Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 6745–6747

TETRAHEDRON LETTERS

A mild procedure for the production of secondary amines from oximes and benzisoxazoles

Mark Searcey,* Sukhwant S. Grewal, Fiorenza Madeo and Petros G. Tsoungas†

Department of Pharmaceutical and Biological Chemistry, University of London School of Pharmacy, 29/39 Brunswick Square, London WC1N 1AX, UK

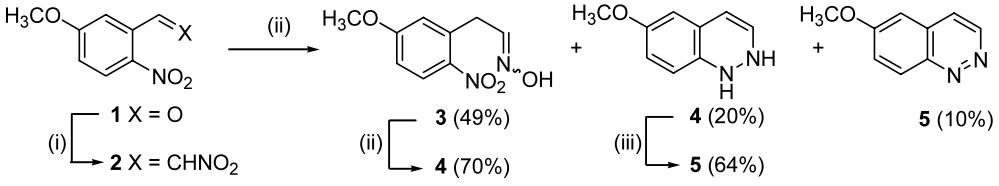
Received 1 May 2003; revised 16 June 2003; accepted 27 June 2003

This paper is dedicated to Mike Cocksedge, who died January 2003

Abstract—2-Hydroxybenzaldoximes are reduced under mild conditions of ammonium formate/Pd–C in methanol to give secondary amines. Benzisoxazoles react under the same mild conditions to give the same products. A possible mechanism is suggested, involving the intermediacy of the benzisoxazole in the oxime conversion.

During studies on the synthesis of heterocyclic compounds that may be useful as chromophores for the study of drug–DNA interactions,[1] we needed a mild and efficient method for the reduction of 4-methoxy-1-nitro-2-[(*E*)-2-nitrovinyl]benzene **2**, an intermediate in the synthesis of a cinnoline derivative **5**. As we required a method that would allow us to control the reduction of the aromatic nitro group versus the aliphatic nitro group, and thus the eventual cyclisation to the cinnoline, we screened a number of different reducing agents. It was found that even the relatively mild action of hydrogen/Pd–C led to an intractable mixture of products. Ammonium formate/Pd–C is a transfer hydrogenation catalyst, which we have used extensively in other systems.[2] To our surprise, exposure of **2** to ammonium formate/Pd–C in methanol led to the clean formation of three products, including, albeit in low yield, the cyclised dihydrocinnoline and the fully aromatized cinnoline (Scheme 1). Efforts to study this system and enhance the yields of the target compounds are continuing.

This observation prompted us to study the effects of the HCO_2NH_4/Pd–C system en route to a number of other heterocycles. Ammonium formate has been shown to act as an *N*-formylating agent[3] as well as a source of hydrogen and we speculated that, perhaps, we were observing an instance of *O*-formylation, giving an efficient leaving group, followed by attack of the aromatic amine. To test this hypothesis, a series of salicylaldoximes **6a**–**e** were made with varying substituents in the aromatic ring. The compounds were synthesised by simple reflux of the aldehyde in the presence of hydroxylamine hydrochloride and ammonium acetate and were obtained in good yield.[4] They were then treated in methanol with HCO_2NH_4/Pd–C at room temperature.[5]

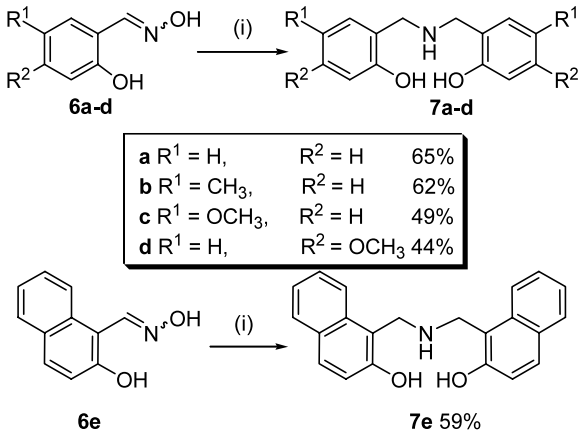


Scheme 1. *Reagents and conditions*: (i) CH_3NO_2, NH_4OAc, AcOH, Δ, 2.5 h; (ii) HCO_2NH_4, Pd–C (10%), CH_3OH, rt, 5 h; (iii) $Pb(OAc)_4$, THF, 0°C–rt, 12 h.

* Corresponding author. Tel.: +44-020-7753-5873; fax: +44-020-7753-5964; e-mail: mark.searcey@ulsop.ac.uk

† Permanent address: Ministry of Development, Dept. of Research and Technology, Messogion Ave. 14-18, Athens GR-11510, Greece.

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01623-X

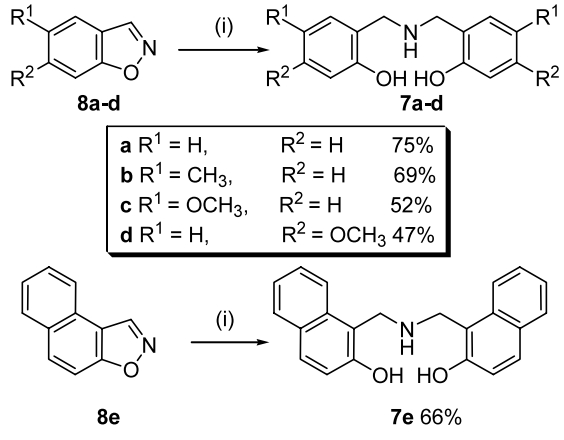


Scheme 2. *Reagents and conditions*: (i) HCO_2NH_4, Pd–C (10%), CH_3OH, rt, 16 h.

A mildly exothermic reaction was noted and after stirring for 16 h, TLC analysis of the mixtures showed the formation of only one major product. Isolation of the compound by filtration and purification by flash column chromatography gave a series of secondary amines **7a**–**e** (see Scheme 2).[6]

The formation of secondary amines under reducing conditions has some precedent in the literature. Caddick and co-workers[7] noted that aromatic nitriles give secondary amines when treated with sodium borohydride and suggested a mechanism that involved attack of the primary amine formed on an imine intermediate, followed by loss of ammonia. Aromatic oximes may be converted to nitriles under basic conditions[8] and it is possible that the dehydration of the oxime, perhaps involving formylation of the hydroxyl prior to its elimination, would lead to the nitrile. However, when the nitriles were synthesised separately and subjected to similar conditions, only the primary amines were isolated.

A second potential mechanism involves the intermediacy of a benzisoxazole. Formylation of the oxime oxygen is followed by attack of the *ortho*-OH group rather than by dehydration. In order to test this mechanism, a series of benzisoxazoles **8a**–**e** were synthesised by thionyl chloride-induced cyclisation of the oxime.[9] The resulting benzisoxazoles were subjected to the same reducing conditions as the oximes and formed the secondary amines in similar yields (Scheme 3).



Scheme 3. *Reagents and conditions*: (i) HCO_2NH_4, Pd–C (10%), CH_3OH, rt, 16 h.

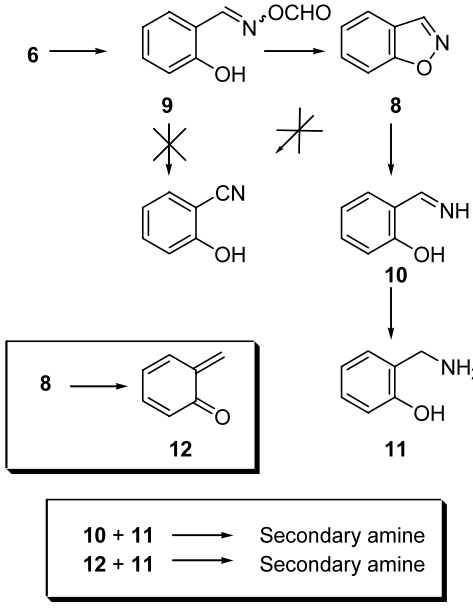
These results suggest that the conversion to the secondary amine is occurring with initial cyclisation through displacement of the formylated oxime oxygen to give the benzisoxazole (i.e. **6** to **9** to **8**, Scheme 4). Subsequent reaction may be through reductive opening of the N–O bond to give the hydroxyimine **10**, which is further reduced to the amine **11**. Reaction of **10** with **11** will then generate the secondary amine. Alternatively, benzisoxazoles have been shown to generate *ortho*-quinonemethides such as **12**,[10] which could also react with **11** to give the final product.

Interestingly, whilst the 2-hydroxybenzonitrile derivative gave only the primary amine, both benzonitrile and benzaldoxime gave the secondary amines when subjected to the same conditions. This suggests that the direct mechanism previously reported by Caddick[7] can operate for nitriles that do not contain the *o*-OH group and, also, that direct loss of the oxime –OH may occur without the intermediacy of the benzisoxazole.

In conclusion, we have shown that oximes and benzisoxazoles can be converted to secondary amines under mild conditions. We are continuing studies of this reaction and of the use of the ammonium formate/Pd–C couple in heterocyclic chemistry.

Acknowledgements

We gratefully acknowledge funding for an EU Marie Curie Senior Research Fellowship and the Ministry of



Scheme 4.

Development, Dept. of Research and Technology, Greece for a sabbatical leave (P.G.T.). We thank Dr. M. Zloh for ^{1}H and ^{13}C NMR and Mr. M. Cocksedge for mass spectra.

References

1. Tsoungas, P. G.; Searcey, M. *Tetrahedron Lett*. **2001**, *42*, 6589.
2. (a) Boger, D. L.; Santillán, A.; Searcey, M.; Brunette, S. R.; Wolkenberg, S. E.; Hedrick, M. P.; Jin, Q. *J. Org. Chem*. **2000**, *65*, 4101; (b) Boger, D. L.; Boyce, C. W.; Garbaccio, R. M.; Searcey, M. *Tetrahedron Lett*. **1998**, *39*, 2227.
3. (a) Reddy, G. P.; Kishore Kumar, G. D.; Baskaran, S. *Tetrahedron Lett*. **2000**, *41*, 9149; (b) Pratai, T. V.; Baskaran, S. *Tetrahedron Lett*. **2001**, *42*, 1983; (c) Olah, G. A.; Ohannessian, L.; Arvanaghi, M. *Chem. Rev*. **1987**, *87*, 671.
4. Giurg, M.; Mlochowski, J. *Pol. J. Chem*. **1997**, *71*, 1093.
5. *Experimental Procedure for* ***7a–e*** *via oxime or benzisoxazole*. *Synthesis of* ***7a***. Salicylaldoxime (1 g, 7.3 mmol) was stirred in CH_3OH (10 mL) with HCO_2NH_4 (2.3 g, 5 equiv. 36 mmol) and 10% Pd–C (300 mg) for 16 h. EtOAc (50 mL) was then added, the mixture filtered through Celite and the Celite was washed with EtOAc (50 mL). The combined organics were concentrated. Chromatography (SiO_2, gradient 0–30% CH_3OH/DCM) gave the product as a yellow solid (1 g, 65%).
6. Compound **7a**: ^{1}H NMR (DMSO-d^6, 250 MHz) δ 7.07 (m, 4H), 6.74 (m, 4H), 3.75 (s, 4H), 2.49 (s, 1H); ^{13}C NMR (DMSO-d^6, 62.9 MHz) δ 156.5, 129.0, 127.8, 124.1, 118.5, 115.0, 48.8; FABMS m/z 230 (50%, M$^+$+H), 197 (25), 135 (55), 115 (50), 107 (100), HRMS calcd for $C_{14}H_{16}NO_2$: 230.1176. Found M+H$^+$ 230.1181. Anal. calcd for $C_{14}H_{16}NO_2 \cdot 0.2H_2O$; C, 72.22; H, 6.62; N, 6.01. Found: C, 72.48; H, 6.45; N, 6.07%. **7b**: ^{1}H NMR (DMSO-d^6, 250 MHz) δ 7.30 (m, 4H), 7.00 (m, 2H), 4.10 (s, 4H), 2.60 (s, 6H), 2.49 (s, 1H); ^{13}C NMR (DMSO-d^6, 62.9 MHz) δ 154.0, 129.0, 128.0, 126.5, 123.8, 115.0, 48.8; 20.0 FABMS m/z 258 (30%, M$^+$+H), 185 (15), 136 (40), 121 (100), HRMS calcd for $C_{16}H_{20}NO_2$: 258.1478. Found M+H$^+$ 258.1494. Anal. calcd for $C_{16}H_{20}NO_2 \cdot 1H_2O$; C, 69.91; H, 7.63; N, 5.09. Found: C, 70.08; H, 7.23; N, 5.68. **7c**: ^{1}H NMR (DMSO-d^6, 250 MHz) δ 6.72 (m, 2H), 6.65 (m, 4H), 3.70 (s, 4H), 3.68 (s, 6H); ^{13}C NMR (DMSO-d^6, 62.9 MHz) δ 152.0, 150.0, 125.0, 116.0, 115.0, 113.0, 55.0, 47.0; FABMS m/z 290 (100%, M$^+$+1), 199 (55), 176 (22). Anal. calcd for $C_{16}H_{19}NO_4 \cdot 0.2H_2O$; C, 65.62; H, 6.63; N, 4.78. Found: C, 65.31; H, 6.51; N, 4.75. **7d**: ^{1}H NMR (DMSO-d^6, 250 MHz) δ 7.40 (m, 2H), 6.60 (m, 4H), 4.00 (s, 2H), 3.90 (s, 2H), 3.60 (br s, 6H); FABMS m/z 289 (15%, M$^+$), 288 (75), 152 (100), 137 (100), 107 (25), HRMS calcd for $C_{16}H_{18}NO_4$ 288.1231. Found M−H$^+$ 288.1236. **7e**: ^{1}H NMR (DMSO-d^6, 250 MHz) δ 9.5 (s, 2H), 7.64 (d, J=8.52 Hz, 2H), 7.76 (d, J=7.97 Hz, 2H), 7.60 (d, J=8.80 Hz, 2H), 7.44 (dd, J=7.42, 7.42 Hz, 2H), 7.25 (dd, J=7.28, 7.28 Hz, 2H), 7.17 (d, J=8.52 Hz, 2H), 3.32 (s, 1H), 2.40 (s, 4H); ^{13}C NMR (DMSO-d^6, 62.9 MHz) δ 152.0, 134.0, 128.1, 127.9, 126.5, 126.0, 122.5, 122.0, 118.0, 114.5, 10.0; FABMS m/z 329 (55%, M$^+$), 289 (25), 173 (100).
7. Caddick, S.; Haynes, A. K.; de, K.; Judd, D. B.; Williams, M. R. V. *Tetrahedron Lett*. **2000**, *41*, 3513.
8. (a) Molina, P.; Alajarin, M.; Vilaplana, M. J. *Synthesis* **1982**, *12*, 1016; (b) Arrieta, A.; Aizpurua, J. M.; Palomo, C. *Tetrahedron Lett*. **1994**, *25*, 3365.
9. (a) Kalkoute, V. R.; Goswami, D. D. *Aust. J. Chem*. **1977**, *30*, 1847; (b) Poissonnet, G. *Synth. Commun*. **1997**, *27*, 3839.
10. (a) Gilchrist, T. L. *Adv. Heterocycl. Chem*. **1987**, *41*, 41; (b) Barardi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Simoni, D. *Synthesis* **1987**, 857; (c) Rewcastle, G. W.; Katritzky, A. R. *Adv. Heterocycl. Chem*. **1993**, *56*, 155; (d) Iddon, B. *Heterocycles* **1994**, *37*, 1263; (e) Katritzky, A. R.; Zhang, Z.; Lan, X.; Lang, H. *J. Org. Chem*. **1994**, *59*, 1900.