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First Highly Stereoselective Synthesis of Fungicide Systhane

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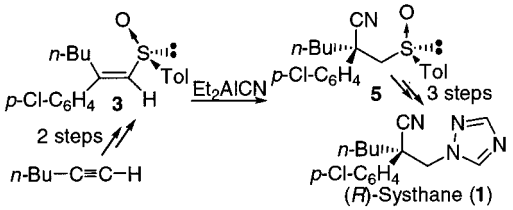
ABSTRACT



Highly enantiopure (*R*)-2-*p*-chlorophenyl-2-(1*H*-1,2,4-triazol-1-ylmethyl)hexanenitrile 1 (myclobutanil or systhane) was obtained in six synthetic steps from commercially available 1-hexyne (35% yield, 92% *ee*). The sulfinyl group controls the two key steps of the synthetic sequence, the highly stereoselective hydrocyanation of vinyl sulfoxides with Et_2AlCN and the further introduction of the proper functionality into the molecule.

2-*p*-Chlorophenyl-2-(1*H*-1,2,4-triazol-1-ylmethyl)hexanenitrile **1** (myclobutanil, also known as systhane) (Figure 1) is

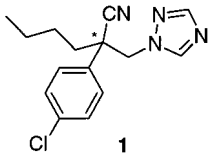


Figure 1. Structure of systhane.

a polyfunctionalized non-natural compound which is used as a fungicide due to its ability as inhibitor in the biosynthesis of the ergosterol.[1] Its fungicide effectiveness has proved to be superior to the conventional pesticides for controlling powdery mildews in different plant species, either by itself[2] or in synergistic fungicidal compositions.[3] From a stereochemical point of view, its main structural feature is the presence of a quaternary chiral center at the α-position of a cyano group.

Commercially available systhane (from Rohm ad Haas Co, U.S.A.) is racemic, and there is no reported evidence on the biological activity of each enantiomer. Additionally, although its racemic synthesis is well documented via butylation and condensation with paraformaldehyde and 4-chlorobenzyl cyanide, followed by alkylation of a triazole salt,[4] to our knowledge no preparation of enantiopure systhane has been so far reported either by enzymatic resolution or by asymmetric synthesis. To date, the closest approach to the obtention of both enantiomers of systhane in their optically pure form has been reported by the enzymatic resolution of a racemic analogue, (±)-2-cyano-2-phenyl-hexanol **2**,[5] which was performed using *Pseudomonas fluorescens* lipase (*S*-enantiomer, 99% ee) and *Candida rugosa* lipase (*R*-enantiomer, 98% ee), although with moderate yields.[6] Quite

(1) Haug, G.; Hoffmann. *Chemistry of Plant Protection − Sterol Biosynthesis, Inhibitors and Antifeeding Compounds*; Springer: Berlin, 1986; p 25.

(2) McGrath, M. T.; Shishkoff, N. *Plant Dis.* **2001**, *85*, 147. Berrie, A. M.; Burgess, C. M. *Acta Hortic.* **1997**, *439*, 791. Warkentin, T. D.; Rashid, K. Y.; Xue, A. G. *Can. J. Plant Sci.* **1996**, *76*, 933.

(3) Wachendorff-Neumann, U.; Gayer, H.; Heinemann, U.; Seitz, T.; Krueger, B.-W.; Kraemer, W.; Assmann, L. Ger. Offen. 2001, 58 pp (Patent No. DE 10021412). Reuveni, M.; Harpaz, M.; Reuveni, R. *Eur. J. Plant Pathol.* **1998**, *104*, 853. Reuveni, M.; Oppenheim, D.; Reuveni, R. *Crop Prot.* **1998**, *17*, 563. Reuveni, M.; Reuveni, R. *Indian J. Pharm. Sci.* **1995**, *57*, 311.

(4) Graves, D. D. U.S. Patent 1996, 5 pp (Patent No. US 5510493). Li, X.; Liu, L. Hu, X.; Hong, L. *Nongyao* **2001**, *40*, 11.

(5) Miller, G. A.; Carley, H. E.; Chan, H. F. DOS 2 604 047, 1976, Rohm ad Haas Company.

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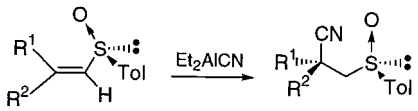
recently a high-performance chiral separation of systhane by sulfated β-cyclodextrin-mediated capillary electrophoresis has been reported,[7] although no characterization of the enantiomerically pure title compound was provided.

Recently we reported a straightforward highly stereoselective method to achieve the hydrocyanation of double bonds of vinyl sulfoxides with Et_2AlCN, which was claimed as a potentially useful procedure for the synthesis of any kind of enantiomerically enriched compounds bearing tertiary or quaternary chiral carbons, after chemical modification of the sulfinyl and cyano group (Scheme 1).[8]

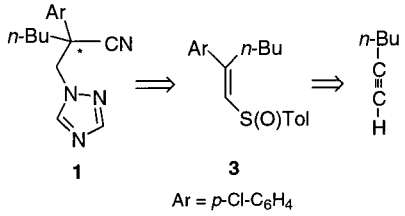
Scheme 1



In the herein reported synthesis of systhane, we take advantage of the usefulness of this reaction as well as the chemical versatility of the sulfinyl group to be transformed into other functional groups.

In Scheme 2 is depicted a plausible retrosynthetic sequence

Scheme 2

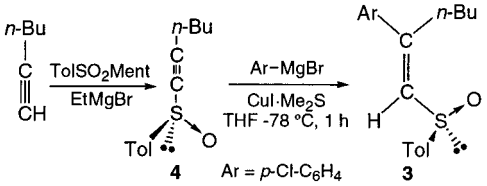


to prepare optically pure systhane (**1**). This compound is a nitrile derivative bearing a quaternary chiral carbon at C-α, which could be obtained by hydrocyanation of the proper vinyl sulfoxide. The configuration at this carbon can be controlled by choosing either that of the sulfinyl sulfur or the *Z* or *E* stereochemistry of the starting olefin. The triazol moiety would be obtained by appropriate modification of the sulfinyl function. The synthesis of the vinyl sulfoxide **3** could be easily performed from commercially available 1-hexyne by making use of well-known reactions in sulfoxide chemistry.

Taking into account that reactivity of vinyl sulfoxides with Et_2AlCN decreases with the size of the substituents in *cis*-arrangement with respect to the sulfinyl group, we decided to start from (*E*)-vinyl sulfoxide **3** and therefore to control the configuration of the quaternary chiral center with that of the sulfinyl sulfur. To complete the synthesis of (*R*)-systhane, in full agreement with the stereochemical pathway of the hydrocyanation,[8] it was necessary to start from the (*S*)-sulfoxide.

The synthesis of optically pure (*S*)-**3** was performed as indicated in Scheme 3. The sulfinylation of the commercially

Scheme 3



available 1-hexyne with (*S*)-menthyl sulfinate, following the previously reported method,[9] yielded (+)-(*S*)-hexynyl *p*-tolyl sulfoxide (**4**), which reacted with a mixture of 4-chlorophenylmagnesium bromide and CuI−dimethyl sulfide in THF,[10] affording optically pure (1*E*,S*S*)-(−)-2-*p*-chlorophenyl-1-hexenyl *p*-tolyl sulfoxide (**3**)[11] in 90% yield (Scheme 3).

Hydrocyanation of vinyl sulfoxide **3** with Et_2AlCN at room temperature proceeded in 1 h in a highly stereoselective manner to give a 96:4 diastereomeric mixture of β-sulfinyl nitriles **5**[11] (55% isolated yield) along with unaltered starting material (40%) which could be reused.[12] The configuration of the major isomer was established as (2*S*,S*R*) on the basis of the stereochemical pathway of these reactions, which presumably involves the association of the aluminum of the reagent with the sulfinyl oxygen, as a step previous to the intramolecular cyanide transfer through the most stable chairlike TS (Scheme 4).[8]

The reported method to prepare the racemic fungicide describes the transformation of the alcohol **5** in systhane by

(6) Im, D. S.; Cheong, C. S.; Lee, S. H.; Youn, B. H.; Kim, S. C. *Tetrahedron* **2000**, *56*, 1309.

(7) Wu, Y. S.; Lee, H. K.; Li, S. F. K. *J. Chromatogr.* **2001**, *912*, 171.

(8) García Ruano, J. L.; Cifuentes García, M.; Laso N. M.; Martín Castro, A. M.; Rodríguez Ramos, J. H. *Angew. Chem., Int Ed.* **2001**, *40*, 2507. The general procedure for the hydrocyanation reaction consists of the treatment of the corresponding alkenyl sulfoxide with Et_2AlCN (1 equiv) in refluxing THF and further quenching with aqueous potassium sodium tartrate.

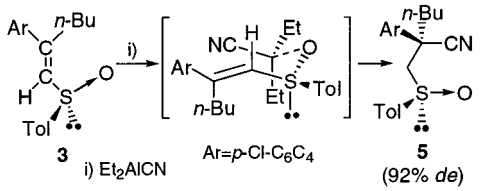
(9) Kosugi, H.; Kitaoka, M.; Tagami, K.; Takahashi, A.; Uda, H. *J. Org. Chem.* **1987**, *52*, 1078. García Ruano, J. L.; Esteban Gamboa, A.; Martín Castro, A. M.; Rodríguez, J. H.; López-Solera, M. I. *J. Org. Chem.* **1998**, *63*, 3324.

(10) Marfat, A.; McGuirk, P. R.; Helquist, P. *J. Org. Chem.* **1979**, *44*, 3888.

(11) ^{1}H NMR ($CDCl_3$) and specific rotations. Compound **3**: $[\alpha]^{20}_D$ −27.1 (*c* 0.5, $CHCl_3$); δ 7.56 and 7.28 (AA′BB′ system, 4H), 7.31 (m, 4H), 6.39 (s, 1H), 3.01 (t, 2H, *J* 7.0), 2.37 (s, 3H), 1.49−1.38 (m, 4H), 0.89 (t, 3H, *J* 7.0). Compound **5** (de assigned by integration of well-separated signals (CH_2S) in the ^{1}H NMR spectrum of the crude mixture): $[\alpha]^{20}_D$ +59.5 (*c* 0.7, $CHCl_3$); ^{1}H NMR (for major diastereomer) δ 7.47 and 7.24 (m, 8H), 3.42 and 3.19 (AB system, 2H, *J* 13.6), 2.39 (s, 3H), 2.12 (m, 2H), 1.52−1.09 (m, 4H), 0.84 (t, 3H, *J* 7.0). Compound **2**: $[\alpha]^{20}_D$ = −6.1 (*c* 0.2, $CHCl_3$); ^{1}H NMR δ 7.44−7.31 (s, 4H), 3.89 and 3.84 (AB system, 2H, *J* 13.6), 2.13−2.03 (m, 1H), 1.89−1.79 (m, 1H) 1.49−1.09 (m, 4H), 0.84 (t, 3H, *J* 7.0). Compound **1**: $[\alpha]^{20}_D$ = −43.1 (*c* 0.1, $CHCl_3$); ^{1}H NMR δ 7.88 (s, 1H), 7.87 (s, 1H), 7.37 and 7.25 (AA′BB′ system, 4H), 4.61 and 4.49 (AB system, 2H, *J* 14.5 Hz), 2.16−2.04 (m, 2H), 1.47−1.11 (m, 4H), 0.86 (t, 3H, *J* 7.0).

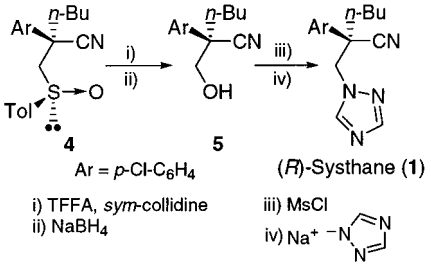
(12) When the reaction was conducted at 0 °C the reaction rate substantially decreased, 7 days being needed to get a 20% yield, along with a 72% of recoverable starting material. However, the diastereomeric excess increased up to >98%; $[\alpha]^{20}_D$ = +59.5 (*c* 0.7, $CHCl_3$). These new conditions allow for preparation of enantiomerically pure systhane, although in moderate overall yield. The low yield of the hydrocyanating stage at low temperature prompted us to follow the sequence with the enantiomerically enriched (92% de) mixture obtained at room temperature.

Scheme 4



mesylation into the corresponding methanesulfonate derivative, followed by treatment with triazole sodium salt.[4] Therefore, we decided to determine the experimental conditions to transform the sulfinyl moiety into a hydroxyl group. This reaction was accomplished by a one-pot two-step sequence involving Pummerer conditions[13] and subsequent reduction of the resulting hemithioacetal with $NaBH_4$ (see Scheme 5).

Scheme 5

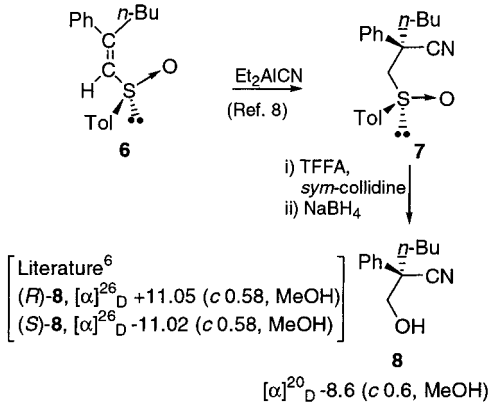


The choice of the Pummerer conditions are of utmost importance in the resulting yield. Thus, when the base employed was 2,4,6-trimethylpyridine,[14] **2** was obtained in 52% yield,[11,15] which was improved up to 70% by using *sym*-collidine under the same reaction conditions. The optical purity of (*S*)-**2** was established as 92% ee by ^{1}H NMR using α-methoxy-α-trifluoromethylphenylacetic acid (Mosher's reagent) as the chiral derivatizating agent (CH_2O AB systems as diagnostic signals).

Compound (*S*)-**2** was transformed into (*R*)-systhane (**1**)[11] under the conditions depicted in Scheme 5, according to the procedure reported in the ref 6. The ee of the systhane was determined as 92% by ^{1}H NMR (C_4H_6 as diagnostic signals) using $Yb(hfc)_3$ as the LSR. This value was identical to that found for the alcohol **2**, and both were consistent with the diastereomeric ratio resulting from the hydrocyanation reaction. These results prove that the optical purity of systhane was defined in the hydrocyanation step and was not modified in further steps.

As none of the compounds involved in the synthetic sequence of systhane afforded crystals suitable to be studied by X-ray diffraction, its absolute configuration could not be unequivocally established. On the other hand, the specific rotation of the synthesized systhane {$[\alpha]^{20}_D$ −43.1 (*c* 0.1, $CHCl_3$) for the sample of 92% ee} could not be correlated because enantiomerically pure systhane has not been reported so far (see above). Therefore, to unequivocally establish the configuration of the quaternary chiral carbon created in the hydrocyanation step, we prepared (−)-2-phenyl-2-hydroxymethylhexanenitrile (**8**) from compound **4**, following the same sequence used in the synthesis of the alcohol **2** precursor of systhane (Scheme 6). The comparison of the specific rotation

Scheme 6



of the so obtained compound **8** with those of both enantiomers of this compound, obtained by enzymatic resolution of the racemic mixture,[6] allowed us to conclude that its absolute configuration was *S*, as can be deduced from Scheme 6. Its high optical purity (>98% ee) was determined by ^{1}H NMR using Mosher's reagent as the chiral derivatizating agent. This result strongly supports the fact that configuration *S* must also be assigned to the alcohol **2**, which agrees with that predicted from the stereochemical course of the hydrocyanation.[8]

In conclusion, in this paper we describe the first highly stereoselective synthesis of the (2-*p*-chlorophenyl-2-(1*H*-1,2,4-triazol-1-ylmethyl)hexanenitrile), a fungicide known as myclobutanil or systhane, in high optical purity (92% ee) in just six steps starting from commercially available 1-hexyne, involving the highly stereoselective hydrocyanation of vinyl sulfoxides as the key step of the reaction.

Acknowledgment. We thank CAICYT (Grants BQU2000-0246 and PB98-0102) for financial support.

Supporting Information Available: Experimental section containing characterization of compounds **1**−**3** and **5**, and the intermediate 2-(4-chlorophenyl)-2-cyanohexyl methanesulfonate. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Bravo, P.; Frigerio, M.; Resnati, G. *J. Org. Chem.* **1990**, *55*, 4216.
(15) Although some stable derivatives of **2** were prepared, none of them showed suitable crystals to be studied by X-ray analysis.