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LETTERS

A NEW, ECONOMICAL, PRACTICAL AND RACEMIZATION-FREE METHOD FOR THE REDUCTIVE REMOVAL OF 2-OXAZOLIDINONES FROM N-ACYLOXAZOLIDINONES WITH SODIUM BOROHYDRIDE

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Abstract: A new, economical, practical and racemization-free method for the reductive removal of 2-oxazolidinones by a reduction of N-acyloxazolidinones with sodium borohydride in THF and water is described.

Pioneering work of Evans[1] has resulted in the development of 2-oxazolidinones as popular and widely used chiral auxiliaries in asymmetric synthesis.[2,3] The removal of these chiral auxiliaries, after attaining the desired asymmetric induction, could prove problematic with base-sensitive molecules because of the possibility of racemization. Development of new methods for the removal of these auxiliaries without destroying the stereogenic center remains a topic of interest.[4] Lithium aluminum hydride and lithium borohydride have been reported for the reductive removal of these auxiliaries.[5-7] Both of these reagents have limitations. Lithium aluminum hydride is useful for molecules which do not contain other groups which may be susceptible to reduction. Lithium borohydride is an expensive reagent and is not readily available on a commercial scale. We were recently faced with the challenge of developing a non-destructive method for the reductive removal of these auxiliaries in a molecule which contained a nitrile functional group, and it was also susceptible to racemization under basic conditions. Herein, we report the development of a new economical, practical and racemization-free method for the reductive removal of 2-oxazolidinones by inexpensive sodium borohydride in a mixture of tetrahydrofuran and water. The use of sodium borohydride for this purpose is not known in the literature to the best of our knowledge.

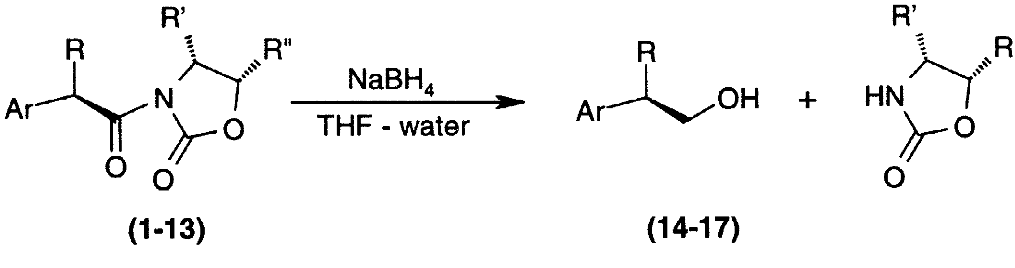

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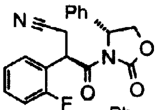
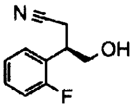
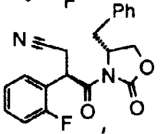
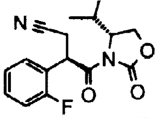
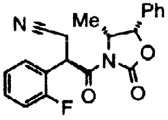
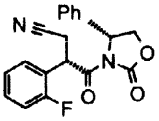
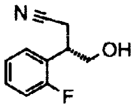
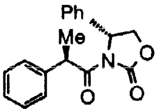
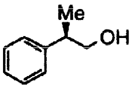
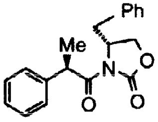
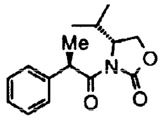
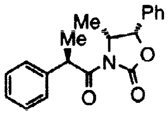
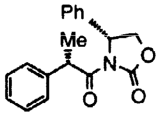
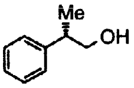
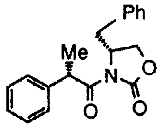
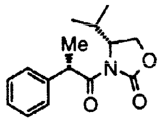
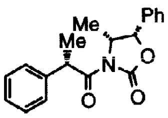
Table 1. Reduction of N-Acyloxazolidinones with $NaBH_4$ in THF and water

Entry	Substrate	Product	Yield (%)	ee (%)
1	 (1)	 (14)	95	>99
2	 (2)	(14)	91	>99
3	 (3)	(14)	80	>99
4	 (4)	(14)	85	>99
5	 (4)	 (15)	75	>99
6	 (6)	 (16)	95	>99
7	 (7)	(16)	84	>99
8	 (8)	(16)	88	>99
9	 (9)	(16)	84	>99
10	 (10)	 (17)	87	>99
11	 (11)	(17)	78	>99
12	 (12)	(17)	89	>99
13	 (13)	(17)	76	>99

Reduction of (**1**) was initially studied using lithium borohydride in THF at 0 °C under the reported conditions.[7] These conditions yielded alcohol (**14**) with ~10% racemization as determined by a chiral HPLC method. Reduction of (**1**) with lithium aluminum hydride, as expected, yielded a complex mixture. Sodium borohydride is known to reduce esters to alcohols in the presence of alcoholic solvents and water.[8,9] We next investigated the reduction of (**1**) with this reagent. Reduction of (**1**) with 4 equivalents of sodium borohydride in THF using methanol as the co-solvent led to ~17% racemization at room temperature and ~10% at –8 °C. However, reduction of (**1**) with this reagent in a mixture of THF and water at 0 °C yielded alcohol (**14**) with undetectable amounts of racemization.[10] Similar results were obtained when the reduction was done at room temperature. The auxiliary was recovered in >90% yield and was satisfactorily recycled. To test the general synthetic utility of this method, we studied the reduction of several substrates (**1** - **13**) possessing different chiral 2-oxazolidinones.[11,12] The results are listed in Table 1. No significant racemization could be detected[13] in any of these cases, and the optical purity of the resulting alcohol was comparable to the optical purity of the starting material. In all cases the chiral auxiliaries were recovered in 85-95% yield. Reduction of (**1**) with an aqueous solution of sodium borohydride, which was aged at room temperature for two weeks, led to ~2% racemization. These results suggested that a freshly prepared solution of sodium borohydride in water should be used to avoid any racemization.

In summary, a new, economical, practical and racemization-free method for the reductive removal of 2-oxazolidinones by a reduction of N-acyloxazolidinones with sodium borohydride in THF and water is described.

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References and Notes:

1. Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23-32 .
2. Ager, J. A.; Prakash, I.; Schaad, D. R. *Aldrichimica Acta* **1997**, *30*, 3-12.
3. Ager, J. A.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835-875.
4. Fukuzawa, S.; Hongo, Y. *Tetrahedron Lett.* **1998**, *39*, 3521-3524.
5. Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737-1739.
6. Barnett, C. J.; Wilson, T. M.; Evans, D. A.; Somers, T. C. *Tetrahedron Lett.* **1997**, *38*, 735-738.
7. Penning, T. D.; Djuric, S. W.; Haack, R. A.; Kalish, V. J.; Miyashiro, J. M.; Rowell, B. W.; Yu, S. S. *Synth. Commun.* **1990**, *20*, 307-312.
8. Brown, M. S.; Rapoport, H. *J. Org. Chem.* **1963**, *28*, 3261-3263.
9. Bianco, A.; Passacantilli, P.; Righi, G. *Synth. Commun.* **1988**, *18*, 1765-1771.
10. Typical procedure: To a mixture of the starting material (29.6 mmol) in THF (90 mL) was added a solution of sodium borohydride (118.5 mmol; 4 equivalents) in water (28 mL) at a rate to maintain the internal temperature at 20-25 °C. The mixture was stirred at room temperature for 1-6 h, and the completion of the reaction was monitored by tlc. To the reaction mixture was added 2 N HCl (80 mL) at a rate to maintain the internal temperature at 20-25 °C. The reaction mixture was extracted with ethyl

acetate (2 X 150 mL). The combined organic layers were washed with brine (150 mL), concentrated under vacuum, and purified by silica gel chromatography.

11. All the compounds gave satisfactory spectral data.

12. The starting materials were available by known chemistry. For cyanomethylation also see Azam, S.; D'Souza, A. A.; Wyatt, P. B. *J. Chem. Soc., Perkin Trans. 1* **1996**, 621-627.

13. The optical purities were determined by chiral HPLC method on a Rainin Dynamax system using a Daicel Chiralcel OJ column (4.6 X 250 mm) and a mixture of hexane : ethanol : TFA (93 : 7 : 0.1 mL) as the mobile phase (isocratic at a flow rate of 1 mL/min and UV detector at 260 nm) for compounds **14** and **15**; and a Daicel Chiralpak AD column (4.6 X 250 mm) and a mixture of hexane : ethanol : methanol : TFA (96 : 2 : 2 : 0.1 mL) as the mobile phase (isocratic at a flow rate of 0.8 mL/min and UV detector at 254 nm) at 30 °C for **16** and **17**.