Tetrahedron Letters,Vol.28,No.2,pp 179-182,1987 0040-4039/87 $3.00 + .0
Printed in Great Britain Pergamon Journals Ltd.

# ASYMMETRIC SYNTHESIS WITH CHIRAL HYDROXYLAMINES. SYNTHESIS OF OPTICALLY PURE 4-SUBSTITUTED AZETIDINONES

S. W. Baldwin and J. Aubé
Paul M. Gross Chemical Laboratory
Duke University
Durham, North Carolina 27706

Summary: The reaction between β-substituted acrylate esters and α-methylbenzyl hydroxyl amine affords diastereoisomeric 5-isoxazolidinones, convenient precursors of simple optically pure 2-azetidinones.

A consistent structural feature of β-lactam biology is the dependence of activity on molecular chirality,[1] a fact which underscores the need for new methods for the synthesis of these compounds in optically active form. Current synthetic strategies include most if not all of the normal techniques for incorporating chiral bias. Reported here is a new general approach to the synthesis of simple optically active 2-azetidinones (β-lactams), which makes use of some novel chemistry of α-methylbenzyl hydroxylamine.

During a study of the reactions of different substrates with optically active hydroxylamines, it was discovered that reaction of α-methylbenzyl hydroxylamine[2] oxalate salt **2** with various acrylic esters **1** in refluxing benzene containing suspended potassium carbonate led to good yields of 3-substituted isoxazolidinones **3a**, **3b**.[3] In fact, the reaction appears to be general for a variety of β-substituted acrylates, the yields of isoxazolidinone products generally being in the 70-95% range. Of particular interest was the observation that the ratio of diastereoisomers produced in this reaction was usually in excess of 80:20, varying little for a series of β-substitutents except for the decrease to 68:32 noted for methyl cinnamate (Table). In general, it was possible to separate the diastereoisomers either by simple chromatography or fractional crystalization.

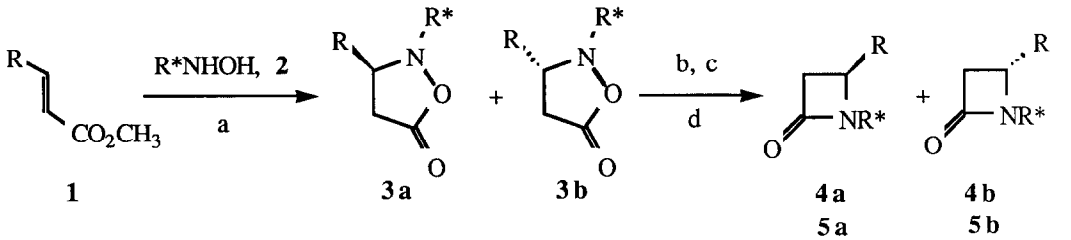
It was subsequently found that the isoxazolidinones can be readily converted to optically active 4-substituted azetidinones. Thus, hydrogenolysis of the labile N-O bond ($H_2$; Pd/C) followed by cyclization of the resultant β–amino carboxylic acids[4,5] cleanly affords azetidinones **4**, the α-methylbenzyl groups of which were then removed by brief exposure to $Na/NH_3$[6a] to give the simple azetidonones **5**. As shown in the Table, yields for this overall process are generally very good.

Not only did the azetidinones represent a simple solution to the problem of synthesis of optically pure β-lactams, they also allowed a ready determination of the absolute sense of chirality transfer in the formation of the isoxazolidinones by analysis of the derived circular dichroism spectra.[7,8] In all cases studied it was found that C-4 of the major azetidinone product derived from (R)-α-methylbenzyl hydroxylamine was as indicated in **3**, that is (R). Opposite results were obtained from (S)-α-methylbenzyl hydroxylamine, the major azetidinone isomer in this case being (S). These results were particularly gratifying because they provide predictabilty for planning future synthetic applications.

We are suggesting that the reaction proceeds by initial conjugate addition of the hydroxylamine nitrogen to the α,β-unsaturated system followed by lactonization.[9] In fact the conjugate addition intermediates can be isolated in pure form if the initial reaction is conducted at room temperature. All indications are that the reaction is irreversible since pure isoxazolidinones do not equilibrate under the reaction conditions (benzene, suspended carbonate, 1 eq. methanol, reflux). Moreover, the purified uncyclized conjugate addition products lead to single isoxazolidinones on exposure to the above reaction conditions.

The precise origin of the diastereoselectivity is unclear at this time. Addition of the parent α–methylbenzyl amine to crotonic acid affords a 1:1 mixture conjugate addition isomers.[10] It would appear, therefore, that the OH group of the hydroxylamine plays a pivotal role, possibly by coordinating with the ester oxygen as shown below. Consistent with this view is the observation that the diastereoselectivity of the methyl crotonate reaction drops off as the solvent is made more polar (90:10, hexane; 80:20, benzene; 70/30, ether; 65:35, glyme). By this picture, crotonate face selectivity would appear to be the result of a hydrogen bonded transition state which minimizes interactions between the acrylate β-alkyl group and the medium ($CH_3$) and small (H) groups on the hydroxylamine. It is curious that an increase in the size of the β-substituent from $CH_3$ to $i$-$C_3H_7$ has virtually no affect on the diastereoselectivity of the overall process. As shown, this picture also predicts that the reaction should be independent of double bond stereochemistry since a change in both crotonate geometry and face accessibility (two inversions) would result in net retention of configuration at the β-carbon. This prediction has been verified with methyl isocrotonate (Table, entry 2).[11] The relative simplicity of this mneumonic is valuble for predictive purposes and makes it an attractive candidate for a more thorough mechanistic investigation.

In conclusion, we present a simple four-step route to optically pure β-lactams by a reaction which employs the diastereoselective reaction between β-substituted acrylates and optically active α-methylbenzyl hydroxylamine as the key reaction. The ready availablity of α-methylbenzyl hydroxylamine in either optically active form and the predictable stereochemical regularity of the process provide flexibility for planning other synthetic efforts.[14]



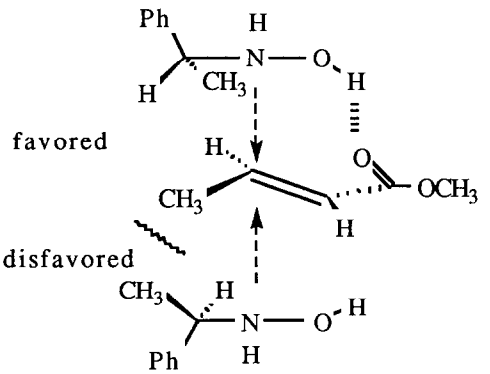

**1**, **2**, **3**, **4**; R* = α-methylbenzyl. **5**; R* = H.

[a]PhH/$K_2CO_3$; 80°C. [b]$H_2$; Pd/C, EtOH. [c]n-$Bu_4NHSO_4$/aq. $KHCO_3$//$CHCl_3$/MsCl. [d]Na/$NH_3$

**TABLE**: REACTION OF ACRYLATES WITH α-METHYLBENZYL HYDROXYLAMINE

| Entry | R | % Yield (**3**) | **3a**:**3b**[a] | % Yield (**5**)[b] | Configuration R*NHOH[c] | Configuration C-4[d] |
|---|---|---|---|---|---|---|
| 1 | $CH_3$ | 91 | 80:20 | 91[e] | R | R |
| 2 | $CH_3$ | 84 | 19:81 | 69[e] | S | S |
| 3 | $CH_3$ (*cis*) | 22 | 86:14 | 83 | R | R |
| 4 | $CH_2CH_2CH_3$ | 80 | 82:18 | 50[f] | R | R |
| 5 | $CH(CH_3)_2$ | 74 | 80:20 | 66[g] | R | S[h] |
| 6 | $C_6H_5$ | 54 | 69:31 | 32[i,j] | R | S[h] |
| 7 | $CH_2CH_2OMOM$ | 80 | 80:20 | 51 | R | R |
| 8 | $CH_2CH_2OMOM$ | 76 | 18:82 | 39 | S | S |
| 9 | $CH_2CO_2CH_3$ | 65 | 70:30 | --[k] | R | R |

[a]Determined from integrations of 250 MHz 1H NMR spectra of crude reaction mixtures. [b]Combined yield for cyclodehydration and Na/ammonia treatment of pure isomer 3. [c]R*NHOH = α-methylbenzyl hydroxylamine. [d]References 7 and 8. [e]Reference 6. [f]Reference 13a. [g]Reference 13b. [h]Reversal of configuration designation due to the Cahn, Ingold, Prelog priority change for the C-4 substituent. [i]Reference 13c. [j]Data for product of N-O cleavage and cyclodehydration steps only. [k]Footnote 12.



## References and Notes

1. For reviews of recent advances in new β-lactam antibiotics see (a) R. D. G. Cooper in "Topics in Antibiotic Chemistry," P. G. Sammes, Ed., Halstead Press: New York, 1980; Vol. 3, pp. 39-199. (b) "Recent Advances in the Chemistry of the β-Lactam Antibiotics," G. I. Gregory, Ed., The Royal Society of Chemistry: London, 1981. (c) "Chemistry and Biology of β-Lactam Antibiotics," R. B. Morin & M. Gorman, Eds., Academic Press: New York, 1982, Vol.2.

2. (a) T. Polonski and A. Chimiak, Tetrahedron Lett., 2453 (1974). (b) T. Polonski and A. Chimiak, Bull. Acad. Pol. Sci., Ser. Sci. Chim., **27**, 459 (1979).

3. A report describing isoxazolidinone formation by the addition of alkyl hydroxylamines to acrylate esters has recently appeared. The authors included one example using α-methylbenzyl hydroxylamine, but with limited discussion of the stereochemical aspects of the reaction. J. E. Baldwin, L. M. Harwood. and M. J. Lombard, Tetrahedron, **40**, 4363 (1984).

4. Y. Watanabe and T. Mukaiyama, Chem. Lett., 443 (1981).

5. S. Kobayashi, I. Iimori, T. Izawa, and M. Ohno, J. Am. Chem. Soc., **103**, 2406 (1981).

6. (a) R. G. Kostyanovsky, I. M. Gella, V. I. Markov, and Z. E. Samojlova, Tetrahedron, **30**, 39 (1974). (b) L. Birkofer and J. Schramm, Leibigs. Ann. Chem., 2195 (1975).

7. (a) H. Rehling and H. Jensen, Tetrahedron Lett., 2793 (1972). (b) H. Ogura, H. Takanayagi, K. Kubo, and K. Furuhata, J. Am. Chem. Soc, **95**, 8056 (1973).

8. R. Busson, E. Roets, and H. Vanderhaeghe, J. Org. Chem., **43**, 4434 (1978).

9. See also H. Stamm and H. Steudle, Tetrahedron Lett., 3607 (1976), and references contained therein.

10. A. P. Terent'ev, A. Gracheva, and T. F. Dedenko, Dok'l. Akad. Nauk., SSSR, 386 (1965), C. A., **63**, 11344b (1965), and results from this laboratory.

11. C. Rappe, "Organic Synthesis," **53**, 123 (1973).

12. In the addition of α-methylbenzyl hydroxylamine to dimethyl glutaconate, the C-3 chirality of the 5-isoxazolidinone product is generated during a diastereoselective cycliaztion (second step) rather than in the initial Michael addition.

13. (a) E. Testa, L. Fontanella, and V. Aresi, Leibigs Ann. Chem., **673**, 60 (1964). (b) R. Graf, Ibid., **661**, 111 (1963). (c) C. Belzecki and E. Rogalska, J. Chem. Soc., Chem. Commun., 57 (1981).

14. (a) The authors wish to thank Dr. D. Metcalf for his assistance in collecting the CD data. Yields have not been optimized. All new compounds gave satisfactory elemental analyses and spectral data (ir, nmr) consistent with the assigned structures. (b) A portion of this work was presented at the 186th National Meeting of the American Chemical Society, August 28 - September 2, 1983, Washington, DC; ORGN 179. (c) Partial suport from the National Institutes of Health is gratefully acknowledged (GM 31364).

(Received in USA 7 October 1986)