Pergamon

Tetrahedron Letters, Vol. 36, No. 25, pp. 4471-4474, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00755-5

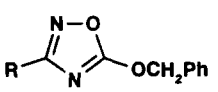
3-Substituted-1,2,4-Oxadiazolin-5-one; A Useful Amidine Precursor and Protecting Group

Richard E Bolton, Steven J Coote*, Harry Finch,
Andrew Lowdon, Neil Pegg and M Victoria Vinader

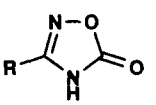
Glaxo Research and Development Ltd,
Glaxo Medicines Research Centre,
Gunnels Wood Road,
Stevenage, Herts, SG1 2NY, UK

Abstract: *5-Benzyloxy-1,2,4-oxadiazoles and 1,2,4-oxadiazolin-5-ones are useful precursors to, and protecting groups for the amidine moiety. The latter compounds are readily prepared from amidoximes or alternatively via cycloaddition of nitrile oxides to trichloroacetonitrile and subsequent hydrolysis. Both protecting groups may be readily removed upon hydrogenation, liberating the parent amidine. In addition, 1,2,4-oxadiazolin-5-ones may be utilised for the facile synthesis of N-alkyl amidines.*

A number of synthetic inhibitors of trypsin-like enzymes possess a highly basic guanidinium group that confers primary specificity for the active site of the enzyme[1]. During the course of our work on serine protease inhibition we reasoned that an amidine could subserve the function of the guanidinium moiety and we sought to explore the effect of utilising an amidine group to confer primary specificity in a series of novel thrombin inhibitors. The highly basic nature of the amidine moiety normally necessitates that suitable protection for this group is achieved before subsequent chemical manipulation. Although a number of such protecting groups have been reported in the literature[2], we sought a protecting group that was base-stable and that could be removed under mild conditions. We describe herein the utility of the heterocycles 5-benzyloxy-1,2,4-oxadiazole **1** and 1,2,4-oxadiazolin-5-one **2** in this regard.

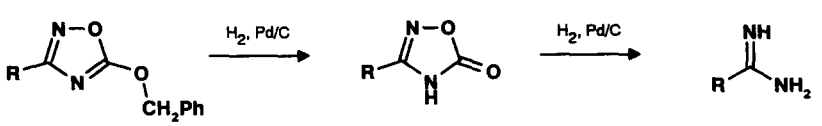


1



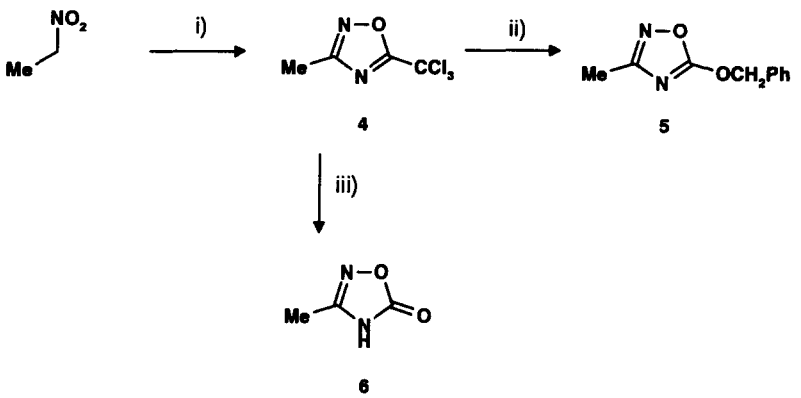
2

Several reports detailing the effect of hydrogenation upon 3-benzyloxy-isoxazoline[3] prompted us to consider the effect of reduction upon 5-benzyloxy-1,2,4-oxadiazole **1**. We rationalised that initial debenzylation would give the corresponding 1,2,4-oxadiazolin-5-one **2** which, under the reaction conditions employed should reduce further to the required amidine **3**.



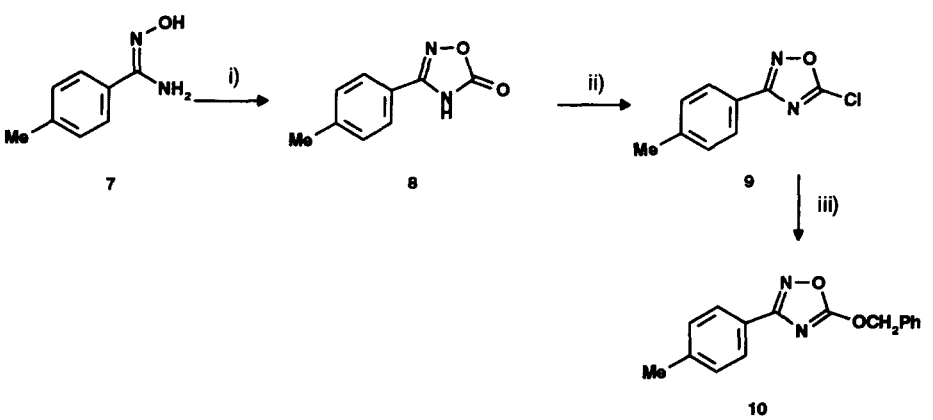
1 **2** **3**

The nitrile oxide derived from nitroethane using phenyl isocyanate[4,5,6] underwent ultrasound-mediated[7] cycloaddition with trichloroacetonitrile to give trichloromethyl oxadiazole[8,9] **4** which was converted to the corresponding 5-benzyloxy-1,2,4-oxadiazole[10] **5** upon direct displacement with the anion of benzyl alcohol[8]. Alternative displacement with hydroxide furnished 3-methyl-1,2,4-oxadiazolin-5-one[8] **6** in good yield.



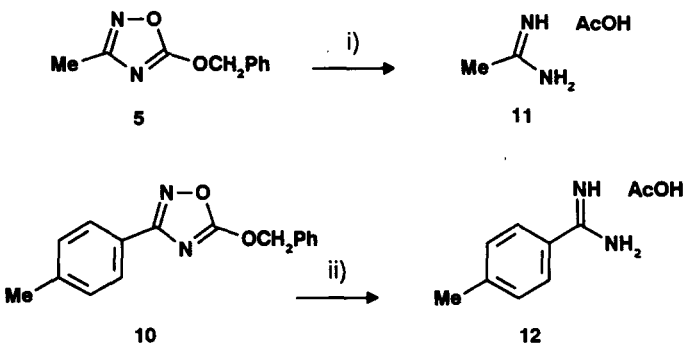
i) Cl_3CCN, PhNCO, toluene, NEt_3, ultrasound 24h (53%); ii) $PhCH_2OH$, NaH, THF, 18h (24%); iii) KOH, EtOH, reflux 10min (80%).

Analogous cycloaddition of the nitrile oxide derived from the oxime of 4-methyl benzaldehyde[11] with trichloroacetonitrile failed; preferentially dimerising to give the corresponding furoxan[12]. An alternative route involving condensation of amidoxime **7** with ethyl chloroformate[13] gave 1,2,4-oxadiazolin-5-one **8** which underwent facile chlorination[14] and subsequent displacement with benzyl alcohol to provide the corresponding 5-benzyloxy-1,2,4-oxadiazole **10**.



i) ClCOOEt, pyridine, reflux 5h (75%); ii) $POCl_3$, pyridine, reflux 1h (54%); iii) $PhCH_2OH$, Na, 18h (76%).

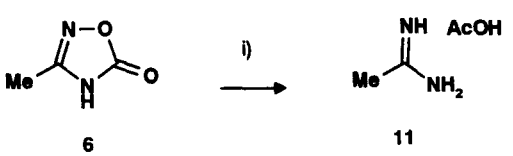
Hydrogenation of an ethyl acetate solution of 5-benzyloxy-1,2,4-oxadiazoles **5** or **10** at atmospheric pressure in the presence of 10% palladium on carbon and at least one equivalent of acetic acid, cleanly gave the corresponding amidines (**11** and **12**[15]) as their acetate salts in essentially quantitative yield. In both cases, subsequent purification proved to be unnecessary. Deprotection could also be achieved upon exposure to zinc and acetic acid[16], although in this case the reaction was less clean and lower yielding (35%).



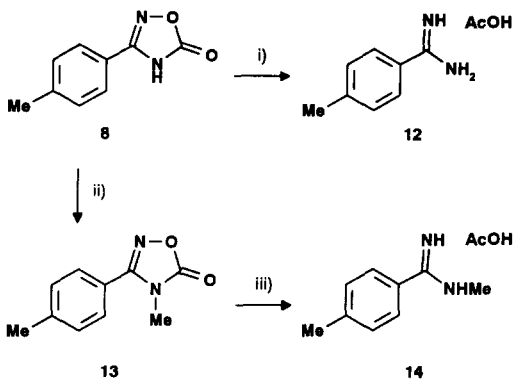
i) H_2, Pd/C, EtOAc, AcOH, 20h (91%); ii) H_2, Pd/C, EtOAc, AcOH, 20h (86%).

We next turned our attention to the functionalisation of the terminal methyl groups in both oxadiazoles **5** and **10**. Related heterocycles have been deprotonated and trapped with electrophiles[17], but attempted deprotonation of 3-methyl-5-benzyloxy-1,2,4-oxadiazole **5** with LDA and electrophilic quench (diiodopropane) returned an unoptimal amount of starting material and benzyl alcohol; the latter compound presumably arising from hydrolysis of the oxadiazole. Indeed, treatment of a benzylically substituted derivative of oxadiazole **10** with tetrabutyl ammonium fluoride gave rise to similar hydrolysis to give the tetrabutyl ammonium salt of the corresponding oxadiazolin-5-one.

Given the apparent sensitivity of the oxadiazole ring, we considered the utility of oxadiazolin-5-ones **6** and **8** as precursors to, and protecting groups for the amidine moiety. The documented acidic nature of this heterocycle[18,19] (pKa 5.1-6.6 depending upon substitution) should render the group considerably more base stable. Not unexpectedly, hydrogenation of an ethyl acetate solution of either compound in the presence of 10% palladium on carbon and at least one equivalent of acetic acid furnished the expected amidines as their acetate salts, again in excellent yield. Sodium hydride-mediated deprotonation of oxadiazolin-5-one **8** gave the corresponding nitrogen anion which could be efficiently trapped with methyl iodide to give methylated oxadiazolin-5-one **13**[18]. Subsequent hydrogenation provided the corresponding alkylated amidine **14** as its acetate salt[20].



i) H_2, Pd/C, EtOAc, AcOH, 20h (98%)



i) H_2, Pd/C, EtOAc, AcOH, 20h (91%); ii) NaH, MeI, THF (54%); iii) H_2, Pd/C, EtOAc, AcOH (99%).

In summary, we have described the utility of 3-benzyloxy-1,2,4-oxadiazoles and 1,2,4-oxadiazolin-5-ones as both precursors to, and protecting groups for amidine functionality. The latter protecting group is base stable, easily removed under mild conditions and should permit ready access to N-alkylated amidines. The acidic nature of 1,2,4-oxadiazolin-5-ones render them potentially useful carboxylic acid bioisosteres.

REFERENCES

1. Barrett A. J.; Salvesen G. *Proteinase Inhibitors, Research Monographs in Cell and Tissue Physiology*; volume 12, Elsevier, 1986.
2. Foloppe, M. P.; Rault, S.; Robba, M. *Tetrahedron Lett.* **1992**, 33, 2803; McBride, L. J.; Kierzek, R.; Beaucage, S. L.; Caruthers, M. H. *J. Am. Chem. Soc.* **1986**, 108, 2040.
3. DeAmici, M.; Misani, V.; DeMicheli, C. *Tetrahedron* **1990**, 46, 1975; DeAmici, M.; DeMicheli, C.; Cateni, F.; Carrea, G.; Ottolina, G. *Tetrahedron Asymmetry* **1993**, 4, 1073; Renaut, P.; Thomas, D.; Bellamy, F. D. *Synthesis* **1991**, 265.
4. Mukaiyama, T.; Hoshino, T. *J. Org. Chem.* **1960**, 82, 5339.
5. Stork, G.; McMurry, J. E. *J. Am. Chem. Soc.* **1967**, 89, 5461.
6. Harada, K.; Kaji, E.; Zen, S. *Chem. Pharm. Bull.* **1980**, 28, 3296.
7. Armstrong, S. K.; Collington, E. W.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 515.
8. Eloy, F.; Moussebois, C. *Helv. Chim. Acta* **1964**, 47, 838.
9. Eloy, F. *Bull. Soc. Chim. Belg.* **1964**, 73, 793.
10. Yurugi, S.; Miyake, A.; Fushim, T.; Imamiya, E.; Matsumura, H.; Imai, Y. *Chem. Pharm. Bull.* **1973**, 21, 1641.
11. Hassner, A.; Lokanatha Rai, K. M. *Synthesis* **1989**, 57; Liu, K.; Shelton, B. R.; Howe, R. K. *J. Org. Chem.* **1980**, 45, 3916; Kim, J.; Ryu, E. K. *Synth. Commun.* **1990**, 20, 1373.
12. Grundmann, C. *Synthesis* **1970**, 344.
13. Falk, F. *Ber. Dtsch. Chem. Ges.* **1885**, 18, 2468; Areschka, A. *Chim. Therap.* **1977**, 12, 87.
14. Fujita, T.; Fujii, T.; Ide, A. *Yakugaku Zasshi* **1964**, 84, 1061(*Chem. Abs.* **1965**, 62, 5270).
15. Krechl, J.; Smrckova, S.; Pavlikova, F.; Kuthan, J. *Collect. Czech Chem. Commun.* **1989**, 54, 2415.
16 LeBel, N. A.; Post, M. E.; Whang, J. J. *J. Am. Chem. Soc.* **1964**, 86, 3759.
17. Jones, R. C. F.; Anderson, M. W.; Smallridge, M. J. *Tetrahedron Lett.* **1988**, 29, 5001; Luke, G. M.; Swigor, J. E. *J. Radiolabel. Chem.* **1990**, 29, 193; Sit, S. Y.; Parker, R. A.; Motoc, I.; Han, W.; Balasubramanian, N.; Catt, J. D.; Brown, P. J.; Harte, W. E.; Thompson, M. D.; Wright, J. J. *J. Med. Chem.* **1990**, 33, 2982.
18. Katritzky, A. R.; Wallis, B.; Brownlee, R. T. C.; Topsom, R. D. *Tetrahedron* **1965**, 21, 1681.
19. Ponzio, Z. *Gazz. Chim. Ital.* **1923**, 53, 819.
20. Burger, K.; Penninger, S. *Synthesis* **1978**, 524.

(*Received in UK* 3 *April* 1995; *accepted* 21 *April* 1995)