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Stereoselectivity in the Thermal Cycloaddition Reactions of Tetrafluoroethylene to Derivatives of α–(4-Ethoxyphenyl)Acrylic Acid

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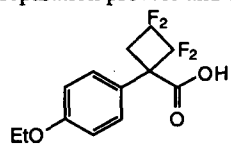
Abstract: Esters of chiral auxiliaries with α–(4-ethoxyphenyl)acrylic acid undergo diastereoselective addition reactions with tetrafluoroethylene at 130°- 170° to afford tetrafluorocyclobutanecarboxylic esters. The oxazoline derived from (+)-(1*S*,2*R*)-norephedrine and α–(4-ethoxyphenyl)acrylic acid shows negligible stereoselectivity.

The useful insecticidal activity associated with 3-phenoxybenzyl esters of 1-aryl-2,2,3,3-tetrafluorocyclobutane carboxylic acid **1**, has stimulated considerable synthetic activity in our laboratories.[2] Significantly, esters derived from the resolved *R*-**1** and *S*-**1** show different insecticidal toxicities. These esters, e.g. **2**, have been prepared by esterification of the resolved *R*- and *S*- acids **1**. The acid **1** is prepared by the thermal [2+2] cycloaddition[3] of tetrafluoroethylene to ethyl α–(4-ethoxyphenyl)acrylate **3**, which proceeds smoothly in 65-70% yields. The reaction also produces small amounts (5-10%) of the tetralin **4** arising from competing [4+2] cycloaddition. The acid **1** can then be resolved by crystallisation of various diastereoisomeric derivatives.[4] While this classical approach to the resolution of **1** is direct, an industrial preparation of homochiral material by this means would incur the cost of the separation process and then the disposal of the unwanted enantiomer.



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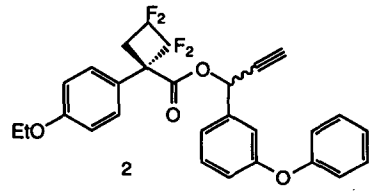

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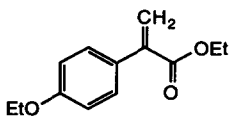

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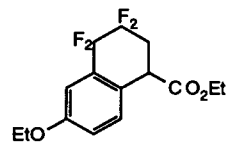

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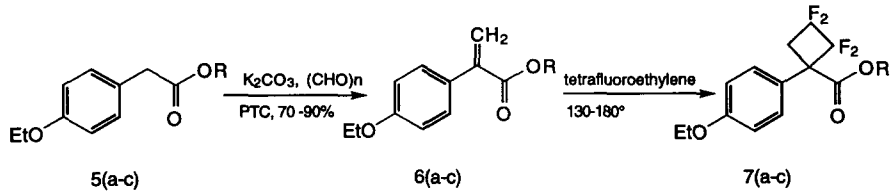
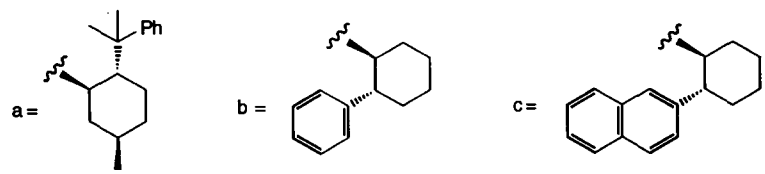
We wished to develop enantioselective approaches to the acid **1** and decided to the investigate the cycloaddition of tetrafluoroethylene to acrylate esters derived from chiral auxiliaries, since acrylates of this type are known to exhibit high diastereofacial selectivity (up to 100%) in other cycloadditions, e.g. Diels-Alder and ene reactions.[5] We noted however, that such reactions, when successful, are generally performed at low temperatures and often take advantage of Lewis acid catalysis to provide a well defined transition state. Some stereocontrol has also been reported in the application of this type of chiral auxiliary strategy in both thermal (ketene cycloaddition[6]) and photochemical cyclobutane formation.[7] To the best of our knowledge there are no examples of stereocontrol in the addition of tetrafluoroethylene to alkenes. We now report the face-directed cycloaddition reactions of tetrafluorethylene to a number of acrylate derivatives containing stereogenic centres.

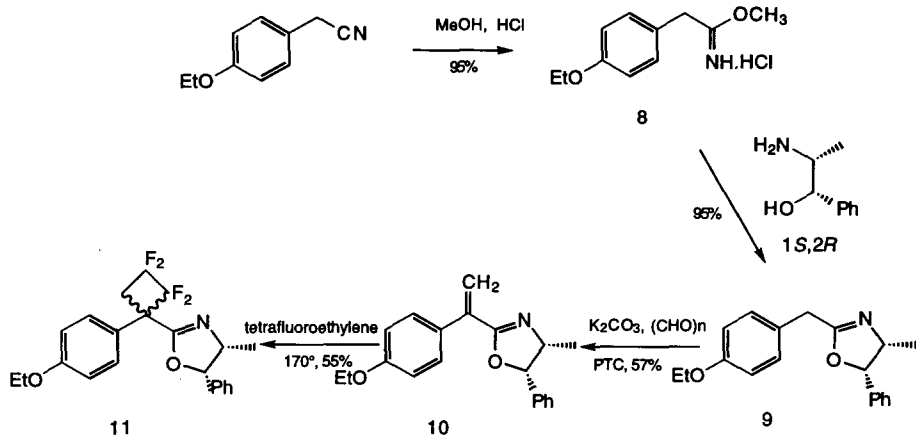
The α-(4-ethoxyphenyl)acrylate esters[8] **6(a-c)** (Scheme 1) were prepared by methylenation (K_2CO_3, paraformaldehyde, triethylbenzylammonium chloride in cyclohexane solvent at 80°; 70-91% yield) of the corresponding 4-ethoxyphenylacetates **5(a-c)**, which were available by condensation of 4-ethoxyphenylacetyl chloride with the appropriate alcohol in the presence of triethylamine in dichloromethane solution in 70-80% yield. The methylenation reactions proceeded cleanly over 4-8 hours. The oxazoline **10** was made from 4-ethoxyphenylacetonitrile by formation of the imidate **8** (anhydrous HCl, MeOH, $CHCl_3$, 0° - RT; KOH, H_2O), condensation of **8** with (+)-(1*S*, 2*R*)-norephedrine (pyridine, CH_2Cl_2, RT) and then methylenation of the resulting oxazoline **9** as for the esters **5(a-c)** in 63% overall yield (Scheme 2).



5(a-c) 6(a-c) 7(a-c)



Scheme 1



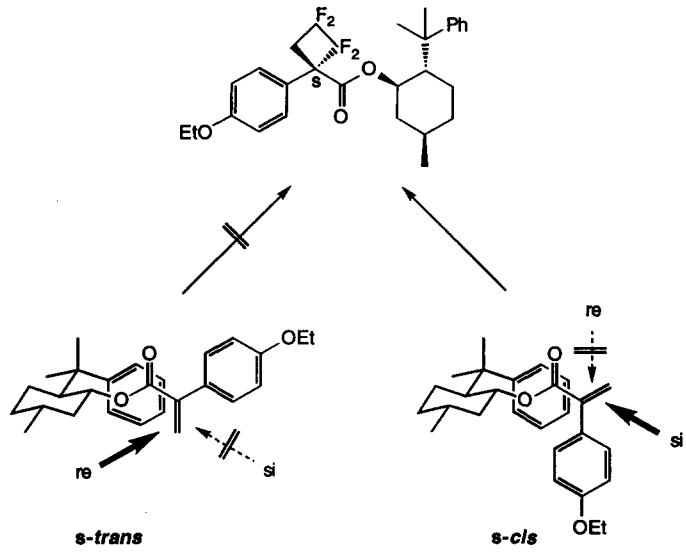
Scheme 2

Cycloaddition reactions of **6(a)** and **6(b)** with tetrafluoroethylene (> 2 eq.) were carried out in cyclohexane solution at 170° for 15 hours in an evacuated stainless steel bomb. These reactions gave the tetrafluorocyclobutane esters **7(a)** and **7(b)** in unoptimised yields of 87% and 73% respectively. In these reactions minor amounts of the tetralin products, identified by gcms and readily removed by chromatography, were apparent. Product diastereomer ratios were determined by glc. The largest stereoselectivity, d.e. = 43% (87% conversion), was found for the case of (-)-(1*R*, 2*S*, 5*R*)-8-phenylmenthyl ester **6(a)**. The d.e. could be increased to 57% by conducting the reaction at 130°, but this reduced the conversion to only 70% after 72 hours. The possibility of further enhancing the stereoselectivity by using titanium tetrachloride as a Lewis acid catalyst was also briefly explored. However, the only recovered products appeared to result from polymerisation of the acrylate **6(a)** with no cyclobutane formation detected.

The major diastereoisomer was identified as the ester **7(a)** of the *S*-acid **1** by separately esterifying [$SOCl_2$; (-)-8-phenylmenthol, pyridine, DMAP, CH_2Cl_2, RT] pure *R* -**1** and *S* -**1** and comparing the products by glc. Thus the addition of the tetrafluoroethylene occurs preferentially to the *si* face of the double bond. This implies that the molecule is adopting an *s-cis* acrylate configuration, shielding the *re* face. This configuration would be expected where π stacking[9] is an important contributing factor to substrate conformation. In the absence of a π-stacking contribution the more stable conformation would be expected to be the *s -trans* acrylate conformation (Scheme 3). This effect did not operate with the more π-extended naphthyl substituent in **6(c)** (d.e. = 14%), while the phenylcyclohexyl case **6(b)** also showed poor stereoselectivity (d.e. = 10%). The isoxazoline **10** showed no stereoselectivity in its conversion to **11**.

Unfortunately we were unable to effect hydrolysis of the cyclobutane esters **7(a-c)**, forcing conditions leading to decomposition. This is presumably a consequence of the steric hindrance around the ester linkage. Most literature reports in this area process the chiral esters to alcohols using lithium

aluminium hydride rather than recover the parent acids by hydrolysis. As the diastereoselectivity occurring in the cycloadditions is a result of steric hindrance, coupled with the π-stacking effect, it is likely that while chiral auxiliaries may be available to increase diastereoselectivity, a further increase in difficulty of hydrolysis would result. The method is thus unsuitable for the direct synthesis of tetrafluorocyclobutanecarboxylic acids of the desired type.



Scheme 3

In conclusion, we have demonstrated for the first time stereoselective cycloaddition reactions of tetrafluoroethylene and, in addition, the use of a chiral auxiliary to direct the face selectivity of a cycloaddition at unprecedented high temperatures.

References and Notes

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3. The reaction mechanism may be biradical in nature. However we saw no evidence favouring either a concerted or diradical mechanism in this work.
4. As one example see Duke, C. C. and Wells, R. J. *Aust. J. Chem.,* **1987**,*40,* 1641-54.
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