Pergamon

Tetrahedron Letters, Vol. 38, No. 17, pp. 3101-3102, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00555-8

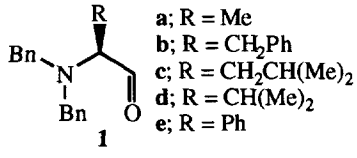
An Unusual Rearrangement of N,N-Dibenzyl-2-aminopropanal to N,N-Dibenzyl-1-aminopropanone.

Maqsood Adia, Nadine Hénaff and Andrew Whiting*.

Department of Chemistry, Faraday Building, U.M.I.S.T., P.O. Box 88, Manchester M60 1QD, U.K.

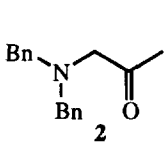
Abstract: N,N-dibenzyl-2-aminopropanal **1a** derived from alanine rearranges to the corresponding ketone, N,N-dibenzyl-1-aminopropanone upon exposure to either silica gel or pyridinium acetate. Similar rearrangements do not occur with aldehydes derived from phenylalinine, valine, leucine, proline or phenylglycine. One mechanistic explanation for the rearrangement is a facile 1,2-methyl shift, followed by 1,2-hydrogen shift. © 1997 Elsevier Science Ltd.

α-Amino-acid derived aldehydes[1-3] are useful precursors for the synthesis of stereodefined α-amino alcohols and in particular N,N-dibenzylamino-α-amino-aldehydes **1**[4] have recently been widely used for stereoselective synthesis.[4,5] As part of a programme aimed at using novel herbicide derivatives[6], we had occasion to prepare aldehyde **1a** using standard procedures[4] and found that a single rearranged product was isolated after attempted purification. In this communication we report the details of this surprising rearrangement and attempts to observe similar processes on related α-amino aldehydes to **1a**.

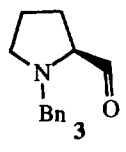


1

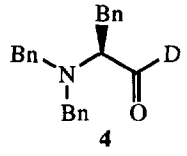
a; R = Me
b; R = CH_2Ph
c; R = $CH_2CH(Me)_2$
d; R = $CH(Me)_2$
e; R = Ph



2



3



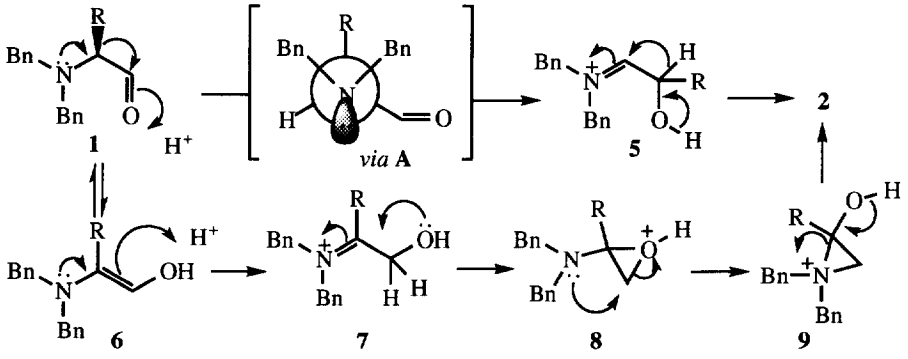
4

Mono-substituted α-amino-aldehyde analogues are known to be sensitive towards racemisation[1-3], however N,N-dibenzylamino derivatives **1** are thought to be reasonably configurationally stable[4,5] despite the fact that such aldehydes are generally used in a crude form to avoid any chance of racemisation occurring. Having prepared[4] crude alanine derivative **1a** attempts were made to purify the aldehyde by silica gel chromatography which resulted in the isolation of a single rearranged product **2** in 50 % yield[7] (from the corresponding alcohol). This surprising result led to attempts to examine if other reagents could accomplish the same rearrangement as that triggered by silica gel. It was found that acids and Lewis-acids [acetic acid, aq. HCl, boron trifluoride and titanium(VI) chloride] were ineffective at catalysing the reaction of crude aldehyde **1a** to rearranged product **2**. However, pyridinium acetate could catalyse the rearrangement of **1a** to **2** in 52 % isolated yield. These results caused us to speculate as to the mechanism that is operative in the conversion of **1a** to **2**. Related rearrangements are rare, however the transposition of amino aldehyde to amino acetones is known[8] requiring addition of a secondary amine to accomplish conversion. For a related mechanism to occur in the present case, hydrolysis of **1a** must first occur to release dibenzylamine; a process which we have been unable to observe. Therefore more likely are the alternative mechanisms shown in **Scheme 1**, involving either a 1,2-methyl shift to give **5** followed by a reverse 1,2-hydrogen shift to give **2**, or by initial aldehyde to enol (**6**) equilibration and subsequent rearrangement *via* oxiranium and aziridinium ions **8** and **9** respectively. In order to probe this matter further, attempts were made to make aldehydes **1b-e** and **3**.

Phenylalanine derived aldehyde **1b** failed to rearrange under either silica gel or pyridinium acetate conditions, however complete racemisation did occur. This racemisation occurred purely through the enol form **6**, as evidenced by the fact that deuterated aldehyde **4** racemised upon silica gel chromatography, but with complete retention of the deuterium on the aldehyde function, hence ruling out reversible hydrogen-migration similar to that shown for alkyl migration if the conversion of **1** to **5** (**Scheme 1**).

In contrast to either phenylalanine aldehyde **1b** or alanine aldehyde **1a**, both leucine and valine derived aldehydes **1c** and **d** respectively gave a complex mixture of products upon exposure to either silica gel or pyridinium acetate from which no major component could be identified. Similarly, proline aldehyde **3** decomposed completely upon exposure to silica gel and phenyl glycine aldehyde **1e** was not isolable at all in a crude state from the oxidation of the corresponding primary alcohol. Complete decomposition always occurred despite numerous attempts to oxidise the corresponding alcohol with a wide range of reagents, including the standard Swern process[4] used successfully for **1a-d**.

Scheme 1.



The fact that only the alaninal derivative **1a** rearranges cleanly could be attributable to the particularly fast 1,2-methyl and subsequent hydrogen shift, effectively preventing hydrolysis of the intermediate **5** (**Scheme 1**). Further, the observation that complete decomposition of products derived from the prolinal **3** or phenylglycinal **1e** derivatives occured, tends to support the idea of a rearrangement occuring *via* **5**. Similarly, the fact that phenylalaninal derivative **1b** simply racemises *via* an enol of type **6**, suggests that the first 1,2-alkyl shift (i.e. **1** to **5**) is too slow in this case due to unfavourable interactions in structure **A** (**Scheme 1**) and also that further rearrangement of **6** (R = CH_2Ph) through **7**, **8** and **9** respectively fails to occur. Thus, the observed rearrangement of alaninal derivative **1a** is probably due to stereoelectronic effects; the smaller methyl group of **1a** is able to adopt the necessary *syn*-planar orientation relative to the aldehyde π-system and the nitrogen lone pair therefore orientates to an *anti*-periplanar orientation relative to the shifting σ-bond (i.e. *via* **A** in **Scheme 1**); a process which presumably becomes precluded as the size of the alkyl of **1** increases due to steric repulsion between the N-benzyl groups and the alkyl group R.

Acknowledgements.

We acknowledge U.M.I.S.T. for partial funding for a studentship (to N.H.).

References and notes.

1. a) B.E. Evans, K.E. Rittle, C.F. Homnick, J.P. Springer, J. Hirshfield and D.F. Veber, *J. Org. Chem.* 1985, **50**, 4615; b) K.E. Rittle, C.F. Homnick, G.S. Ponticello and B.E. Evans, *ibid,* 1982, **47**, 3016.
2. D.H. Rich, A.S. Boparai and E.T. Sun, *J. Org. Chem.* 1978, **43**, 3624.
3. A. Ito, R. Takahashi and Y. Baba, *Chem. Pharm. Bull. Jpn.,* 1975, **23**, 3081.
4. a) M.T. Reetz, M.W. Drewes, A. Schmitz, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 1141; b) M.T. Reetz, *ibid*, 1991, **30**, 1531.
5. P.L. Beaulieu, D. Wernic, *J. Org. Chem.*, 1996, **61**, 3635.
6. a) S.P. Mackay and P.J. O'Malley, *Z. Naturforsch* 1993, **48c**, 782; b) M. Adia, P.J. O'Malley, S.P. Mackay, A. Whiting, unpublished results.
7. All analytical and spectroscopic data were identical to those reported: E.S. Stratford and R.W. Curley, Jr., *J. Med. Chem.*, 1983, **26**, 1463.
8. a) A. Kirrmann, L. Duhamel and P. Duhamel, *Bull. Soc. Chim. Fr.* 1966, 1732; b) L. Duhamel, P. Duhamel and A. Jarry, *ibid*, 1970, 1797.
9. Deuterated aldehyde **4** was prepared as described[4] for compounds **1a-d** and **3**, except that $LiAlD_4$ was used in place of $LiAlH_4$ to produce >95% D incorporation.

(*Received in UK* 17 *February* 1997; *revised* 20 *March* 1997; *accepted* 21 *March* 1997)