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DIASTEREOSPECIFIC SYNTHESIS OF FUNGICIDAL THREO- AND ERYTHRO- α-HYDROXY AMINALS

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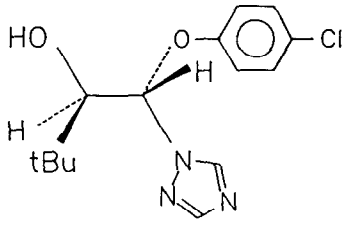
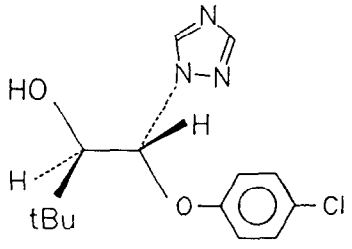
Abstract: *Sequential reactions of 2-chloro- or 2-bromo-3-tert-butyloxirane with p-chlorophenolate and then with sodium triazolate lead in two stereocontrolled steps to threo-Triadimenol; by inverse addition of the two nucleophiles the erythro-isomer is obtained.*

1-(4-Chlorophenoxy)-3,3-dimethyl-1-(1,2,4-triazol-4-yl)butanol-2 (Triadimenol^{R}, Baytan^{R})[1], 1, is an important systemic fungicide. The *threo*-isomer 1a is about ten times more active than the *erythro*-isomer 1b.[2,3] Thus, a synthetic approach to the pure diastereomers, particularly to 1a, is of much interest as it would allow a reduction in the amount of fungicide that has to be applied. However, the presently reported processes[1,4] lead to mixtures of the diastereomers 1a and 1b which have to be separated to provide the pure isomers.



1a

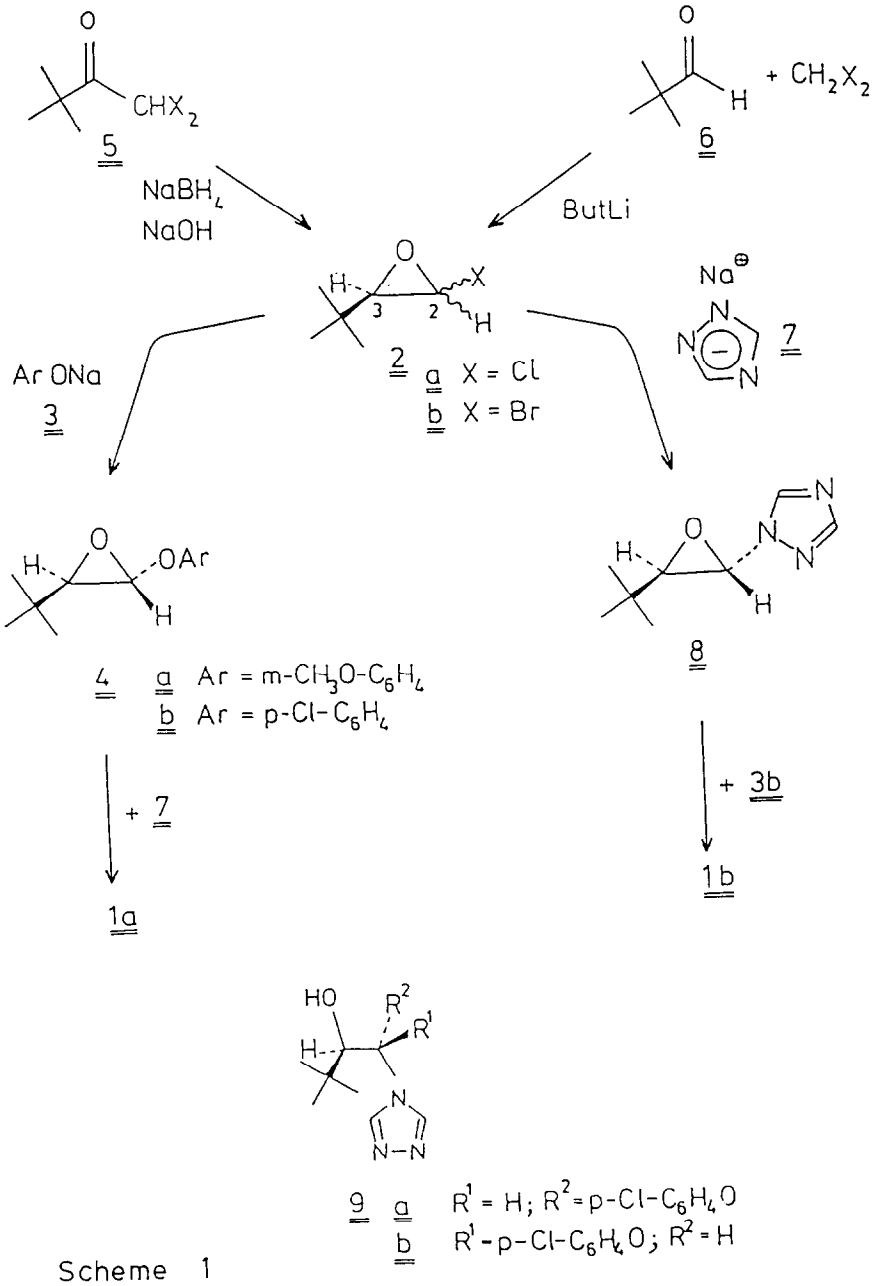
threo



1b

erythro

The oxidation states of the carbon atoms 1 and 2 in 1 show that they can be considered as derivatives of α-hydroxy aldehydes. In previous work we have demonstrated that 2-halooxiranes[5] are useful intermediates for the synthesis of α-substituted carbonyl compounds.[6-9] This idea can be taken one step further on the basis of the findings reported in the preceding communication.[10] In compounds 2 with a *tert*-butyl group in position 3 of a 2-halooxirane, the attack


O
CHX2
5
NaBH4
NaOH
O
H
+ CH2X2
6
ButLi
O
H
X
3
2
H
2 a X = Cl
b X = Br
Na⊕
N
N
7
Ar ONa
3
O
H
OAr
H
4 a Ar = m-CH3O-C6H4
b Ar = p-Cl-C6H4
+ 7
1a
O
H
N
N
N
H
8
+ 3b
1b
HO
R2
R1
H
N
N–N
9 a R1 = H; R2 = p-Cl-C6H4O
b R1 = p-Cl-C6H4O; R2 = H

Scheme 1

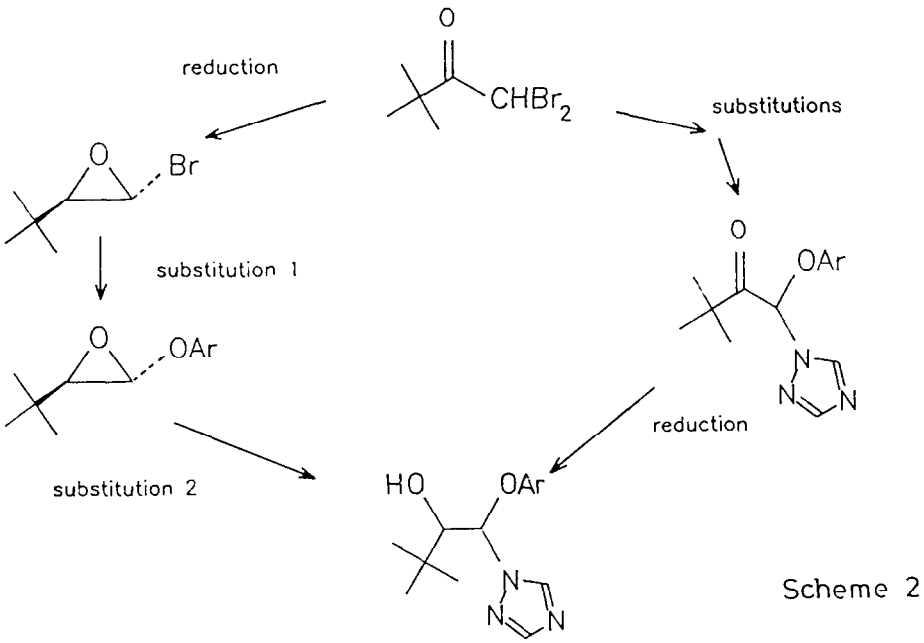
of a phenolate 3 is directed from C-3 to C-2, without, however, changing the oxidation states of the two carbon atoms. The stereochemical course of this reaction can be put to synthetic use, and together with the stereochemistry of a nucleophilic ring-opening of an oxirane, provides a two-step diastereospecific synthesis of 1a, and ,independently, of 1b.

Reaction of 2 with 3b in CH_3CN gives, by analogy with the reaction with 3a,[10] only the *trans* compound 4b (bp= 55°C/0.01 Torr; ^{1}H-NMR ($CDCl_3$): δ= 1.01(s, 9H, t-Bu), 3.02(d, 0.8Hz, 1H, H-C3) 4.85 (d, 0.8Hz, 1H, H-C2), 6.84-7.40(m, 4H, Ar)) in 71% yield. Elevated temperatures with an excess of nucelophile should be avoided otherwise disubstitution occurs by ring-opening of 4b.[11] Both *cis*- and *trans*-2 lead to *trans*-4b. An additional incentive for designing this synthesis was that in the preparation of 2, the more reactive *trans*-compounds are produced in large excess. Thus, reaction of dibromopinacolone 5 with sodium borohydride and sodium hydroxide gives an 80% yield of 2b in a 90:10 *trans:cis* mixture,[5] whereas reaction of pivalaldehyde 6 with dibromomethyllithium provides 2b in 54% yield as a 98:2 *trans:cis* mixture.

Reaction of 4b with triazole with acid catalysis (excess of triazole or a trace of TosOH) leads to a 1:1 mixture of 1a and 1b together with a mixture of the 4-H triazole isomers, *threo*- and *erythro*-9. Thus, with acid catalysis the stereochemical information contained in 4b is lost, presumably through acid-catalyzed ring-opening to a carbenium ion which is attacked from both sides by the nucleophile. However, ring-opening of 4b with sodium triazolate, 7, in methanol occurs with inversion at C-2 leading to 1a (mp. 138°C) which can be isolated in 60% yield together with the *threo*-compound 9a (mp. 216-218°C, yield 6%).[12]

By changing the order of addition of the two nucleophiles 3 and 7, the *erythro*-compound 1b can be prepared selectively. The presence of 10 mole per cent 15-crown-5 increases both the solubility and the nucleophilicity of 7. Under these conditions 2b reacts with 7 in CH_3CN to give only the trans-oxirane, 8 (bp= 34°C/0.004 Torr; ^{1}H-NMR ($CDCl_3$): δ= 1.09(s, 9H, t-Bu), 3.52(d, 1.2Hz, 1H, H-C3), 5.16 (d, 1.2Hz, 1H, H-C2), 8.00(s, 1H, H-C3'), 8.29(s, 1H, H-C5')). Of additional significance is the observation that only the 1(H)-triazole isomer 8 is obtained and none of the 4(H)-triazole product. Regioselective alkylation of 1,2,4-triazole is usually difficult to achieve, and presumably occurs in this case because of the relatively high reactivity of the halooxirane 2b. Reaction of 8 with 3b in methanol occurs with inversion at C-2 to give 1b (mp. 132°C).

Both this synthesis and the technical process[1,4,13] to 1 start from dibromopinacolone 5. By reversing the order of events - first ketone reduction, then reaction with the two nucleophiles - we have succeeded in arriving at the two diastereomers 1a and 1b independently and selectively. The successful outcome depends on the stereochemistry of ring closure to 2, and its subsequent nucleophilic substitutions (Scheme 2). The point to be learned from our synthesis is the use of the potential of a stereodifferentiating group, such as the bulkiness of *tert*-butyl, as early as possible in controlling the stereochemistry of a product. Therefore, the first step to be performed is reduction of the carbonyl group, which produces an asymmetric center adjacent to the *tert*-butyl group. In this way, a variety of disubstituted *threo*- or *erythro*-compounds can be synthesized by using different nucleophiles in the two subsequent substitution steps.



Scheme 2

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References

1. Bayer AG (Krämer, W.; Kaspers, H.; Frohberger, P.E.; Büchel, K.H.; Meiser, M.), D.O.S. 23 24 010 (12. Mai 1973); CA 82, 156 325p (1975).
2. Buchenauer, H.; Grossmann, F., Z. Pflanzen Krankh. 89, 309 (1982).
3. Krämer, W.; Büchel, K.H.; Draber, W., Proceed. IUPAC-Symp. "Pesticide Chemistry", Kyoto, Japan, 1982.
4. a) Bayer AG (Krämer, W.; Büchel, K.H.; Pflugbeil, W.D.; Frohberger, P.E.; Brandes, W.), D.O.S. 27 43 767 (29. Sept. 1977); CA 91, 20 518g (1979).
   b) Bayer AG (Kranz, E.), D.O.S. 30 07 079 (26. Februar 1980); CA 95, 187 270q (1981).
5. Gasteiger, J.; Herzig, C., J. Chem. Res. (S) 1981, 113; (M) 1981, 1101.
6. Gasteiger, J.; Herzig, C., Angew. Chem. 93, 933 (1981); Angew. Chem.,Int. Ed. Engl. 20, 868 (1981).
7. Gasteiger, J.; Herzig, C., Tetrahedron 37, 2607 (1981).
8. Herzig, C.; Gasteiger, J., Chem. Ber. 114, 2348 (1981).
9. Gasteiger, J.; Herzig, C., Tetrahedron Lett, 1980, 2687 ; Chem Ber. 115, 601 (1982).
10. Gasteiger, J.; Kaufmann, K.; Herzig, C.; Bentley, T.W., preceding paper.
11. cf. Griesbaum, K.; Lie, G.O.; Keul, H., J. Org. Chem. 49, 697 (1984).
12. A 4-H triazole isomer is also produced in the synthesis of Triadimefon,[13] the precursor in the technical process to Triadimenol.
13. Bayer AG (Meiser, W.; Büchel, K.H.; Krämer, W.; Grewe, F.), D.O.S. 22 01 063 (11. Jan. 1972 CA 79, 105 257y (1973).

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