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2-IMINOXETANES FROM KETENIMINE-ALDEHYDE CYCLOADDITIONS. PART 1 : SYNTHESIS AND CONTROLLED RING OPENING OF 2-N-p-TOLYLIMINO-3,3-DIMETHYL-4-PHENYLOXETANE

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Summary: *Regiospecific cycloaddition of benzaldehyde to dimethylketene-N-p-tolylimine, catalyzed by lanthanide shift reagents, afforded the corresponding 2-iminoxetane. Controlled ring opening showed the oxetane to be a versatile building block for the synthesis of the corresponding acyclic -aminoalcohol, β-keto and β-hydroxyamide. In addition isomerization produced the corresponding 2-azetidinone (β-lactam).*

2-Iminoxetanes have drawn our attention as possible key intermediates for the synthesis, through controlled ring opening, of highly functionalized acyclic derivatives. Moreover ring isomerization could give rise to a quite new approach toward the corresponding regioisomeric 2-azetidinones (β-lactams).

The synthesis of some 2-iminoxetanes, by photochemically induced cycloadditions of carbonyls to ketenimines is reported in the literature along with that of the regioisomeric 3-iminoxetanes, the latter being more often the major isomers.[1] Owing to the low selectivity, associated with the moderate overall yields, we have explored the possibility of activating the thermal reactions of aldehydes to ketenimines, using Lewis acid catalysts.[2] Attempts, as a first selected example, to cycloadd benzaldehyde **1** to dimethylketene-*N*-*p*-tolylimine **2** ,[3] in presence of $TiCl_4$, $AlCl_3$, and Et_2AlCl failed, due to a very fast oligomerization process of the ketenimine.[4] It has been recently observed, by Danishefsky et al.[5] that milder Lewis acids, such as lanthanide shift reagents catalyzed various hetero- Diels-Alder reactions, between activated dienes and various aldehydes, leading to many types of oxygen heterocycles. We have employed this procedure and we have found that a very smooth reaction occurred at 40°C in CCl_4 with a 0.5 mole percent of YtFOD or EuFOD as catalysts. Inspection of the crude by ^1H NMR revealed the presence of the oxetane **3** (Scheme I) in nearly quantitative (*ca* 85%) yields, as a sole regio-

isomer.[6] This constitute the first example of lanthanide-catalyzed 1,2-cycloaddition. Elution on a chromatographic column (Silica, benzene/diethyl ether 13:2) gave rise to a partial formation of the corresponding β-hydroxyamide **4** (Scheme I), through ring opening, followed by addition of water .[7]

Instead, using a flash chromatographic technique the oxetane could be isolated in 70% yield.[8] It was also possible to realize an asymmetric synthesis between **1** and **2** by taking the chiral complexes $Eu(HFC)_3$ and $Yt(HFC)_3$. In the former case a *ca* 20% of enantiomeric excess has been found, while the latter gave an e.e. of *ca* 40%.[9]

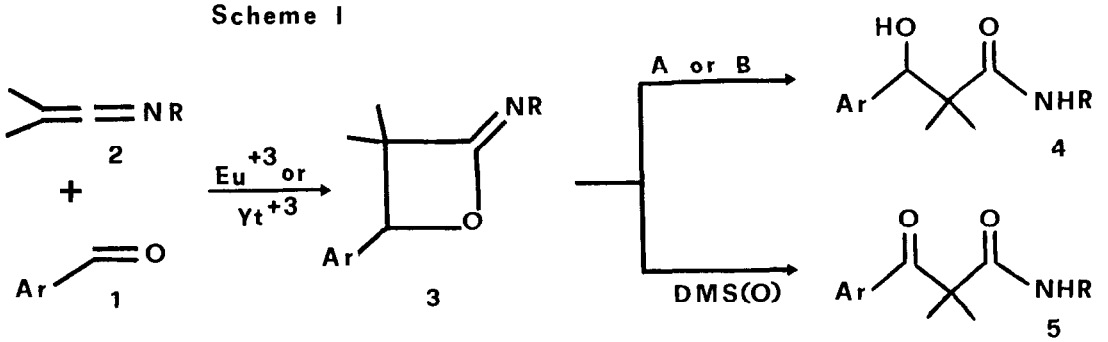
REACTIVITY OF 2-IMINOXETANE : a) Formation of β-hydroxyamide **4** : the synthesis of β-hydroxyamides via aldehyde-ketenimine homologation, followed by hydrolitic ring opening of the intermediate 2-iminoxetane, provide a convenient new source to highly functionalized β-hydroxyamides. Actually this class of compounds constitute the starting materials for the syntheses of β-lactams by $N\text{-}C_4$ ring closure.[10] However, the oxetane was surprisingly stable, when the hydrolitic ring opening was attempted at r.t., both in acid and basic conditions, being recovered unaltered after several hours. Reaction under reflux in acidic aqueous solutions (H_2SO_4, 2N) afforded several unidentified products, the hydroxyamide being obtained only in small amounts. These results clearly outlined the pivotal role of silica as a heterogeneous catalyst for the ring opening of **4** during the chromatographic work-up. However solvent-assisted ring opening, followed by addition of water, occurred in $DMSO/H_2O$ solutions at 120 C, leading to the hydroxyamide **4** (Scheme I) in a 80% yield.[11]

In a typical experiment the oxetane **3** , dissolved in a mixture of $DMSO/H_2O$, was heated, in a sealed ampoule at 120°C for one hour. The solvent was removed and the residue was chromatographed (SiO_2, CH_2Cl_2/ethyl acetate 10:3) .

b) Formation of the β-ketoamide **5** : when the same reaction was performed in anhydrous DMSO, the β-ketoamide **5** (Scheme I) was obtained by solvent-assisted ring opening;[12] the oxidation of the open intermediate by DMSO followed.

Also β-ketoamides are interesting starting materials for syntheses of β-lactams. In fact microbiological or enantioselective chemical reductions may also provide a chiral means of synthesizing β-hydroxyamides.

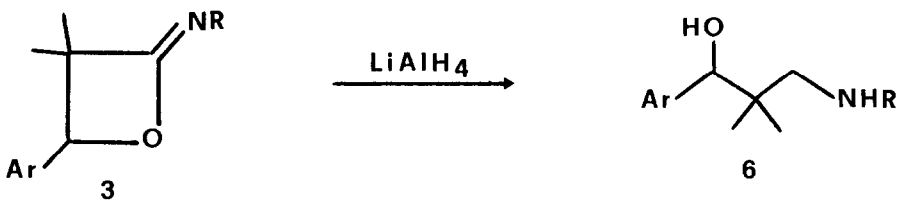
Scheme I



Ar = C_6H_5- ; R = C_6H_4-p-Me ; A = $SiO_2 \cdot n H_2O$; B = DMSO / H_2O

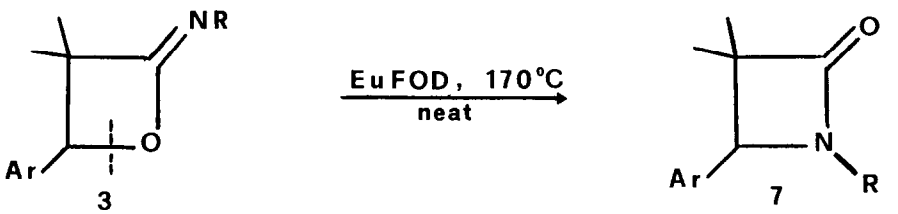
c) Formation of γ-aminoalcohol **6** : the oxetane **3** in benzene was added to a suspension of $LiAlH_4$ and refluxed for 3 hours. Reductive ring opening of **3** afforded the 3-*N*-*p*-tolylamino-1-phenylpropanol **6**[11] (Scheme II). A quite similar result has been achieved in the reductive ring opening of five membered cyclic imino-ethers, viz the *N*-alkyliminotetrahydrofurans, for which the corresponding 4-alkylaminobutanoles were obtained.[13]

Scheme II



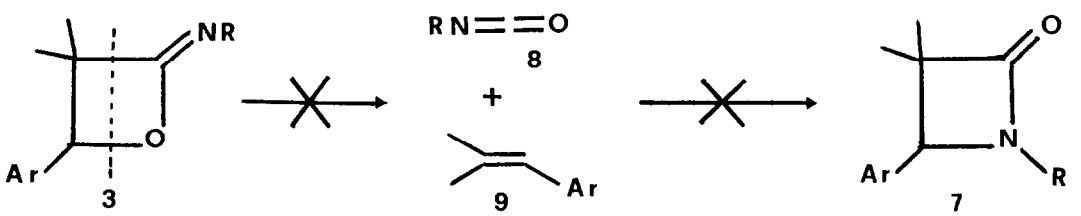
d) Ring isomerization to the corresponding β-lactam **7** : the oxetane **3** was stable when heated in xylene solution at 140°C. Pyrolysis above 200°C produced only tarry material. The presence of 0.5 mole percent of EuFOD catalyzed, in a pure state only, isomerization to the corresponding β-lactam in a few minutes at 170°C,[14] so that the formation of **7** , starting from ketenimine **2** and benzaldehyde can be considered as one-pot reaction (Scheme III).

Scheme III



e) Attempted cycloaddition of *N*-*p*-tolylisocyanate **8** and 1-phenyl-isobutene **9** : the possibility of 2-iminoxetane to 2-azetidinone conversion via an initial cycloreversion of **3** leading to **8** and **9** (Scheme IV), followed by a 1,2-cycloaddition of the two fragments, prompted us to try this reaction by an independent route. Attempts to cycloadd **9** with the isocyanate **8** at 170°C, in a pure state and in presence of 2 mole percent of EuFOD failed, only polymeric material from the reagents being detected in the crude.

Scheme IV



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REFERENCES AND NOTES

I) a: L.A. Singer, and P.D. Bartlett, Tetrahedron Lett., I887, (I964); b: L.A. Singer, G.A. Davis, and V.P. Muralidharan, J. Amer. Chem. Soc., 9I 897, (I969) and references therein.

2) Our attempts to thermally react the ketenimine 2 with benzaldehyde failed even at high temperatures (xylene I30°C), or using very polar solvents (CH_3CN). It is reported in the literature that diphenylketene-*N*-*p*-tolylimine and the electrophilically activated *bis*(trifluoromrthyl)ketone form the iminoxetane at II0°C: A. Weidle-Kubanek and M. Litt, J. Org. Chem., 33, I844, (I968).

3) The ketenimine was prepared according to standard procedures: C.L. Stevens and J.C. French, J. Amer. Chem. Soc., 76, 4398, (I954).

4) G. Barbaro, A. Battaglia, P. Giorgianni and A. Dondoni, J. Org. Chem., 49, 2200, (I984).

5) S.J. Danishefsky, E. Larson, D. Askin, and N. Kato, J. Amer. Chem. Soc., I07, I246 (I985) and references therein.

6) The remainder consisted mainly of the amide $Me_2CHCONHC_6H_4$-*p*-CH_3 and the hydroxyamide 4.

7) Hydratative ring opening of 3 was also observed by the authors of ref. I

8) Relevant spectral data, proving the structure of 3 were an IR band at I745 cm^{-I} (Lit. I740); ^{I}H NMR ($CDCl_3$) showed selected resonances at 0.87 and I.54 ppm for the two non-equivalent methyls at C_3 and at 5.36 for the CH at C_4; ^{I3}C NMR ($CDCl_3$) showed selected resonaces at 5I.85 (C_3), 87.53 (C_4) and I64.69 (O-C=N).

9) The enantiomeric excess was determined by ^{I}H NMR (Yt(HFC)$_3$).

I0) For an exhaustive account on this topic see: A.K. Bose, D.P. Saha, M.S. Manhas, J. Org. Chem., 46, I229 (I98I).

II) The title compound had mass spectrum, ^{I}H and ^{I3}C NMR and elemental analysis consistent with the proposed structure.

I2) The role of DMSO in the assisted ring opening of 3, both during the formation of the β-hydroxy- and the β-ketoamide is clearly revealed by the oxetane stability, in the absence of lanthanides (see point d), upon the thermolysis in a pure state, or in solvents at high temperatures.

I3) C.J.M. Stirling, J. Chem. Soc., 255 (I980).

I4) In a typical experiment the oxetane and EuFOD (0.5 mole percent) were dissolved in several ml of CH_2Cl_2 in an ampoule. After solvent removal the ampoule was sealed under vacuum and heated in an oil bath at I50°C for ten minutes. Elution on a chromatographic column of the reaction mixture (silica, benzene/ethyl acetate I3:2) gave 7 in 70% yield. Relevant spectral data of 7 were an IR band (CCl_4) at I765 cm^{-I} (C=O); ^{I}H NMR ($CDCl_3$) exhibited two resonances at 0.83 and I.5 ppm for the two non-equivalent methyls at C_3 and at 4.77 for the CH at C_4; ^{I3}C NMR ($CDCl_3$) showed selected resonances at 55.6 (C_3), 66.54 (C_4), I64.7 (CO).

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