Tetrahedron Letters 52 (2011) 2221–2223

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of *N*-arylhydroxylamines by Pd-catalyzed coupling

Daniel Beaudoin [†], James D. Wuest [*]

Département de Chimie, Université de Montréal, Montréal, Québec, Canada H3C 3J7

ARTICLE INFO

Article history:
Available online 15 December 2010

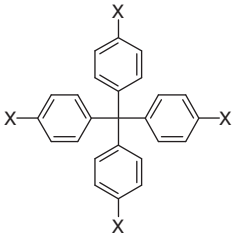
ABSTRACT

Pd-catalyzed coupling of aryl halides with TeocNHOTBS, followed by treatment of the products with TBAF, provides effective access to a wide range of *N*-arylhydroxylamines by a route that produces stable doubly-protected intermediates and allows the protective groups to be removed under mild conditions that do not cause extensive degradation of the final product.

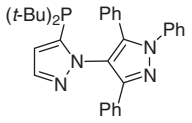
N-Arylhydroxylamines and their derivatives are widely used as intermediates in synthesis,[1,2] and they show significant biological activity.[2–5] In particular, they have been used to inhibit enzymes and release NO,[3] and their formation as metabolites appears to be responsible for the toxicity, mutagenicity, and carcinogenicity of diverse arylamines and nitroarenes.[4,5] *N*-Arylhydroxylamines form a class of inherently unstable compounds, and they readily degrade by acid-induced Bamberger rearrangement, disproportionation, and other processes.[6–9] The toxic, mutagenic, and carcinogenic effects of *N*-arylhydroxylamines can be attributed to subsequent reactions of electrophilic species generated by their degradation.[8]

To be able to exploit the useful properties of *N*-arylhydroxylamines, chemists have worked for many decades to develop effective ways to make them.[7,10–12] However, the intrinsically high reactivity of these compounds continues to make their synthesis very challenging, especially when they must be isolated and purified before use in subsequent steps. The classic way to make *N*-arylhydroxylamines, discovered more than a century ago by Bamberger,[7] involves reducing the corresponding nitroarenes using metals under acidic conditions. Despite later refinements,[12] however, precise control of the conditions is needed to prevent over-reduction or decomposition of the desired product, and full purification is often difficult. Indeed, the standard preparation of *N*-arylhydroxylamines by reducing nitroarenes with zinc in the presence of ammonium chloride has been described as 'frustratingly erratic, and may be entirely unsatisfactory in some cases'.[13] As a consequence, modified reductive methods for transforming nitroarenes into *N*-arylhydroxylamines continue to be published frequently,[2] demonstrating a need for further improvement.

In the course of work related to the construction of predictably ordered molecular solids, we tried to prepare *N*-arylhydroxylamine **1a** by reducing tetrakis(4-nitrophenyl)methane (**1b**) under various established conditions. All attempts led to complex mixtures containing the products of over- and under-reduction, and we were unable to obtain target **1a** in pure form. We therefore turned to newer methods based on metal-catalyzed coupling,[14,15] and the procedure of Tomkinson and co-workers appeared to be particularly attractive.[14] In this approach, aryl halides undergo efficient Pd-catalyzed coupling with doubly N- and O-protected derivatives of hydroxylamine in the presence of the ligand Bippyphos (**2**).[16] A single example of O-deprotection by removal of a *t*-butyldimethylsilyl (TBS) group was reported to give an *N*-arylhydroxylamine N-protected with a *t*-butyloxycarbonyl (Boc) group; however, in no case was complete N- and O-deprotection effected to provide an isolated *N*-arylhydroxylamine. In our attempts to carry out further N-deprotection, we found that *N*-arylhydroxylamines degrade rapidly under the acidic conditions used for removal of Boc groups, and we could not obtain material of acceptable purity.



1a (X = NHOH)
1b (X = NO_2)
1c (X = Br)
1d (X = N(Teoc)OTBS)

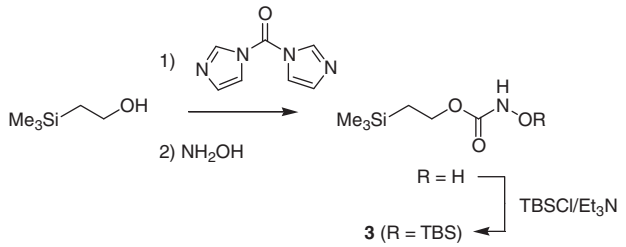


2

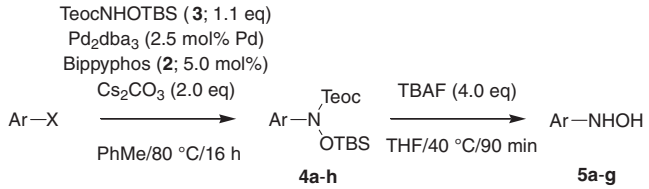
To solve the problem of making *N*-arylhydroxylamines, we developed a modified coupling procedure using a derivative of hydroxylamine protected with TBS and [2-(trimethylsilyl)ethoxy]carbonyl (Teoc) groups.[17] TeocNHOTBS (**3**) was synthesized in 75% overall yield by the route summarized in Scheme 1, which is based in part on a published method for making 2-(trimethyl-

* Corresponding author.
E-mail address: james.d.wuest@umontreal.ca (J.D. Wuest).
† Fellow of the Natural Sciences and Engineering Research Council of Canada.

0040-4039/$ - see front matter © 2011 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2010.12.034



Scheme 1.



Scheme 2.

Table 1
Pd-catalyzed coupling of aryl halides with TeocNHOTBS (**3**) and subsequent deprotection to give *N*-arylhydroxylamines

Entry	Ar-X	Ar-N(Teoc)OTBS (% yield)	Ar-NHOH (% yield)
1	C_6H_5Br	**4a** (96)	**5a** (85)
2	C_6H_5I	**4a** (81)	—
3	4-MeC_6H_4Br	**4b** (95)	**5b** (83)
4	4-ClC_6H_4Br	**4c** (84)	**5c** (88)
5	3-CNC_6H_4Br	**4d** (90)	**5d** (92)
6	4-$CO_2EtC_6H_4Br$	**4e** (96)	**5e** (95)
7	4-$NO_2C_6H_4I$	**4f** (79)	**5f** (79)
8	3,5-$Me_2C_6H_3I$	**4g** (73)	**5g** (42)
9	2-MeC_6H_4I	**4h** (<5)	—

silyl)ethyl carbamate.[18] The conditions used by Tomkinson and coworkers to couple aryl halides with BocNHOTBS gave only modest yields when applied to analog **3**, but we found that the combination of Bippyphos (**2**) with dibenzylideneacetone (dba) complex Pd_2dba_3 was generally very effective (Scheme 2, Table 1).[19] Aryl bromides were found to give higher yields than iodides. Hindered substrates coupled poorly and gave only traces of product, even at elevated temperatures (entry 9). In the cases studied, coupled products could be deprotected efficiently with tetrabutylammonium fluoride (TBAF) in THF to give the desired *N*-arylhydroxylamines in pure form.[20,21] No examples with highly electron-donating substituents such as methoxy were examined because *N*-arylhydroxylamines of this type are known to be particularly prone to degradation.[22] The relatively low overall yield in Entry 8 presumably reflects the inherent instability of *N*-arylhydroxylamines with electron-donating groups; nevertheless, our methodology is effective even in this demanding example.

These results gave us confidence that our modified method could be used to make more complex *N*-arylhydroxylamines such as compound **1a**.[23] Indeed, coupling of tetrabromide **1c**[24] under the standard conditions of Scheme 2 gave a 62% yield of protected derivative **1d**, which was then converted by the action of TBAF into target **1a** in 77% yield. This demonstrates that our methodology provides effective access to a wide range of *N*-arylhydroxylamines by a route that offers two key advantages: (1) It produces stable doubly-protected intermediates that can be purified easily and (2) it allows the protective groups to be removed under mild conditions that do not cause extensive degradation of the final product.

Acknowledgments

We are grateful to the Natural Sciences and Engineering Research Council of Canada, the Ministère de l'Éducation du Québec, the Canada Foundation for Innovation, the Canada Research Chairs Program, and the Université de Montréal for financial support.

Supplementary data

Supplementary data (characterizations of all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.12.034.

References and notes

1. For recent references, see: Rios, R.; Ibrahem, I.; Vesely, J.; Zhao, G.-L.; Córdova, A. *Tetrahedron Lett.* **2007**, *48*, 5701–5705; Evans, D. A.; Song, H.-J.; Fandrick, K. R. *Org. Lett.* **2006**, *8*, 3351–3354; Chatterjee, A.; Bhattacharya, P. K. *J. Org. Chem.* **2006**, *71*, 345–348; Sridharan, V.; Karthikeyan, K.; Muthusubramanian, S. *Tetrahedron Lett.* **2006**, *47*, 4221–4223; Ding, X.; Taniguchi, K.; Hamamoto, Y.; Sada, K.; Fujinami, S.; Ukaji, Y.; Inomata, K. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1069–1083; Srivastava, R. S.; Khan, M. A.; Nicholas, K. M. *J. Am. Chem. Soc.* **2005**, *127*, 7278–7279; Young, I. S.; Williams, J. L.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 953–955; Murugan, E.; Siva, A. *Synthesis* **2005**, 2022–2028; Tian, L.; Xu, G.-Y.; Ye, Y.; Liu, L.-Z. *Synthesis* **2003**, 1329–1334; Takeuchi, H.; Tateiwa, J.-i.; Hata, S.; Tsutsumi, K.; Osaki, Y. *Eur. J. Org. Chem.* **2003**, 3920–3922; Yadav, J. S.; Reddy, B. V. S.; Sreedhar, P. *Adv. Synth. Catal.* **2003**, *345*, 564–567; Spence, J. D.; Raymond, A. E.; Norton, D. E. *Tetrahedron Lett.* **2003**, *44*, 849–851; Ho, C.-M.; Lau, T.-C. *New J. Chem.* **2000**, *24*, 859–863; Heydari, A.; Larijani, H.; Emami, J.; Karami, B. *Tetrahedron Lett.* **2000**, *41*, 2471–2473; Romine, J. L. *Org. Prep. Proc. Int.* **1996**, *28*, 249–288.
2. For recent references, see: Rong, Z.; Du, W.; Wang, Y.; Lu, L. *Chem. Commun.* **2010**, *46*, 1559–1561; Porzelle, A.; Woodrow, M. D.; Tomkinson, N. C. O. *Synlett* **2009**, 798–802; Liu, S.; Wang, Y.; Jiang, J.; Jin, Z. *Green Chem.* **2009**, *11*, 1397–1400; Takenaka, Y.; Kiyosu, T.; Choi, J.-C.; Sakakura, T.; Yasuda, H. *Green Chem.* **2009**, *11*, 1385–1390; Shi, Q. X.; Lu, R. W.; Jin, K.; Zhang, Z. X.; Zhao, D. F. *Chem. Lett.* **2006**, *35*, 226–227; Ung, S.; Falguières, A.; Guy, A.; Ferroud, C. *Tetrahedron Lett.* **2005**, *46*, 5913–5917; Li, F.; Cui, J.; Qian, X.; Zhang, R.; Xiao, Y. *Chem. Commun.* **2005**, 1901–1903; Kim, B. H.; Cheong, J. W.; Han, R.; Jun, Y. M.; Baik, W.; Lee, B. M. *Synth. Commun.* **2001**, *31*, 3577–3586.
3. For recent references, see: Johansson, E.; Parkinson, G. N.; Denny, W. A.; Neidle, S. *J. Med. Chem.* **2003**, *46*, 4009–4020; McGill, A. D.; Zhang, W.; Wittbrodt, J.; Wang, J.; Schlegel, H. B.; Wang, P. G. *Bioorg. Med. Chem.* **2000**, *8*, 405–412; Smith, D. G.; Gribble, A. D.; Haigh, D.; Ife, R. J.; Lavery, P.; Skett, P.; Slingsby, B. P.; Stacey, R.; Ward, R. W.; West, A. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3137–3142.
4. Miller, J. A. *Cancer Res.* **1970**, *30*, 559–576.
5. For recent references, see: Khan, F. D.; Vyas, P. M.; Gaspari, A. A.; Svensson, C. K. *J. Pharm. Exp. Ther.* **2007**, *323*, 771–777; Kurian, J. R.; Chin, N. A.; Longlais, B. J.; Hayes, K. L.; Trepanier, L. A. *Chem. Res. Toxicol.* **2006**, *19*, 1366–1373; Ahmad, F.; Hughes, J. B. *Environ. Sci. Technol.* **2002**, *36*, 4370–4381; Haack, T.; Erdinger, L.; Boche, G. *Mutat. Res.* **2001**, *491*, 183–193; Bolchoz, L. J. C.; Budinsky, R. A.; McMillan, D. C.; Jollow, D. J. *J. Pharm. Exp. Ther.* **2001**, *297*, 509–515.
6. Pereira, M. M. A.; Santos, P. P. In *The Chemistry of Hydroxylamines, Oximes and Hydroxamic Acids. Part 1*; Rappoport, Z., Liebman, J. F., Eds.; John Wiley & Sons: Chichester, 2009; pp. 343–498.
7. Bamberger, E. *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 1548–1557; Bamberger, E. *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 1347–1350.
8. Fishbein, J. C.; McClelland, R. A. *Can. J. Chem.* **1996**, *74*, 1321–1328; Novak, M.; Kahley, M. J.; Lin, J.; Kennedy, S. A.; James, T. G. *J. Org. Chem.* **1995**, *60*, 8294–8304.
9. Porzelle, A.; Woodrow, M. D.; Tomkinson, N. C. O. *Eur. J. Org. Chem.* **2008**, 5135–5143.
10. Schmidt, A. *Sci. Synth.* **2007**, *31b*, 1739–1772.
11. Melman, A. In *The Chemistry of Hydroxylamines, Oximes and Hydroxamic Acids. Part 1*; Rappoport, Z., Liebman, J. F., Eds.; John Wiley & Sons: Chichester, 2009; pp. 117–162.
12. Oxley, P. W.; Adger, B. M.; Sasse, M. J.; Forth, M. A. In *Organic Syntheses*; Wiley: New York, 1993; Collect. Vol. 8, pp. 16–19; Kamm, O. In *Organic Syntheses*; Wiley: New York, 1941; Collect. Vol. 1, pp. 435–437; Marvel, C. S.; Kamm, O. *J. Am. Chem. Soc.* **1919**, *41*, 276–282.
13. Smith, P. A. S. In *The Chemistry of Open-Chain Organic Nitrogen Compounds*; Benjamin: New York, 1966; Vol. 2, p.15.
14. Porzelle, A.; Woodrow, M. D.; Tomkinson, N. C. O. *Org. Lett.* **2009**, *11*, 233–236.
15. Jones, K. L.; Porzelle, A.; Hall, A.; Woodrow, M. D.; Tomkinson, N. C. O. *Org. Lett.* **2008**, *10*, 797–800; Peng, J.; Lin, W.; Yuan, S.; Chen, Y. *J. Org. Chem.* **2007**, *72*, 3145–3148; Peng, J.; Jiang, D.; Lin, W.; Chen, Y. *Org. Biomol. Chem.* **2007**, *5*, 1391–1396; Dongol, K. G.; Tay, B. Y. *Tetrahedron Lett.* **2006**, *47*, 927–930.
16. Withbroe, G. J.; Singer, R. A.; Sieser, J. E. *Org. Process Res. Dev.* **2008**, *12*, 480–489.
17. Carpino, L. A.; Tsao, J.-H.; Ringsdorf, H.; Fell, E.; Hettrich, G. *Chem. Commun.* **1978**, 358–359.

18. Reddy, K. L.; Dress, K. R.; Sharpless, K. B. *Tetrahedron Lett.* **1998**, *39*, 3667–3670.
19. General procedure for the formation of doubly-protected *N*-arylhydroxylamines: A solution of Ar-X (2.0 mmol), TeocNHOTBS (**3**; 640 mg, 2.2 mmol), Bippyphos (**2**; 51 mg, 0.10 mmol), and Pd_2dba_3 (23 mg, 0.025 mmol) in toluene (8 mL) was treated with Cs_2CO_3 (1.3 g, 4.0 mmol). N_2 was bubbled through the mixture for 30 min, and then the mixture was heated and stirred at 80 °C for 16 h under N_2. The resulting mixture was purified directly by column chromatography (EtOAc/hexanes).
20. General procedure for the formation of unprotected *N*-arylhydroxylamines: To a solution of Ar-N(Teoc)OTBS (1 mmol) in THF (6 mL) was added a solution of TBAF in THF (4 mL, 1 M, 4 mmol), and the resulting mixture was stirred at 40 °C for 90 min under N_2. The mixture was then treated with aqueous phosphate buffer (10 mL, 0.1 M, pH 7). The desired product was extracted with EtOAc, the extracts were dried over Na_2SO_4, and the volatiles were removed by evaporation under vacuum. The residue was purified by column chromatography ($MeOH/CH_2Cl_2$). CAUTION: *N*-Arylhydroxylamines are inherently unstable compounds and present a risk of explosions.[21]
21. Rondestvedt, C. S., Jr.; Johnson, T. A. *Synthesis* **1977**, 851–852.
22. For example, see: Fountain, K. R.; Hutchinson, L. K.; Mulhearn, D. C.; Xu, Y. B. *J. Org. Chem.* **1993**, *58*, 7883–7890.
23. For two previous publications that report complex *N*-arylhydroxylamines but do not describe their purification and characterization, see: Jain, V. K.; Mandalia, H. C.; Suresh, E. *J. Incl. Phenom. Macrocycl. Chem.* **2008**, *62*, 167–178; Jayswal, K. P.; Patela, J. R. *Acta Chim. Slov.* **2008**, *55*, 502–507.
24. Rathore, R.; Burns, C. L.; Guzei, I. A. *J. Org. Chem.* **2004**, *69*, 1524–1530; Grimm, M.; Kirste, B.; Kurreck, H. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1097–1098.