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CYCLOFUNCTIONALISATION REACTIONS OF EPOXYALCOHOL DERIVATIVES. 3. CYCLISATION-ACYL MIGRATION OF N-BENZOYLCARBAMATES TO STEREODEFINED OXAZOLIDINONES. A NEW, DIASTEREOSPECIFIC ROUTE TO THIAMPHENICOL.

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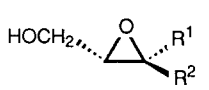
Abstract : N-Benzoylcarbamates formed in situ from 2,3-epoxyalcohols and PhCONCO undergo clean N to C-2 cyclisation followed by N to O acyl migration on treatment with catalytic sodium imidazolide or other bases . Subsequent benzoate cleavage (NaOMe) is accompanied by equilibration of the N-unsubstituted oxazolidinones ; cleavage without significant isomerisation is achieved with MeLi or Zn(BH4)2. This methodology is applied in a diastereospecific , 6-step conversion of methyl 4-bromophenyl sulfone to racemic Thiamphenicol .

In recent papers , we have described methods for intramolecular delivery of carbon[1] and oxygen[2] to C-2 of epoxy-alcohol derivatives under basic conditions where strict S_N2 behaviour was obtained . To deliver a nitrogen atom , two groups[3] have reported the cyclisation of anions derived from N-benzylcarbamates . This route has been used to prepare aminopolyols[4] , the sequence being completed by oxazolidinone hydrolysis followed by reductive cleavage (H_2/Pd or Na/NH_3) of the benzyl group ; attempts to cyclise unsubstituted or silylated carbamates failed .

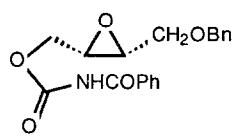
In connection with studies on beta-lactam and chloramphenicol antibiotics , we required a method which would effect nitrogen delivery under less basic conditions , and also avoid problems associated with reductive debenzylation . In this paper, we report the base catalysed cyclisation/isomerisation of 2,3-epoxyalcohol N-benzoylcarbamates , and a new route to Thiamphenicol based on this chemistry .

Treatment of the cis epoxyalcohol (1) with PhCONCO[5] (2 , 1.05 eq , THF , 0°) rapidly gave a solution of (3) to which was added 10% w/v DMSO and 0.1 to 0.2 eq of NaH and imidazole . After 24h at RT , workup and chromatography provided benzoate (4)[6] in 86% yield . A similar sequence on trans epoxyalcohol (5) gave (6)[6] (79%. , mp 91-93°) . The cyclisation/ rearrangement of (3) to (4) also proceeded efficiently in MeCN with potassium carbonate and 5 mol % of methyl trioctylammonium chloride .



1 $R^1 = CH_2OBn$, $R^2 = H$

5 $R^1 = H$, $R^2 = n\text{-}C_5H_{11}$



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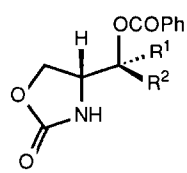
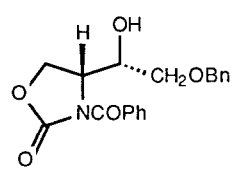


4 $R^1 = CH_2OBn$, $R^2 = H$

6 $R^1 = H$, $R^2 = n\text{-}C_5H_{11}$



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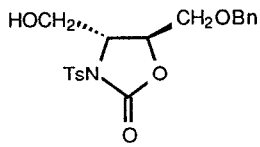

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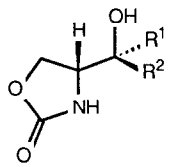
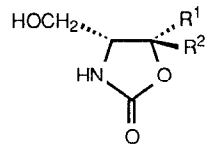


9 $R^1 = CH_2OBn$, $R^2 = H$

11 $R^1 = H$, $R^2 = n\text{-}C_5H_{11}$



10 $R^1 = H$, $R^2 = CH_2OBn$

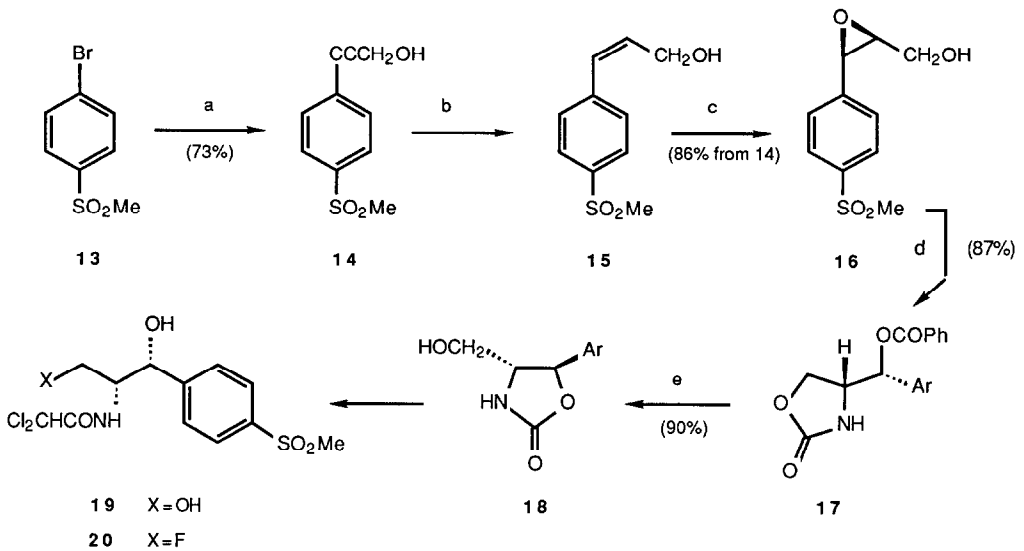
12 $R^1 = n\text{-}C_5H_{11}$, $R^2 = H$

Presumed intermediate (7) was not detected during these reactions , suggesting rapid N to O migration of the activated benzoyl group. When an N-sulfonyl group was present , oxazolidinone equilibration occurred : reaction of (1) with 4-TsNCO followed by Na imidazolide gave 83% of (8) , arising from epoxide opening followed by C=O migration to afford the more stable trans disubstituted product .

Standard ester cleavage (K_2CO_3-MeOH, 25°, 4h) of (4) provided quantitatively a readily separable mixture of regioisomers (9) and (10) in 1:6 ratio . Oxazolidinone equilibration proceeded at a rate comparable to ester cleavage , although a higher proportion of (9) was found (TLC) at partial conversion of (4) .Similar treatment of (6) produced a 3:2 mixture of (11)[6] , mp 75-77° and (12)[6] , mp 95-96° . Cleavage of (6) to (11) exclusively occured with CH_3Li(4 eq, -70° , 1 min) or $Zn(BH_4)_2$ (THF , 25°) .The structures of the isomeric oxazolidinones were evident from the ^1H NMR spectra[6] of the alcohols and their derived adducts with CCl_3CONCO . As expected , the primary alcohols were more polar ; benzoylation of the less polar isomers regenerated samples of (4) and (6) .

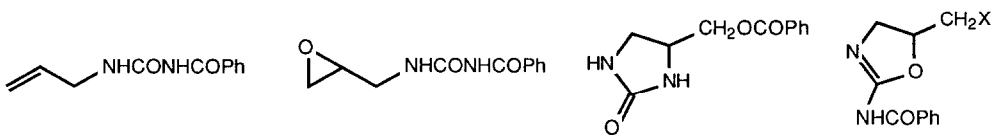
The Scheme shows the use of this methodology in a new , diastereospecific synthesis of the antibiotic Thiamphenicol (19) in racemic form . Syntheses of Chloramphenicol-type antibiotics frequently rely on either a diastereoselective condensation of ArCHO with a glycine anion equivalent[7](followed by ester reduction) , or a diastereoselective $Al(Oi\text{-}Pr)_3$ reduction of the appropriate 2-acetamido-3-hydroxypropiophenone[8] . For this conceptually different route , methyl-4-bromophenyl sulfone (13)[9] was converted in good yield to the arylpropynol (14) by a known Cu(I) / Pd(0) - catalysed process[10] using CuI and $Cl_2Pd(PPh_3)_2$ in Et_2NH . Reduction with Zn-HOAc in MeOH[11] followed by mCPBA oxidation then gave the racemic[12] cis epoxyalcohol (16)[6] , mp 72-74°. Reaction with PhCONCO followed by NaH-imidazole (THF-DMSO , 48h at 25°) gave (17)[13], mp 181-183°, which was stirred with NaOMe (0.05 eq) in MeOH , resulting in the precipitation of pure (18), mp 165-167°. (18) is a convenient substrate for -CH_2OH modification[14], and was converted to a sample of racemic Thiamphenicol by acidic hydrolysis followed by reaction with methyl dichloroacetate .

Scheme



REAGENTS a : $HCCCH_2OH$, $HNEt_2$, cat.CuI + $PdCl_2(PPh_3)_2$, 55° , 5h. b : Zn - HOAc , MeOH , 65° , 4h. c : mCPBA , CH_2Cl_2 , 25° , 8h. d : PhCONCO - THF , 0° , 0.25h ; 0.1eq NaH / imidazole , THF - DMSO , 25° , 48h. e : 0.05 eq NaOMe , MeOH , 25° , 6h.

This sequence illustrates the application of the methodology to the preparation of a relatively base-sensitive, benzylic aminodiol, where the benzylcarbamate method could not be used. Preliminary studies indicate that imidazolidinones (and derived 1,2-diamines) may be obtained in an analogous manner: reaction of allylamine with (2) gave (21), which was epoxidised (mCPBA , CH_2Cl_2) to (22). Treatment of this material with NaH-imidazole afforded (23)[6] as the major product, with a lesser quantity of (24)[6], from O-attack and intermolecular acyl transfer. Exclusive attack by the urea oxygen took place under neutral conditions: protic cyclisation of (21) [0.2 eq MsOH , CH_2Cl_2 , 0.5h] gave only (25)[6], and bromomethyl compound (26)[6] was the sole product from (21) and N-bromosuccinimide.



21 22 23

24 X = OCOPh
25 X = OH
26 X = Br

Acknowledgements : We thank the staff of the Physical - Analytical department for spectra and microanalyses .

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5. Prepared from $PhCONH_2$ and $(COCl)_2$ according to A. J. Speziale and L. R. Smith , J. Org. Chem. , 1962 , 27 , 3742 . Stored at 5° after vacuum distillation. All new compounds gave correct microanalyses. Selected PMR values (ppm, in $CDCl_3$ unless otherwise indicated) : (4) : 3.18(d,2,J=4.5) , 3.5-3.9(m,3) , 3.96(s,2) , 4.58(m,1) and 5.43,s,1, exch. D_2O). (6) : 0.85(t,3) , 1.2-1.4(m,6) , 1.5-1.8(m,2) , 4.08(m,1) , 4.3-4.6(m,2) , 5.22(m,1) and 6.24(s,1,exch. D_2O) (8) : 2.36(s,3) , 2.8(br.s,1,exch. D_2O) , 3.52(d,2,J=3.0) , 3.7-4.2(br.m,becomes ABX,J=3.3,4.5 and 12 after D_2O exch.) , 4.35(s,2) , 4.3(m,1) and 4.61(br.q,J=3). (11) : 0.88(t,3) , 1.2-1.6(m,8) , 3.55(br.s,1,exch. D_2O) , 3.69(m,1, sharpened by D_2O exch.) , 3.84(m,1) , 4.3-4.5(m,2) and 6.65(s,1,exch. D_2O). (12) : 0.88(t,3) , 1.2-1.4(m,6) , 1.5-1.9(m,2) , 3.0(br.s,1,exch. D_2O) , 3.7(m,2) , 3.80(m,1) , 4.64(m,1) and 6.43(s,1,exch. D_2O). (16) : 1.85(br.s,1,exch. D_2O) , 3.07(s,3) , 3.4-3.6(m,3) and 4.25(d,1,J=4.0). (18) [in DMSO-d_6] : 3.21(s,3) , 3.35(s,1,exch. D_2O) , 3.45-3.6(m,3) , 5.2(br.s,1,exch. D_2O) and 5.44(d,1,J=4.5). (23) : 3.36(dd,1,J=5.5 and 11) , 3.71(t,1,J=11) , 4.1-4.5(m,3) , 5.14(br.s,1,exch.D_2O) , and 5.37(br.s,1,exch.D_2O). (24) : 3.7-4.2(m,2) , 4.54(br.d,2) , 5.05(m,1) , 7,2-7.6(m,6) , 8.00 (m,2) , 8.23(m,2) and 9.6(br.m,1,exch.D_2O). (25) [in DMSO-d_6] : 3.4-3,9(m,4) , 4.75(m,1) , 5.19(t,1,J=6,exch.D_2O) 7.3-7.55(m,3) , 8.05(m,2) and 9.5(br.s,1,exch.D_2O). (26) : 3.5-3.75(ABX,2,J=4.5,8.0 and 11) , 3.83(dd,1,J=6.8 and 9.2) , 4.06(t,1,J=9.2) and 5.01(m,1).

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9. Prepared by H_2O_2 - HOAc oxidation of 4-bromothioanisole.

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12. Hindered , cis alcohols including Z-3-Aryl-2-propenols such as (15) represent one of the few classes of allylic alcohols which give epoxides with relatively low (60-70%) e.e. when subjected to the Sharpless asymmetric epoxidation.

13. On occasion , small amounts of the isomeric ester (18-O-benzoate) were produced , presumably via intramolecular acyl transfer reactions. Separation was unnecessary for the subsequent hydrolysis / equilibration to (18).

14. The 3-fluoro-3-deoxy analog (20) is a potent , broad spectrum compound : T. L. Nagabhushan , D. Kandasamy , H. Tsai , W. N. Turner and G. H. Miller , Current Chemotherapy and Infectious Disease Proceedings of the 11th ICC and 19th ICAAC , American Society of Microbiology , 1980 , p442. See also T. W. Schafer , E. L. Moss, Jr. , T. L. Nagabhushan and G. H. Miller , Ibid. , 1980 , p444.

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