Aza-[2,3]-Wittig Sigmatropic Rearrangement of Crotyl Amines

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The first example of an acyclic aza-[2,3]-Wittig sigmatropic rearrangement is presented, and its application to the synthesis of unnatural amino acids is described.

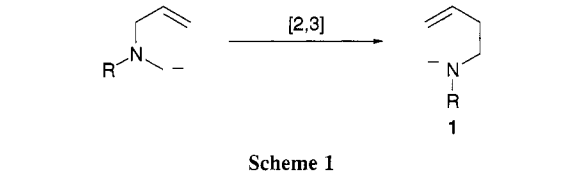
The aza-[2,3]-Wittig sigmatropic rearrangement (Scheme 1) has remained a rare congener of the versatile oxy-[2,3]-Wittig rearrangement.[1]

To date only two true examples of this transformation have been reported. These have involved the base promoted rearrangement of 1-benzyl-4-vinyl-2-azetidinone[2] and vinyl aziridines.[3] The ease with which these particular rearrangements occurred is undoubtedly due to relief of ring strain in the three- and four-membered ring substrates. There have been unsuccessful attempts to perform the acyclic variant which does not involve this driving force.[4]† We have investigated this acyclic aza-[2,3]-Wittig rearrangement as a potential route to unnatural amino acids (Scheme 2),‡ and would like to report our preliminary results here.

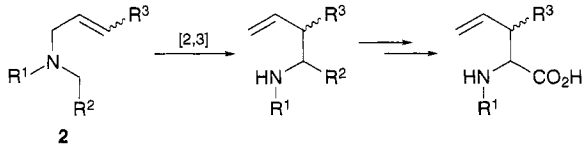
To achieve our goals the aza-[2,3]-Wittig precursor **2** (Scheme 2) required some careful design. We postulated that R^1 should be electron withdrawing so as to stabilise the nitrogen anion formed from the desired rearrangement (**1**, Scheme 1), and thus provide some thermodynamic driving force for the reaction. The Boc protecting group suits this purpose and can be easily removed, if required, from the product. The protons adjacent to R^2 have to be activated towards abstraction by a suitable base,[5] but simultaneously the resultant anion must not be too stable.[4b] This activating group R^2 must also be degradable to a carboxylate function. A phenyl ring would fulfil these requirements. Some sort of regiochemical marker was incorporated so that the [2,3] shift could be differentiated from the potential [1,2] shift.[6] A methyl group provided the simplest marker.

Our initial substrate **3** was prepared in geometrically pure form (>95% *E* by NMR) from the methanesulfonate of commercially available crotyl alcohol (**4**, Scheme 3). Treatment with di-*tert*-butylimidodicarbonate,[7] K_2CO_3, in the presence of a catalytic amount of lithium iodide (5%) in refluxing butanone[8] led to the di-*N*-Boc protected *E*-crotyl amine **5** in 65% yield. Monodeprotection with TFA and benzylation under standard conditions led to **3**§ in 92% yield over two steps. Deprotonation of this benzyl amine, with *n*-butyl lithium at −78 °C in Et_2O with HMPA as a cosolvent (20%) and warming to −40 °C overnight, resulted in the desired [2,3] rearrangement yielding the primary amine **6**§ in 82% yield¶ with a diastereoselectivity of 3 : 2.‖ This rearrangement represents the first acyclic example of an aza-[2,3]-Wittig rearrangement. This rearrangement was supported by the appearance of an extra vinylic signal in the ^1H NMR of **6** and the upfield shift of the vinylic methyl group in going from **3** to **6**.** No product arising from a [1,2]-sigmatropic rearrangement was detected. At present only this combination of base, solvent and temperature facilitates this reaction. The sense of diastereoselection and hence a transition-state model for the major product could be determined by converting substrate **6** into a mixture of protected amino acids **7** and **8** (Scheme 4).

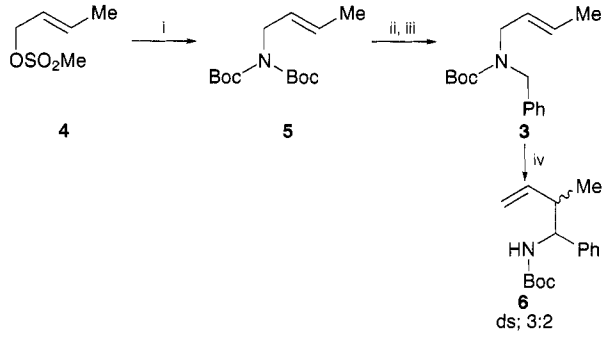
Hydrogenation of the terminal alkene, followed by oxidation of the aromatic ring with catalytic ruthenium trichloride and sodium metaperiodate,[9] furnished a mixture of *N*-Boc protected amino acids in the exact same ratio of diastereoisomers as **6**. Treatment with diazomethane enabled the isolation of **7** and **8** (3 : 2) in an overall yield of 48%. The minor diastereoisomer **8** could be correlated by NMR to an authentic derivative of isoleucine and the major diastereoisomer **7** was then the unnatural diastereoisomer. The degree and sense of diastereoselection is similar to that observed for the oxygen analogue of **3**.[10] In accord with the calculated structure for the oxy-[2,3]-Wittig rearrangement[11] we suggest structure **9** (Scheme 5) represents the transition-state model for the major product from this rearrangement. It is well known in the oxy-[2,3]-Wittig variant that *Z*-alkene substrates give much better diastereoselection upon rearrangement.[1] The corresponding rearrangement of the *Z*-crotyl amine **10**†† under the same conditions however did



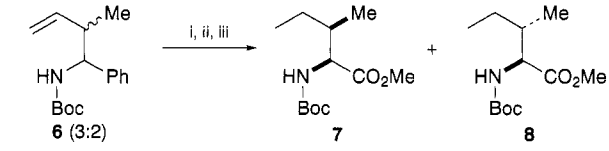
Scheme 1



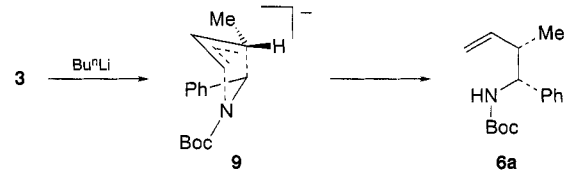
Scheme 2



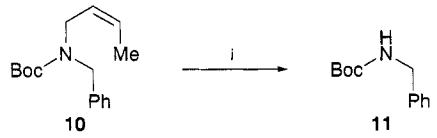
Scheme 3 *Reagents and conditions*: i, Boc_2NH, K_2CO_3, LiI, butanone, 80 °C, 14 h, 65%; ii, TFA, CH_2Cl_2, 14 h; iii, KH, BnCl, 0 °C to room temp. 14 h, 92%; iv, Bu^nLi, Et_2O–HMPA (4 : 1), −78 to −40 °C, 14 h, 82%



Scheme 4 *Reagents and conditions*: i, H_2 1 atm, Pd/C (cat.), methanol, 1 h; ii, $RuCl_3 \cdot nH_2O$ (cat.), $NaIO_4$, CCl_4, MeCN, H_2O, room temp. 48 h; CH_2N_2, CH_2Cl_2, room temp. 48% overall



Scheme 5 Transition-state model for major diastereoisomer



Scheme 6 *Reagents and conditions*: i, Bu^{n}Li, Et_2O–HMPA (4 : 1), −78 to −40 °C, 14 h, 20%

not yield the desired products. Instead the only identifiable products were recovered starting material (15%) and *tert*-butoxycarbonylbenzylamine **11** (20%) (Scheme 6). Under these particular reaction conditions, access to the five-membered ring transition state[11] needed for this rearrangement is of too high energy, and so competing destructive pathways intervene. In our efforts to achieve rearrangement of *Z*-crotyl amine we surveyed a number of nitrogen protecting groups with our *E*-substrate. Only certain protecting groups R[1] (Scheme 2) ensure the success of this rearrangement. For instance, in addition to *N*-*tert*-butoxycarbamate, we have found only *N*-methoxycarbamate (55%, ds; 5 : 4), *N*-diphenylphosphinyl[12] (38%, ds; 3 : 2) and *N*-*tert*-butylformamidine[13] (9%, ds; 7 : 3) will activate the *E*-substrate towards rearrangement, none activate the corresponding *Z*-substrate. Other common protecting groups such as Cbz, tosyl or trifluoroacetyl gave no rearranged material. The exact role of the protecting group is currently under investigation, but these preliminary results suggest a protecting group on nitrogen capable of stabilising metallation is essential to allow this rearrangement.

We have shown that the aza-[2,3]-Wittig rearrangement is possible for carefully designed acyclic substrates. The potential for this rearrangement to provide unusual amino acids has also been demonstrated. Other variables in this procedure which will generate diastereomerically pure and eventually enantioenriched products are under investigation; results will be reported shortly.

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Footnotes

† The rearrangement in ref. 4a has been shown to proceed by a [1,2] mechanism.[4b]

‡ Alternatively the double bond could be oxidised to furnish β-amino acids.

§ All new compounds gave satisfactory ^1H and ^{13}C NMR, IR, mass spectra and analysis and/or high resolution accurate mass spectra.

¶ With 15% recovered starting material.

‖ Measured from integration of the NMR spectrum in $(CD_3)_2SO$.

** Vinylic CH_3 in compound **3** δ 1.68 (3 H, dd, J = 6.2, 1.2 Hz) compares to allylic CH_3 in **6** δ 0.99 (3 H, d, J = 6.3 Hz) major and δ 0.95 (3 H, d, J = 6.1 Hz) minor.

†† Prepared in exactly the same fashion as for **3**, but starting from *Z*-crotyl alcohol obtained in diastereomerically pure form from the Lindlar reduction of propargyl alcohol.

References

1 For a recent review see T. Nakai and K. Mikami, in *Organic Reactions*, 1994, **46**, 105.
2 T. Durst, R. V. D. Elzen and M. J. Le Belle, *J. Am. Chem. Soc.*, 1972, **94**, 9261.
3 J. Ahman and P. Somfai, *J. Am. Chem. Soc.*, 1994, **116**, 9781; I. Coldham, A. J. Collis, R. J. Mould and R. E. Rathnell, *Tetrahedron Lett.*, 1995, **36**, 3557.
4 (*a*) C. A. Broka and T. Shen, *J. Am. Chem. Soc.*, 1989, **111**, 2981; (*b*) Y. Murata and T. Nakai, *Chem. Lett.*, 1990, 2069; (*c*) I. Coldham, *J. Chem. Soc., Perkin Trans 1*, 1993, 1275.
5 In general protons α to phenyl are two orders of pK_a units lower than those α to alkene. *e.g.* pK_a for PhMe and MeCH=CH_2 are 41 and 43 respectively. See D. W. Boerth and A. Streitweiser, Jr., *J. Am. Chem. Soc.*, 1981, **103**, 6443.
6 J. E. Baldwin and J. E. Patrick, *J. Am. Chem. Soc.*, 1971, **93**, 3556 and references therein.
7 L. Grehn and U. Ragnarsson, *Synthesis*, 1987, 275.
8 R. A. T. M. van Benthem, J. J. Michels, H. Hiemstra and W. N. Speckamp, *Synlett*, 1994, 368.
9 P. H. J. Carlsen, T. Katsuki, V. S. Martin and K. B. Sharpless, *J. Org. Chem.*, 1981, **46**, 3936.
10 K. Mikami, Y. Kimura, N. Kishi and T. Nakai, *J. Org. Chem.*, 1983, **48**, 281 and references therein.
11 Y.-D. Wu, K. N. Houk and J. A. Marshall, *J. Org. Chem.*, 1990, **55**, 1421; see also, K. Mikami, T. Uchida, T. Hirano, Y.-D. Wu and K. N. Houk, *Tetrahedron*, 1994, **50**, 5917.
12 H. M. I. Osborn and J. B. Sweeney, *Synlett*, 1994, 145.
13 A. I. Meyers, P. D. Edwards, W. F. Rieker and T. R. Bailey, *J. Am. Chem. Soc.*, 1984, **106**, 3270.