Chapter 18

Synthesis of the New Graminicide Propaquizafop

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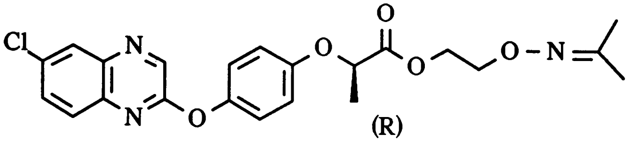
Propaquizafop 1 is a new chiral post-emergence graminicide. Some of the approaches to the synthesis of the required intermediates are presented, and various possibilities for assembling the molecule with sterochemical control are discussed.

Propaquizafop 1 is a new highly active post-emergence graminicide. It combats a broad spectrum of annual and perennial grass species, including johnsongrass, bermudagrass and quackgrass in broadleaved crops like soybeans, cotton, sugarbeet and rape (1).



1 Propaquizafop

2-[(Isopropylideneamino)oxy]ethyl (R)-2-[p-[(6-chloro-2-quinoxalinyl)oxy]phenoxy]propionate

Herein we report some results of the investigations we undertook toward a suitable large scale synthesis of this chiral molecule.

First, we concentrated our efforts on the preparation of the various intermediates which were not commercially available: 2,6-dichloroquinoxaline 2, 2-[(isopropylideneamino)oxy]ethanol 3 and the tosylate 4. Then, we studied the various possiblities of assembling propaquizafop.

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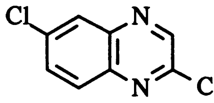

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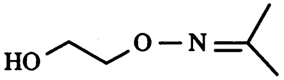
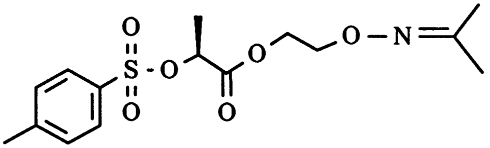


3 (oximeglycol)



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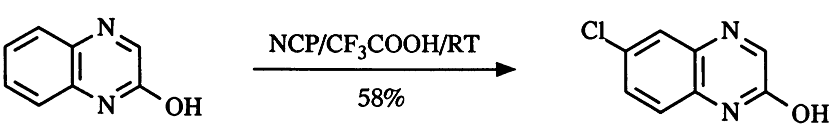
6-Chloro-2(1H)-quinoxalinone 6, the precursor of 2,6-dichloroquinoxaline was our first target. Several methods have been carefully evaluated to prepare this key intermediate which represents the most expensive part of our molecule. The simplest method would certainly be the regioselective chlorination of 2(1H)-quinoxalinone (5). However, the halogenation in acetic acid is known to occur mainly at position 7, (2). Only recently, a direct chlorination of 6 in concentrated sulphuric acid in the presence of silver sulphate has been reported to afford exclusively 6-chloro-2(1H)-quinoxalinone in 51% (3).

We found a method for the selective chlorination at position 6 by using N-chloropiperidine in trifluoroacetic acid (scheme 1), but the yield did not exceed 58%. Furthermore, the conversion was incomplete with both methods. However a process for producing 6 in high yield without contamination by isomeric impurities and starting from a cheap starting material was required.

Scheme 1. Chlorination of 2(1H)-quinoxalinone



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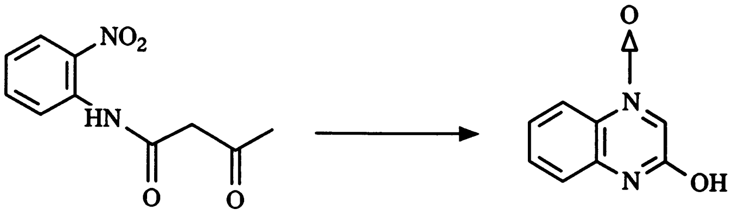
For the synthesis of 2(1H)-quinoxalones, Tennant has reported an intramolecular cyclisation reaction (scheme 2) of 2'-nitroacetoacetanilide 7 to 2(1H)-quinoxalinone-4-N-oxide 8 in aqueous sodium hydroxide. This method has been used (4) also for the regioselective preparation of various substituted 2(1H)-quinoxalinone-4-oxides and extended with a reduction step to afford 6-halo-2(1H)-quinoxalinones (5,6) as intermediates for pharmaceutical and agricultural chemicals. The 2'-nitroacetoacetanilides were obtained from the nitroanilines with diketene and mercuric acetate as catalyst in acetic acid or catalytic amounts of triethylamine in refluxing benzene.

Scheme 2. Intramolecular cyclisation, according to Tennant



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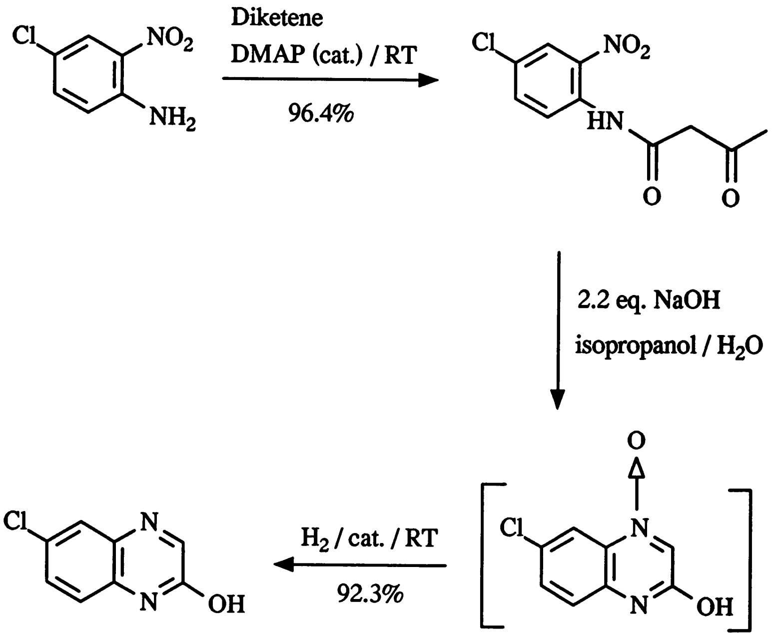
We have utilized this reaction path with some modifications (scheme 3). The diketene addition to 4-chloro-2-nitroaniline occurred spontaneously at room temperature with traces of 4-dimethylaminopyridine. Cyclisation and reduction were then completed in a one-pot procedure in a mixture of isopropanol and water. This allowed the use of only 2.2 equivalents of sodium hydroxide instead of 5 to 6 in water and to control the temperature of the cyclisation at ~65°C. Various catalysts, particularly Raney nickel (7) or palladium on charcoal (8) were known to be efficient for the hydrogenation of the N-oxide. Eventual overreduction to the 3,4-dihydro-2(1H)-quinoxalinone could be smoothly compensated by reoxidising with hydrogen peroxide or air (9).

Scheme 3. Preparation of 6-chloro-2(1H)quinoxalinone from acetoacetanilide



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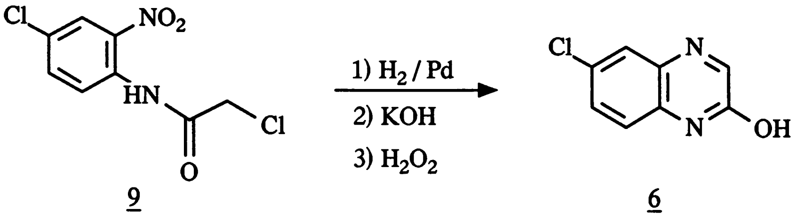
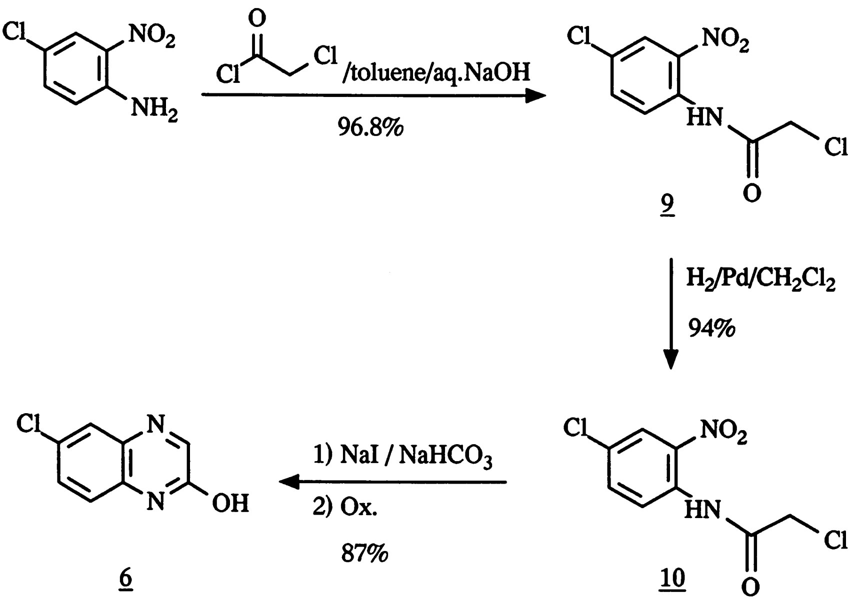
Another regioselective intramolecular cyclisation was found in the patent literature (10). It claims a one-pot procedure to produce the quinoxalone 6 from 4-halo-2-nitro-monohaloacetanilide 9,(scheme 4).

Scheme 4. Jap.Pat.Appl. J5 7062-270



When the published procedure using methanol or ethanol was employed, many additional products were found in the reaction mixture. This procedure was improved by a few odifications (scheme 5).

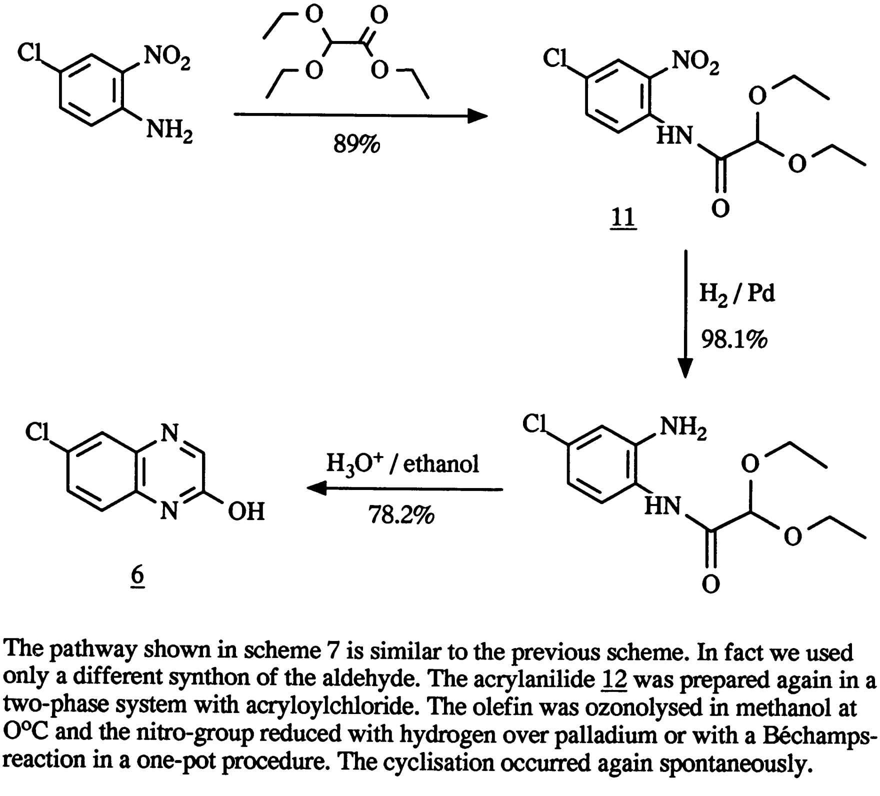
Scheme 5. Preparation of 6-Chloro-2(1H)quinoxalinone form chloroacetanilide 9



The chloroacetanilide 9 was prepared in a two-phase system, without phase-transfer catalyst. The nitro group was reduced by a catalytic hydrogenation in a chlorinated solvent to give a stable product 10. The cyclisation step was initiated with sodium iodide and one equivalent of sodium bicarbonate was added to regenerate the catalyst. Finally, we obtained the product in fair yields after an oxidation with air or hydrogen peroxide (5).

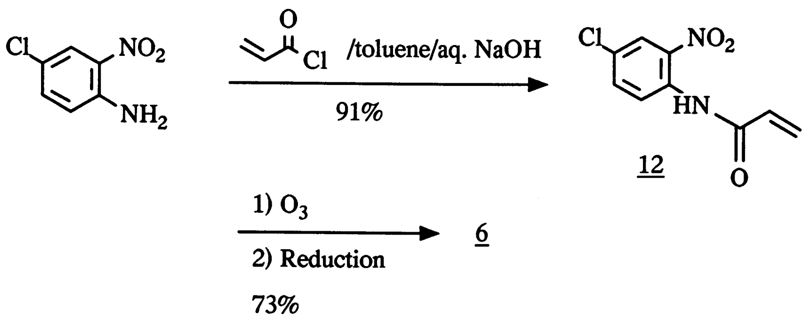
A new alternative approach is shown in scheme 6. 4-Chloro-2-nitroaniline was acylated with methyl dimethoxyacetate. The intermediate 11 is reduced by catalytic hydrogenation. After hydrolysis of the acetal with a sulfonated resin and water, cyclisation was spontaneous and a pure product was isolated in the indicated yield.

Scheme 6. Preparation of 6-chloro-2(1H)quinoxalinone from dimethoxyacetanilide 11



The pathway shown in scheme 7 is similar to the previous scheme. In fact we used only a different synthon of the aldehyde. The acrylanilide 12 was prepared again in a two-phase system with acryloylchloride. The olefin was ozonolysed in methanol at 0°C and the nitro-group reduced with hydrogen over palladium or with a Béchamps-reaction in a one-pot procedure. The cyclisation occurred again spontaneously.

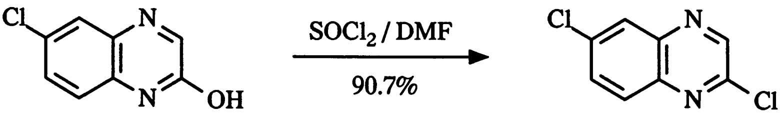
Scheme 7. Preparation of 6-chloro-2(1H)-quinoxalinone by ozonolysis



In all the above sequences, no detectable amount of 7-regioisomers was observed.

The conversion of the quinoxalone 6 into 2,6-dichloroquinoxaline 2 was readily achieved by chlorination in toluene with the Vilsmeier reagent (scheme 8) (11).

Scheme 8. Chlorination of 6-chloro-2(1H)-quinoxalinone



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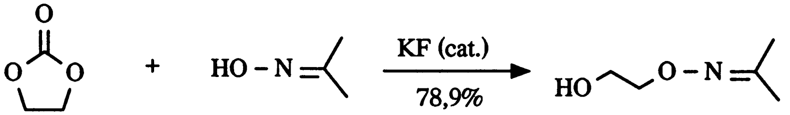
The simplest and most efficient possibility to prepare the oximglycol 3 is the addition of acetoneoxime to ethylene carbonate, catalysed by traces of potassium fluoride and tetramethylammonium chloride in refluxing toluene (scheme 9). After distillation, 3 was obtained in a high degree of purity.

Scheme 9. Synthesis of oximglycol 3



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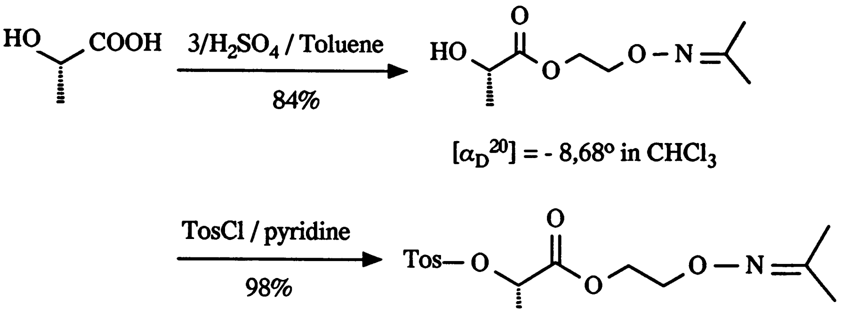
Having the oximeglycol 3, we undertook the synthesis of the tosylate 4. Two ways gave satisfying results. The first one (scheme 10) began with a classical esterification of <s>-lactic acid with oximglycol in toluene (12). The tosylate 4 was obtained in practically quantitative yield, high optical purity (>98% e.e.) and used without further purification in the next step.

Scheme 10. Synthesis of tosylate 4 from <S>-lactic acid



$[\alpha_D^{20}]$ = - 8,68° in $CHCl_3$

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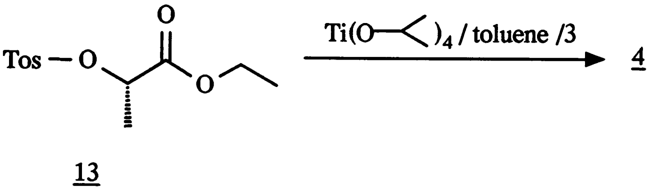
The second variation starts from the known intermediate 13 obtained upon tosylation of <S>-ethyl-lactate (13). It was transesterified with oximeglycol (3), using an ortho-titanate as catalyst (14) in refluxing toluene and under continuous removal of ethanol. The isolated product was again isolated in practically quantitative yield and in high optical purity.

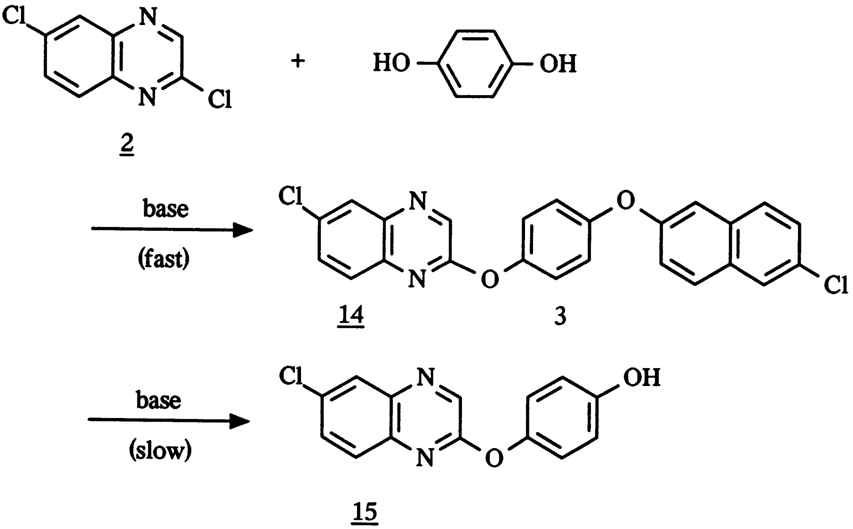
Scheme 11. Synthesis of tosylate 4 from <S>-ethyl lactate



The first possibility of assembling our intermediates was to prepare first the 4-[(6-chloro-quinoxalinyl)-oxy]phenol 15 (scheme 12) which was linked with the tosylate 4 in the next step (scheme 13).

The preparation of 15 has been reported by Sakata et al. (15). 2,6-Dichloroquinoxaline 2 and a three fold excess hydroquinone were refluxed with potassium carbonate in dimethylformamide. The bis-adduct 14 was formed as main product in an early stage and cleaved to 15 with the excess hydroquinone.

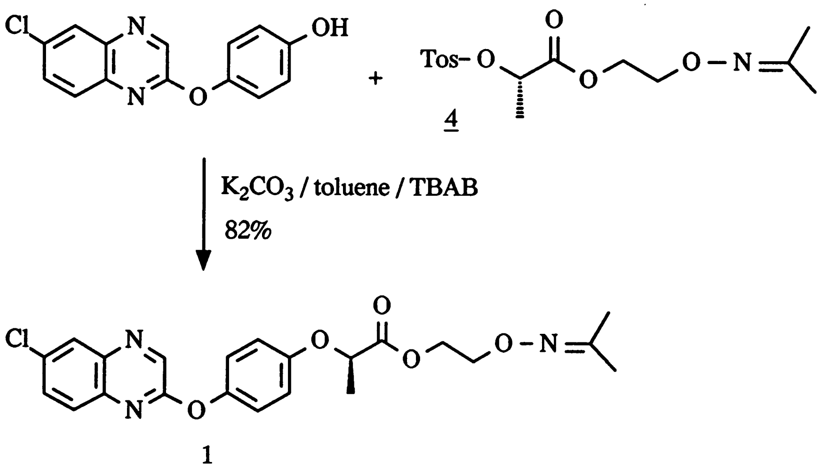
Scheme 12. Synthesis of 4-[(6-chloro-quinoxalinyl)oxy]phenol 15



We performed this reaction in water with potassium hydroxide as a base and an excess hydroquinone. Here, the desired product precipitated as soon as it was formed and only traces of the bis-adduct were detected. A simple filtration allowed the isolation of a very pure product. Products in the filtrate can be recycled.

Linkage of 15 with the tosylate 4 was performed in refluxing toluene with potassium carbonate as a base and tetrabutylammonium bromide as phase transfer catalyst (scheme 13). The conversion was complete within five hours in about 95% e.e. After crystallisation, 1 was isolated in 98% e.e. and 82% yield. However, several percent of the bis-adduct 14 were formed in this reaction. Although it could be removed easily, this lowered considerably the overall yield and represented a drawback for this route.

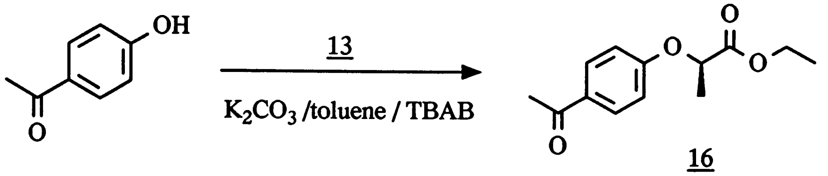
Scheme 13. Linkage of the tosylate 4



The second way of assembling our molecule was to link 2,6-dichloroquinoxaline with 4-(hydroxyphenoxy)propionyl ester 19 in the last step (scheme 16).

To prepare 19, we started with 4-hydroxyacetophenone which acted as a masked form of hydroquinone. It was condensed with the tosylate 13 in refluxing toluene with potassium carbonate as base and tetrabutylammonium bromide as phase-transfer catalyst. The intermediate 16 was isolated in over 98% e.e. and in 94% yield.

Scheme 14. Synthesis of a masked phenolic function



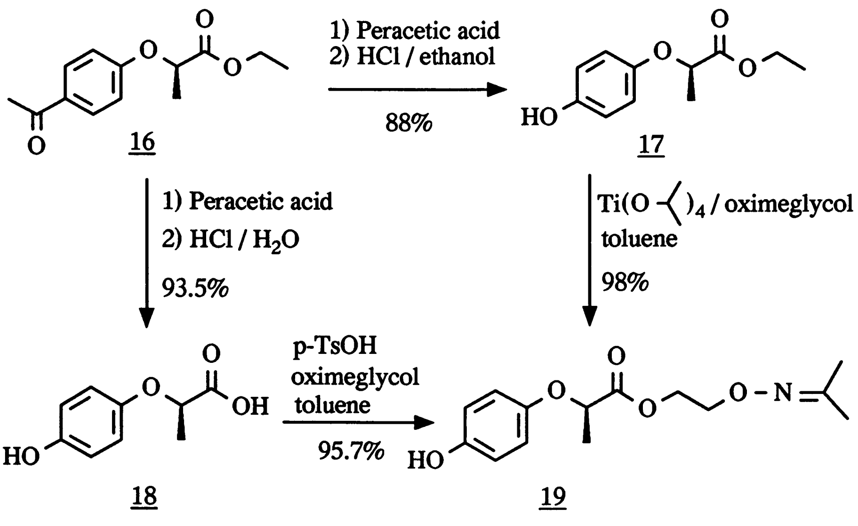
The phenolic function was generated with a Bayer-Villiger reaction (scheme 15). Peracetic acid or sodium perborate were used as oxidising agents in acetic acid at a temperature of 55-60°C. The subsequent transesterification with ethanol and HCl afforded the ester 17 whereas a hydrolysis with aqueous hydrochloric acid gave the 4-(hydroxyphenoxy)propionic acid 18. The desired intermediate 19 was obtained either by transesterification of 17 or by a classical esterification of the acid 18 with only a 0.1 fold excess of oximeglycol in refluxing toluene.

It is noteworthy that no racemisation has been detected in any step of this scheme and that 19 can be introduced into the step without further purification.

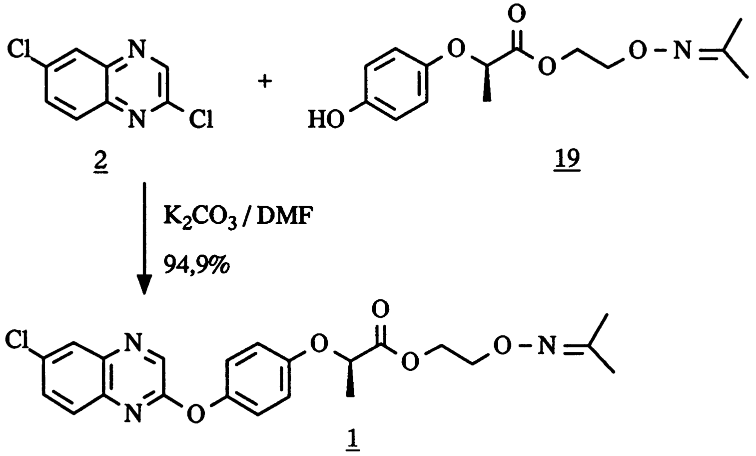
The linkage of 2,6-dichloroquinoxaline 2 with 19 was performed in dimethylformamide with potassium carbonate at 80°C (scheme 16). The conversion was complete within three hours, without racemisation (99% e.e.) and the product 1 isolated in 94.9% yield.

In conclusion, we have developed several efficient methods to prepare 6-chloro-2(1H)-quinoxalinone. Various possibilities of assembling the molecule propaquizafop allow the comparison of their efficiency for the purpose of industrial process.

Scheme 15. Generation of the phenolic function



Scheme 16. Linkage of 2,6-dichloroquinoxaline



Literature Cited

1. P. Bocion, P. Mühlethaler and P. Winternitz; Proc. 1987, British Crop Protection Conference -Weeds, Vol 1, p.55
2. P. Linda and G. Marino, Chem.Abstr., 1963, 59, 7523,
3. G. Sakata and K. Makino, Chemistry letters, 1984, 323
4. B. Miller, J.P. English, US Patent, 3,708,580, 1973
5. G. Sakata, K. Makino and K. Morimoto, Heterocycles, 1985, 23, 143
6. R.F. Davis, US Patent, 4,636,562, 1987
7. R.C. Anderson and R.H. Fleming, Tetrah. letters, 1969, 1581
8. R. Fusco and S. Rossi, Gazz.Chim.Ital., 1964, 94, 3
9. F. Cuiban, Bull.Soc.Chim.Fr., 1963, 356
10. Jap.Patent appl., J5 7062-270, 1982
11. L. Imru, G. Gyertyanffy, G. Scermely; L. Dobos, H. Hahebzade, G. Ledniczky, Hung. Teljes, 16'813, 1979
12. C.H. Holten, A. Müller and D. Rehbinder in Lactic Acid, Verlag Chemie, Weinheim 1971
13. J.H. Chan, F. Walker, Chien K. Tseng, Don R. Baker and D.R. Arneklev, J.Agr.Food.Chem., 1975, 23 (5), 1008
14. K.P. Schnurrenberger, CH-Patent, 319/87
15. G. Sakatu, K. Makino and F. Hashiba; Heterocycles, 1984, 22, 2581

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