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Chiral Oxazolidinones from N-Boc Derivatives of β-Amino Alcohols. Effect of a N-Methyl Substituent on Reactivity and Stereoselectivity

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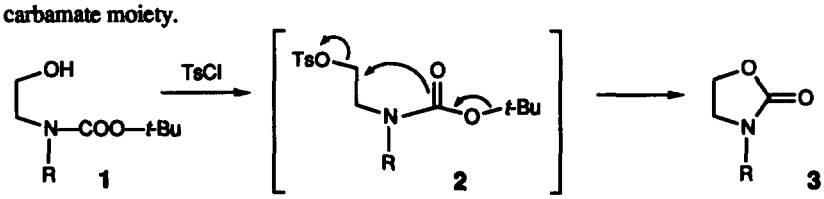
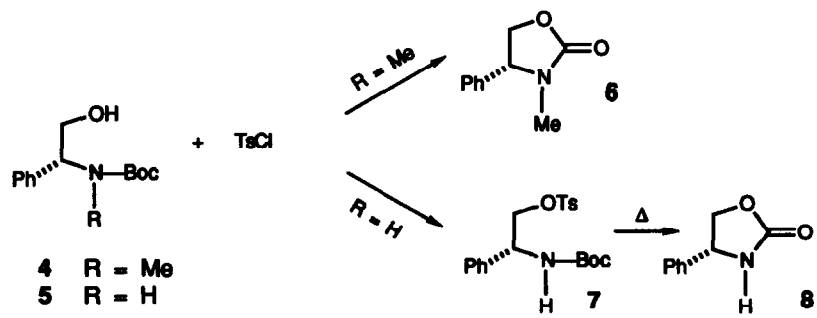
Abstract: Treatment of *N-tert*-butoxycarbonyl derivatives of homochiral β-amino alcohols with *p*-toluenesulfonyl chloride affords 2-oxazolidinones. These heterocycles were produced by intramolecular nucleophilic attack of the carbamate moiety in an intermediate tosylate. The presence of a *N*-methyl substituent enhanced the cyclization rate and this effect was studied by AM1 calculations.

Launched by Evans' seminal work,[1] homochiral oxazolidinones are now well-established versatile auxiliaries in asymmetric synthesis.[2,3] We report here that these heterocycles **3** are obtained when *N-tert*-butoxycarbonyl derivatives (N-Boc) of β-amino alcohols are treated with *p*-toluenesulfonyl chloride (TsCl). Though transformation of amines into urethanes is a widely used protective method,[4] it can be inferred from scarce accounts[5] that, even in non-acidic medium, these protecting groups should not be considered as definitely inert. Actually the reaction hereafter described results from nucleophilic displacement of the tosyloxy leaving group by the carbamate moiety.

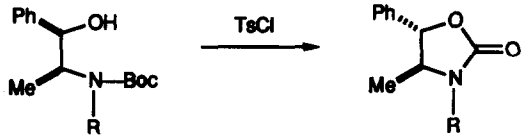


This cyclization is highly promoted by the presence of a *N*-methyl substituent. Thus, whereas reaction of *N*-Boc-*N*-methyl-(*R*)-phenylglycinol **4** with TsCl at 0°C directly leads to oxazolidinone **6**, the same treatment



applied to *N*-Boc-(*R*)-phenylglycinol **5** affords the tosyloxy derivative **7**. Cyclization of compound **7** was effected subsequently by heating at 60°C and yielded oxazolidinone **8**.

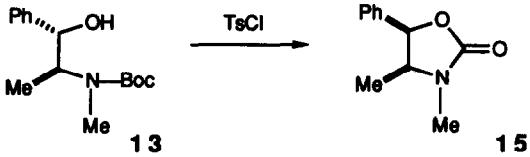
In order to get some insight into the mechanism of the cyclization, we next examined the behaviour of compounds belonging to the ephedrine family. *N*-Boc derivatives of (1*R*,2*S*)-ephedrine **9** and (1*R*,2*S*)-norephedrine **10** led stereoselectively to the corresponding oxazolidinones **11** and **12**. Both compounds **11** and **12** exhibit a *trans* relationship between the ring substituents[6] which arises from inversion of the reactive carbon center. This result is consistent with a S_N2 process involving a nucleophilic attack of the carbamate moiety onto the benzylic center.



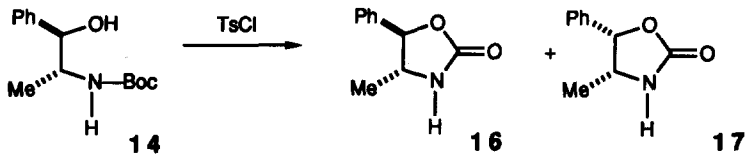
9 R = Me
10 R = H

11 R = Me
12 R = H

On the other hand, *N*-Boc derivatives of (1*S*,2*S*)-pseudoephedrine **13** and (1*R*,2*R*)-norpseudoephedrine **14** are less prone to cyclize; this can be attributed to steric hindrance during the formation of the corresponding oxazolidinones since now the afore-mentioned S_N2 pathway would lead to heterocycles **15** and **17** having a *cis* relationship between ring substituents. Here again, the *N*-methyl substrate **13** reacts faster than **14** and the *N*-methyl group also has an effect on the stereochemical outcome of these cyclizations. While the N-methylated compound **13** stereoselectively affords the *cis* oxazolidinone **15** via a S_N2 intramolecular process,[8] its analogue **14** leads, with a poor yield, to both *trans* and *cis* heterocycles **16** and **17** in a 80:20 respective ratio. This is indicative of a S_N1-like process in the latter case which is devoid of the above nucleophilic enhancement of the carbamate moiety promoted by the *N*-methyl substituent.

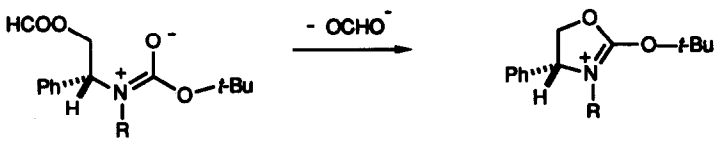


13 **15**



14 **16** **17**

From the early age of mechanisms in organic chemistry[9] to nowadays,[10] rate enhancement due to alkyl substituent is a recurrent event in the field of cyclization reactions.[11] Recently, Jung and Gervay[12] demonstrated that, at least for intramolecular Diels-Alder reactions, the "Thorpe-Ingold effect" can be accounted for by a higher proportion of a more reactive rotamer in the case of *gem*-dialkylated substrates. In the present occurrence, this issue was addressed by means of AM_1 calculations[13] performed on model reactions with molecules **18-19** as substrates and **20-21** as their corresponding cyclized derivatives.



18 R = Me
19 R = H

20 R = Me
21 R = H

Compounds **18** and **19** show similar reactive conformations corresponding to the one depicted above. The most significant data are collected in the Table. Independently of the nature of the R group, the structure *E*, which is required for the cyclization to occur, is preferred over structure *Z*. In agreement with the Thorpe-Ingold effect, there is a compression of the internal C–N=C angle due to *N*-methyl substitution. Moreover these calculations show that there is a significant energy difference during the cyclization processes favoring the reactivity of the *N*-methylated substrate **18**. Owing to the easier production of *trans* oxazolidinones over their *cis* isomers, it can be hypothesized that the cyclization transition state is product-like and that the 6.2 kcal.mole^{-1} energy difference corresponds to relative activation energies.

Table. AM1 Calculations on Carbamate Models **18** and **19**

Substrate	$H_f Z - H_f E$ (kcal.mole^{-1})	C–N=C angle	ΔH of cyclization (kcal.mole^{-1})
18	1.35	118.2°	106.4
19	1.75	121.8°	112.6

This theoretical conclusion most likely can be extended to the above experimental results.[14,15] Therefore a conformational effect would be responsible for the reactivity enhancement promoted by the *N*-methyl substituent.

REFERENCES AND NOTES

1. Evans, D.A.; Bartroli, J.; Shih, T.L. *J. Am. Chem. Soc.* **1981**, *103*, 2127-2129.
2. For concise overviews of this field, see : (a) Evans, D.A. in *Asymmetric Synthesis*; Morrison, J.D. Ed.; Academic Press: London, 1984; Vol. 3, pp. 87-90. (b) Heathcock, C.H. *ibidem*, pp. 184-188.
3. For some recent reports, see: (a) Evans, D.A.; Faul, M.M.; Colombo, L.; Bisaha, J.J.; Clardy, J.; Cherry, J. *J. Am. Chem. Soc.* **1992**, *114*, 5977-5985. (b) Corey, E.J. *J. Am. Chem. Soc.* **1992**, *114*, 7938-7939. (c) Sibi, M.P.; Christensen, J.W.; Li, B.; Renhowe, P.A. *J. Org. Chem.* **1992**, *57*, 4329-4330. (d) Poindexter, G.S.; Owens, D.A.; Dolan, P.L.; Woo, E. *J. Org. Chem.* **1992**, *57*, 6257-6265. (e) Nicolas, E.; Russel, K.C.; Hruby, V.J. *J. Org. Chem.* **1993**, *58*, 766-770. (f) Es-Sayed, M.; Gratkowski, C.; Krass, N.; Meyers, A.I.; de Meijere, A. *Tetrahedron Lett.* **1993**, *34*, 289-292.
4. Kunz, H.; Waldmann, H. in *Comprehensive Organic Synthesis*; Trost, B.M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6, pp.635-642.
5. (a) Heathcock, C.; Hassner, A. *Angew. Chem.* **1963**, *75*, 344-345. (b) Foglia, T.A.; Swern, D. J. Org. Chem. **1969**, *34*, 1680-1684. (c) Bodanszky, M.; Klausner, Y.S.; Bodanszky, A. *J. Org. Chem.* **1975**, *40*, 1507-1508. (d) Jones, J.H.; Witty, M.J. *J. Chem. Soc., Chem Commun.* **1977**, 281-282. (e) Savrda, J; Wakselman, M. *J. Chem. Soc., Chem. Commun.* **1992**, 812-813. (f) Beak, P.; Lee, K.W. *J. Org. Chem.* **1993**, *58*, 1109-1117.

6. Stereochemical relationships within oxazolidinones **11**, **12**, **15**, **16** and **17** were assigned by comparison of their ^1H NMR spectra with literature values.[7]
7. Spassov, S.L.; Stefanovsky, J.N.; Kurtev, B.J.; Fodor, G. *Chem. Ber.* **1972**, *105*, 2462-2466.
8. ^1H NMR data of the crude reaction product showed that compound **15** was produced along with a small amount (4%) of oxazolidinone **11**.
9. Beesley, R.M.; Ingold, C.K.; Thorpe, J.F. *J. Chem. Soc.* **1915**, *107*, 1080-1106.
10. De Corte, F.; Nuyttens, F.; Cauwberghs, S.; De Clercq, P. *Tetrahedron Lett.* **1993**, *34*, 1831-1832.
11. Kirby, A.J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183-278.
12. Jung, M.E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224-232.
13. (a) Dewar, M.J.S.; Zoebisch, E.G.; Healy, E.F.; Stewart, J.J.P. *J. Am. Chem. Soc.* **1985**, *107*, 3902-3909. (b) AMPAC, version 4.0, QCPE No 527.
14. General procedure for *N*-Boc derivative formation: All *N-tert*-butoxycarbonyl derivatives of β-amino alcohols were prepared by refluxing for 12 h a solution of the β-amino alcohol and di-tert-butyl dicarbonate (1 equiv.) in ethyl acetate. After cooling to room temperature, the solution was washed with water and the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. These crude *N*-Boc derivatives (nearly quantitative yields) were used without further purification. The physicochemical properties of known compounds **5**, **9**, **10** and **13** were identical with those described in the literature (**5**[16], **9**[17], **10**[18], **13**[17]). All new compounds gave satisfactory (^1H and ^{13}C NMR) spectral data and elemental analysis.
15. General procedure for ozolidinone formation: *p*-Toluenesulfonyl chloride (12 mmol) was added to a solution of the *N*-Boc derivative of the β-amino alcohol (4 mmol) in pyridine (10 mL). The mixture was kept at 0°C when starting from **4** and was refluxed in the other cases. The reaction was monitored by TLC until completion. After cooling to rt, water (100 mL) was added and the resulting mixture was extracted with ether. The organic layer was washed with a saturated aqueous solution of $CuSO_4$, dried over $MgSO_4$ and concentrated under reduced pressure. Oxazolidinones were obtained from this residue by flash chromatography. Yields are in the range 70-80%, except when starting from **14** (29%). Optical rotations and NMR data of known compounds **11**, **12** and **15** were identical with those described in the literature.[7,19] The mixture of oxazolidinones **16** and **17** was analyzed by ^1H NMR and the data were compared with those already reported.[7] Oxazolidinone **6**: mp 78°C;$[\alpha]_D^{20}$ -69 (*c* 2, $CHCl_3$); ^1H NMR ($CDCl_3$): 2.17 (s, 3H), 4.07 (dd, J = 5.7 and 7 Hz, 1H), 4.6-4.8 (m, 2H), 7.2-7.5 (m, 5H); ^{13}C NMR ($CDCl_3$): 29.4, 62.2, 69.9, 127, 129.2, 129.5, 137.8, 158.8; IR ($CHCl_3$): 1740 cm^{-1}. Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 7.90; N, 6.26. Found: C, 67.58; H, 7.84; N, 6.35.
16. Correa, A.; Denis, J.N.; Greene, A.E. *Synth. Commun.* **1991**, *21*, 1-9.
17. Coote, S.J.; Davies, S.G.; Middlemiss, D.; Naylor, A. *Tetrahedron: Asymmetry*, **1990**, *1*, 33-56.
18. Bernardi, A.; Cardani, S.; Pilati, T.; Poli, G.; Scolastico, C.; Villa, R. *J. Org. Chem.* **1988**, *53*, 1600-1607.
19. Fodor, G.; Stefanovsky, J.; Kurtev, B. *Monatsh. Chem.* **1967**, *98*, 1027-1042.

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