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Utilization of structure-property relationships as a guide for achievement of high optical purity in aryloxyphenoxypropionates

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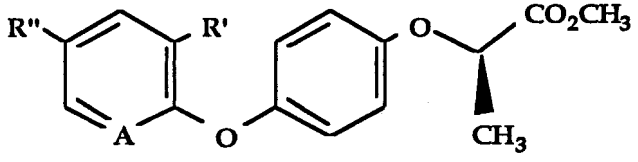
Aryloxyphenoxypropionates (1, A = CH or N)are an interesting and highly effective class of crop protectants. A number of these highly active aryloxyphenoxypropionates have been commercialized by several companies over the past decade.



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These materials are used effectively in a number of crops including soybeans and cereal grains, such as wheat and rice, to control grassy weed pests. In contrast to the more traditional herbicides with high dosage rates, these materials are effective at much lower application rates, in the range of tens of grams per acre in some cases. All of these compounds contain a chiral center in the propionic acid portion of the molecule, and this chiral center is important to the observed biological effectiveness.[1,2] Even though some of these materials are sold as racemic mixtures, it is known that only the R enantiomer is active, whereas the S enantiomer is inactive. Thus, being able to make only the desired optical isomer of these materials with high optical purity becomes one of the prime driving forces in the development of viable commercial synthetic routes to these compounds.

Overall, there are number of potential routes to this goal including the use of resolving agents on the racemic mixture,[3,4] enzymatic resolution, [5,6,7] and direct chemical synthesis.[8,9] From a retrosynthetic viewpoint, there are two main routes to introduction of the desired chirality into these type of molecules, Scheme 1. One route would involve synthesis of the appropriate aryloxyphenol and subsequent reaction with a chiral alkylating agent of the S configuration.[10] Alternatively, the chiral center could be introduced into a monoalkylated hydroquinone intermediate (2-(4-hydroxyphenoxy)propionate) and this could then be coupled to an appropriately substituted aromatic portion.[11,12,13] One obvious requirement of any of these routes would be that it be able to produce a product of relatively high R isomer content, in the range of 95% (90% ee) or greater.

It could be predicted that the coupling of a substituted phenol with a chiral alkylating agent, as in the first mentioned scheme would produce a product whose optical purity would depend on a number of factors (solvent, base). Certainly of importance among these would be the nature of the leaving group, X, in the alkylating agent. In our hands, the reaction of either 2-(4-(3-chloro or -fluoro-5-trifluoromethylpyridinyl)oxy)phenol with 99% S-(-)-methylpropionate tosylate in DMSO using potassium carbonate as the base gave the corresponding R-(+) products with moderate ee, in the range of 84 - 85%. Thus it was apparent that even with relatively good leaving groups, high optical purity products could not be obtained directly. [14] In fact it was our general observation that in working with a number of substituted phenol systems, solvents, and alkylating agents, that a combination of factors were important in order to obtain high optical purity. For example with less reactive phenols, such as 4-isopropenylphenol and 4-mesylphenol, in reactions with S-(-)-methyl 2-chloropropionate in organic solvents, generally the resulting products had relatively low ee, <50%. However, with more reactive phenols, such as hydroquinone[15] or 4-methoxyphenol, in water as the solvent with the same alkylating agent, the resulting products had much higher ee, greater than 80%.

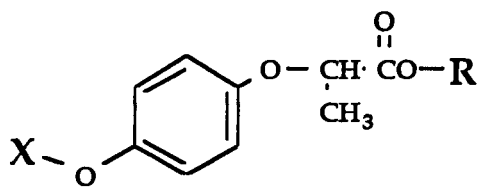
These observations can be understood by a scheme which outlines the various routes by which racemization can occur. One pathway involves racemization of the alkylating agent, ie, methyl 2-chloropropionate by displacement by chloride ion, that occurs before reaction with the phenol can occur. This would be more prevalent in a solvent such as DMSO, where chloride is a better nucleophile, than in water. In addition, with less reactive phenols, the rate of the desired displacement reaction to give the R product, would be less competitive with the rate of racemization by abstraction of a proton from the alkylating reagent to give a planar intermediate and inversion, than with the more reactive phenols. Finally, a third pathway for racemization would involve racemization of the product by proton abstraction and reprotonation.

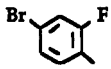
Taking all these factors into consideration, we found that the highest optical purity products could be obtained by a route which involved initial formation of R-(+)-2-(4-hydroxyphenoxy)propionic acid, followed by conversion of this intermediate to the dipotassium salt with potassium carbonate in DMSO , and then coupling of this disalt with the corresponding substituted aromatic portion (typically at 95 °C, 6 hr). This scheme was utilized with aromatic substrates 1,2-difluoro-4-cyanobenzene and 2,3-dichloro-5-(trifluoromethyl)pyridine.

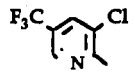
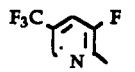
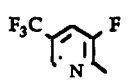
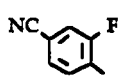
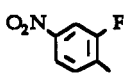
Through formation of the disalt, racemization of the chiral intermediate is prevented since abstraction of the proton at the 2-position to form the planar intermediate would result in two negative charges in close proximity. Similarly, after coupling, racemization of the potassium salt of the acid product is minimal for the same reasons. In the two cases studied, the corresponding esters of the acids were desired, so the intermediate salts were reacted in-situ with methyl iodide to give the methyl esters. Using this approach, we were able to produce very high optically pure products (greater than 99% ee) with essentially no loss in optical purity across the coupling and esterification steps.[16]

In Table I is a listing of melting points of racemates, and the corresponding R enantiomers (including intermediates and products in both acid and methyl ester forms) as well as an indication of those compounds for which X-ray crystal structures have been determined. [17] Correlations can be drawn between the physical properties and the corresponding X-ray structures. First of all it should be noted there is a range of melting points from about 150° C at the high end to 30 - 50° C at the low end.

Table I. Physical Properties of Intermediates and Products



X	R	(+), mp , ° C	(R), mp , ° C	X-Ray Structure
-H	-H	142 - 143	145 - 147	±, R
-CH3	-H	92 - 93	61 7 - 62.8	
	-H	110	82 - 82.7 - anh. (hydrate)	±

	-H	105 - 107	63 - 64 - anh. (hydrate)	±
	-H	135 - 136	glass - anh. (hydrate)	± R (hydrate)
-H	$-CH_3$	55 - 56	64 - 65	R
	$-CH_3$	55 - 56	35 - 36	
	$-CH_3$	57 - 58	68 - 69	± R
	$-CH_3$	80 - 80.5	54 - 56	±, R

Also it can be seen that in some cases there are significant differences in the melting points between the racemic mixtures and the R enantiomers, whereas in other cases the differences are quite small. In general, the mps of the acids are higher than for the corresponding methyl esters, as would be expected, mainly because of hydrogen bonding interactions in the free acids.

The highest melting compound of the series, 2-(4-hydroxyphenoxy)propionic acid (mp 142 -143° C for the racemate, mp 145 -147° C for the R isomer) exhibits few differences between the two crystal structures. The carboxylate group and the 4-hydroxy groups are in a syn juxtaposition in the racemate and in an anti arrangement in the R form. In addition, both of these compounds form an extensive head to tail hydrogen bonded network. This strongly hydrogen bonded network obviously contributes to the higher observed melting points. When the hydroxy acid is converted to the methyl ether, and the 4-hydroxy group is no longer available, the extended hydrogen bonded network is disrupted and the melting point drops considerably. A similar effect is seen for the methyl ester of this compound.

For the three aryloxyphenoxypropionic acids studied, the melting point of the racemic mixtures are all relatively high, above 100° C. In these cases, hydrogen bonding is also a prominent feature in the crystal structure, and it is a head to head arrangement of the carboxylate groups. The unit cell is comprised of an R/S in the racemate pair. When these acids are converted to the methyl esters, the melting points drop as expected and differences in melting points between the racemates and the R isomers vary in an unpredictable fashion. This is likely due to contributions from a number of non-bonded interactions in the individual cases.

One of the most interesting aspects of the behavior of these compounds, and one that can to used to enrich optical purity to a considerable extent is associated with hydration differences in the acid series. In contrast to the racemic acids, the R enantiomer acids crystallize with difficulty from anhydrous media and the mp's are considerably lower than the racemates (indicated by "anh." in the table). However, if sufficient water is present in the crystallization media, then each of these R acids readily forms a crystalline monohydrate (indicated by "hydrate" in the table).

The crystal structure of the R-(+) 2-(3-fluoro-5-(trifluoromethyl)pyridinyloxy) propionic acid reveals that this water is hydrogen bonded at each of the carboxylate groups. Apparently, these materials cannot readily form the head to head pairs seen in the racemic mixture, and prefer instead to substitute a water molecule for the missing S partner in the crystal lattice. This water of hydration is only loosely held in the crystal

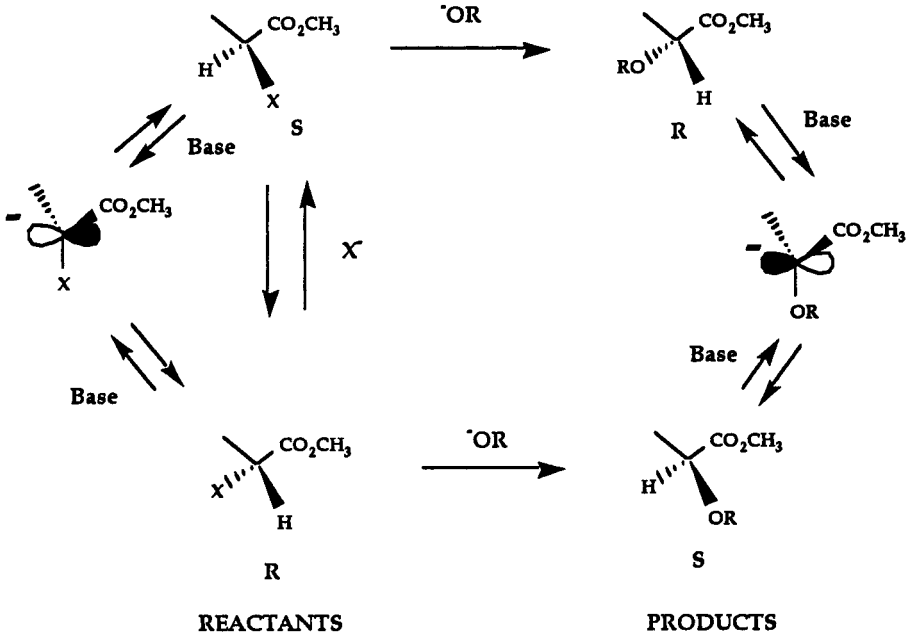
lattice, however, and can be easily removed by heating above 50° C as evidenced by thermal gravimetric analyses of the acid monohydrates.

This hydration behavior difference can be used to enrich optical purity. For example, 100 g of this acid with a R/S ratio of 95/5 (90% ee) was dissolved in 30 ml of perchloroethylene and heated to reflux. The perchloroethylene/water azeotrope was removed to dry the system, and the mixture was allowed to cool. A precipitate was formed and filtered off. This solid was found to consist of 17g of anhydrous acid, with an R/S ratio of 73/27. Water was then added to the solution remaining after filtration. A second precipitate was formed and this was filtered off. This material was found to be 82g of the acid monohydrate, with an R/S ratio of 99.8/0.2..Use of this type of procedure one can increase the optical purity from a moderately high to nearly optically pure.[18]

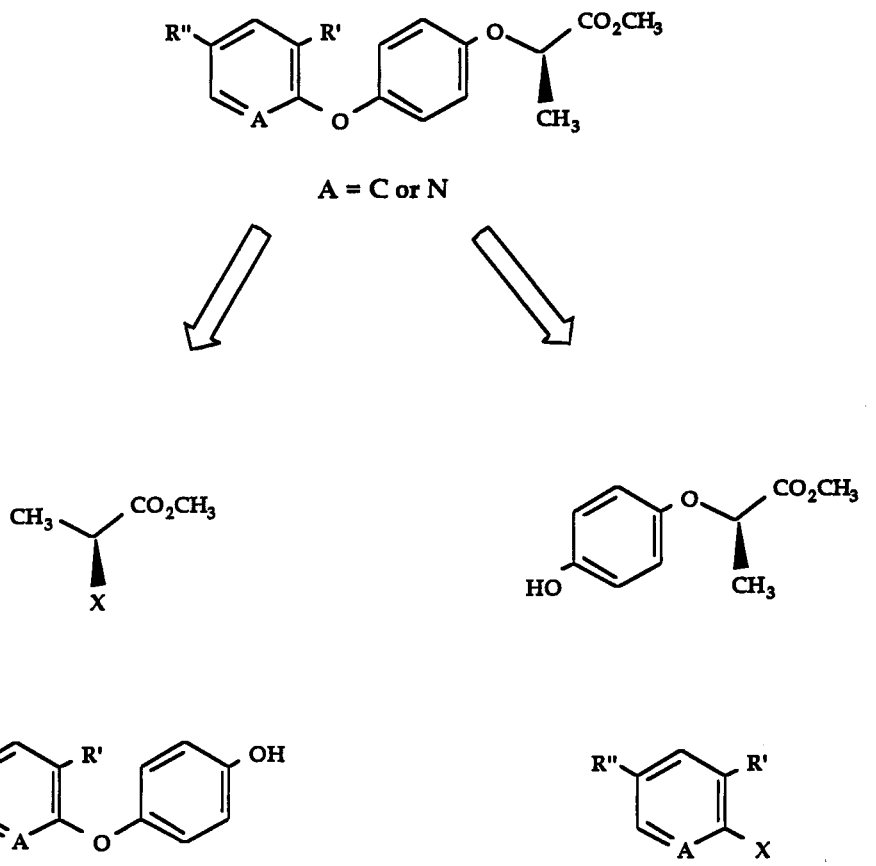
In summary - aryloxyphenoxypropionates are a class of highly effective crop protectants that are effective in only the R enantiomeric form. Several synthetic routes have been used to make the desired products in either moderate optical purity (~95%) by coupling substituted phenols with S-(-)-ester lactate tosylates or by initial formation of a high optical purity 2-(4-hydroxyphenoxy)propionic acid intermediate, followed by coupling of the disalt of this material with the aromatic portion of the final molecule without loss of optical purity.

In addition, we have determined the X-ray crystal structures of a number of these intermediates, acids, and esters and have found correlations with melting point and the extent of hydrogen bonding in these systems. It has also been found that the racemic and R forms of the acids show significant differences in the degree of hydration. This hydration difference can be utilized to produce nearly optically pure products.

Scheme 1. Potential Synthetic Routes



Scheme 2. Racemization Mechanism



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