NOTE

Synthesis of Ethyl 2-[4-(3-Fluoro-2-quinoxalinyloxy)phenoxy]propanoate as Herbicide

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SUMMARY

The syntheses of ethyl 2-[4-(3-fluoro-2-quinoxalinyloxy)phenoxy]-propanoate (1d), a new fluoro analogue of the herbicide quizalofop-ethyl, from 2,3-dichloroquinoxaline (3) and of ethyl 2-[4-(6-chloro-3,4-dihydro-3-oxoquinoxalinyl-2-oxy)phenoxy]propanoate (9) from ethyl 2-[4-(3,6-dichloro-2-quinoxalinyloxy)phenoxy]propanoate (2b) via nucleophilic substitution with cesium fluoride coupled with 18-crown-6 are described.

In connection with our continuing studies on the structure-activity relationship of ethyl 2-[4-(6-chloro-2-quinoxalinyloxy)-phenoxy]propanoate (2a) (code No. NCI-96683, quizalofop-ethyl), a selective herbicide for gramineous weeds and its related compounds

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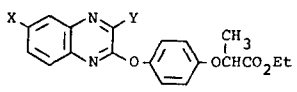
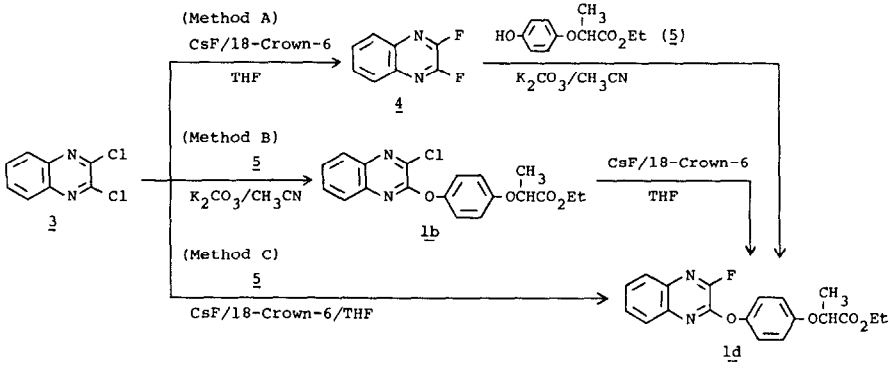
[1-3], we now report the synthesis of new ethyl 2-[4-(3-fluoro-2-quinoxalinyloxy)phenoxy]propanoate (1d), the first 3-fluoro analogue with the most potent activity among those of the 3-substituted analogues involving 1b,c (Fig. 1).



1a; X=H, Y=H 2a; X=Cl, Y=H
1b; X=H, Y=Cl 2b; X=Cl, Y=Cl
1c; X=H, Y=Me 2c; X=Cl, Y=Me
1d; X=H, Y=F 2d; X=Cl, Y=F

Fig. 1. 2-[4-(2-Quinoxalinyloxy)phenoxy]propanoic Acid Derivatives

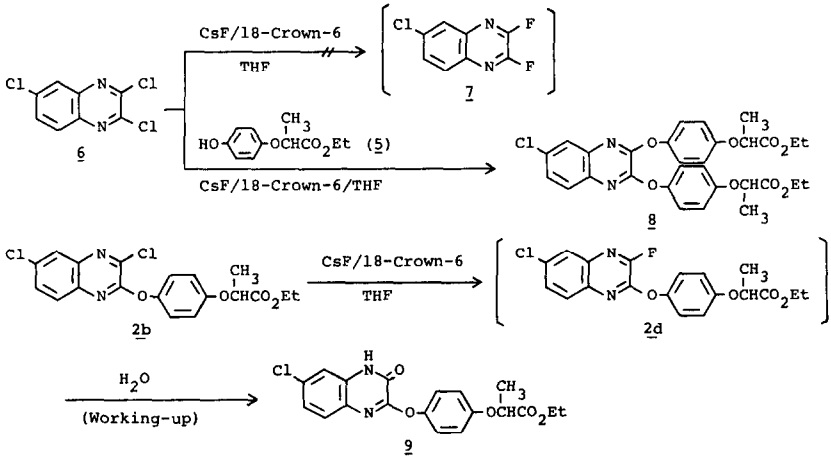
Three methods A, B and C have been developed to synthesize 1d as described in Scheme 1. We recently reported that the substitution of the 2- and 3-chlorine atoms of 2,3-dichloroquinoxaline (3) best proceeded with cesium fluoride (CsF) as coupled with 18-crown-6 in THF at room temperature [4], affording 2,3-difluoroquinoxaline (4) in 64% yield [5]. In the method A, 4 was condensed with ethyl 2-(4-hydroxyphenoxy)propanoate (5) (1 eq) in the presence of anhydrous potassium carbonate (4 eq) in acetonitrile under reflux, and was converted selectively to 1d in 84% yield. In the method B, the



Scheme 1. Synthetic Routes to Ethyl 2-[4-(3-Fluoro-2-quinoxalinyloxy)-phenoxy]propanoate.

3-chloro analogue 1b was prepared from 3 in 81% yield, and the fluorination of the 3-position of 1b was attempted using CsF (6 eq) coupled with 18-crown-6 (1 eq) in THF. After reflux for 18 h, the conversion of 1b to 1d was 45% with no obvious side reactions. Finally, the method A has been modified into an one-pot synthesis of 1d from 3 by nucleophilic fluorination followed by the condensation (the method C), in which 3 was treated with 5 (1 eq) in the presence of CsF (8 eq) - 18-crown-6 (1 eq) in THF under reflux, yielding 1d in 62% yield [A].

Furthermore, 2,3,6-trichloroquinoxaline (6) was applied in these methods for synthesis of 2d, but it gave rise to quite different results from those with 3 (Scheme 2). No obvious products containing halogenated quinoxaline rings were obtained by the method A, and we assume that a potential intermediate 6-chloro-2,3-difluoroquinoxaline (7) is so unstable that it underwent rapid decomposition during working-ups for isolation. In the method B, ethyl 2-[4-(6-



Scheme 2. Methods Applied for Synthesis of Ethyl 2-[4-(6-Chloro-3-fluoro-2-quinoxalinyloxy)phenoxy]propanoate.

chloro-3,4-dihydro-3-oxoquinoxalinyl-2-oxy)phenoxy]propanoate (9) was the sole product in 77% yield [B], which is possibly as a result of spontaneous hydrolysis of the fluorine atom at 3-position. Moreover, the condensation of 6 with 5 (1 eq) in the presence of CsF - 18-crown-6 afforded only 6-chloro-2,3-bis[4-(1-ethoxycarbonylethoxy)-phenoxy]quinoxaline (8) [C] in 29% yield (vs. 6), whereas the condensation with anhydrous potassium carbonate in place of CsF - 18-crown-6 gave 8 as a minor product in addition to 2b and the 3,7-dichloro isomer of 2b as the major.

The growth inhibitory activity of 1a-d to rice plant (Oryza sativa) was examined, and we found that the inhibitory activity (pI_{50}) [D] of 1a-d to rice root growth increased in the following order: 1b <(4.57) < 1c (4.67) < 1d (5.55) < 1a (7.23).

In this study, it has been deduced that the presence of a chlorine atom at the 6-position of the quinoxaline ring of 1a causes a strong electron-withdrawing effect on the 3-position of the quinoxaline ring, as is revealed by the rapid hydrolysis or the further etherification at the 3-position in the attempted synthesis of the 3-fluoro derivatives, and that the herbicidal activity of the 2-[4-(2-quinoxalinyloxy)phenoxy]propanoates increases in the decreasing order of bulkiness of the substituent on the 3-position of the quinoxaline ring.

FOOTNOTES

A The method C for the synthesis of 1d is described: To a suspension of CsF (491 mg, 3.23 mmol) and molecular sieves 4A (1.0 g) in 5 ml of dry THF, was added 18-crown-6 (106 mg, 0.40 mmol) at room temperature under stirring in nitrogen. After stirring for 1 h, 3 (80 mg, 0.40 mmol) and 5 (84 mg, 0.40 mmol) were added and the mixture was refluxed for 6 h. After celite-filtration of the

mixture followed by washing with a small amount of THF, the solvent was evaporated and ethyl acetate (30 ml) was added. The ethyl acetate solution was washed with water and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was chromatographed on silica gel with chloroform to obtain 88 mg (62%) of 1d (nc), mp 98-99°C; IR(KBr): 1736 (O-C=O) cm^{-1}; MS m/z 356 (M^+), 283 (base peak, M^+-CO_2Et), and 255 ($M^+-CH(CH_3)CO_2Et$).

B The reaction procedure for the synthesis of 9 is described: To a suspension of CsF (179 mg, 1.18 mmol) and molecular sieves 4A (1.0 g) in 5 ml of dry THF, was added 18-crown-6 (53 mg, 0.20 mmol) at room temperature under stirring in nitrogen. After stirring for 1 h, 2b (81 mg, 0.20 mmol) was added and the mixture was refluxed for 5 h. After the same working-up as described for 1d (method C), the resultant crude product was purified by column chromatography on silica gel with chloroform to give 60 mg (77%) of 9, (nc), mp 216-217°C; IR(KBr): 1732 (O-C=O) and 1680 (N-C=O) cm^{-1}; MS m/z 388 (M^+, base peak), 315 (M^+-CO_2Et), 260, and 259.

C 8: colorless oil. IR(KBr): 1740 (O-C=O) cm^{-1}; MS m/z 580 (M^+, base peak), 552 ($M^+-CH_2=CH_2$), 507 (M^+-CO_2Et), and 451 ($M^+-CH(CH_3)CO_2Et-CH_2=CH_2$).

D The pI_{50} indicates negative logarithm of the molar concentration required for 50% inhibition of the root growth to the control.

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