Tetrahedron Letters 53 (2012) 4154-4155

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Nitration of *tert*-butyloxycarbonylated aniline and 1,3,5-triaminobenzene by acetyl nitrate

Matthew C. Davis*, Thomas J. Groshens

Chemistry & Materials Division, Naval Air Warfare Center, China Lake, CA 93555, USA

ARTICLE INFO

ABSTRACT

steps with 63% yield.

Article history: Received 13 April 2012 Revised 25 May 2012 Accepted 29 May 2012 Available online 9 June 2012

Keywords: Aromatic nitration Acetyl nitrate Aniline Boc-protection

The aromatic nitration of aniline is difficult owing to its inherent sensitivity to oxidation as well as deactivation toward electrophilic substitution through formation of its ammonium salt by the acidic conditions typically employed.¹ For best results, a protecting group for the amine should be employed that is both convenient to install and later remove. Carboxyl-² and sulfonylamides³ as well as alkyl carbamate (methyl and ethyl)⁴ have been used for this purpose but they often require harsh treatment for subsequent removal (hot sulfuric acid).⁵ The benzyloxycarbonyl (Cbz) was considered but it was thought that it would not work in the present case since further complications would occur such as nitration of the benzyl ring as well as concomitant nitro reduction during typical removal conditions of hydrogenolysis.⁶ The *tert*-butyloxycarbonyl (Boc) group, pioneered by Carpino,⁷ may be the premier amine protecting group in use today. There are only a few reports of nitration in the presence of Boc-protected amines, which is not surprising due to their acid-lability.⁸ It was hypothesized that mild or non-acidic nitration conditions such as mixed anhydrides (RCO₂₋ NO₂),^{9a,9b} dinitrogen pentoxide (N₂O₅),^{9c} *N*-nitropyridinium salts^{9d} or similar might be selective enough to accomplish C-nitration without Boc-deprotection. Herein we describe preliminary studies on the nitration of Boc-protected aniline and 1,3,5-triaminobenzene by acetyl nitrate.

Initial concerns were centered around the sensitivity of nitro derivatives of Boc-aniline (1) during aqueous work-up at which time they would be exposed to an acidic environment created by the hydrolysis of both the acetic anhydride as well as residual acetyl nitrate (Scheme 1). Allowing **1** to react with a previously prepared solution of two equivalents of acetyl nitrate in excess acetic anhydride at ice bath temperature gave, after a cold aqueous work-up, a good yield of a mixture of mono-nitro compounds **2** and **3** in an *ortho/para* ratio of 3:1. This ratio is close to that obtained by Lynch et al.¹⁰ who nitrated acetanilide similarly (*o*/ p = 4.5). With four equivalents nitrating agent Boc-protected 2,4dinitroaniline (**4**) was obtained, albeit in low yield. The single crystal X-ray structure of **4** is shown in Figure 1.¹¹ In contrast to previous work with the ethyl carbamate of aniline,¹² allowing **1** to react with further quantities of acetyl nitrate did not yield a trinitro derivative.

Acetyl nitrate was found to be an effective reagent for aromatic mono- and dinitration of Boc-protected

aminobenzenes. The method was used in a new synthesis of 1,3,5-triamino-2,4-dinitrobenzene in two

Encouraged by these results, similar nitration of fully Boc-protected 1,3,5-triaminobenzene (**5**) was conducted (Scheme 2). Here, the nitration reaction was started out at -78 °C and care was again taken during work-up to keep the temperature near 0 °C. With slightly more than one equivalent of acetyl nitrate the unreported mononitro **6** was isolated in modest yield (not optimized). How-



AcONO₂

NHBoc

NHBoc

Scheme 1. Nitration of compound 1 by acetyl nitrate.







^{*} Corresponding author. Tel.: +1 760 939 0196; fax: +1 760 939 1617. *E-mail address:* matthew.davis@navy.mil (M.C. Davis).



Figure 1. Crystal structures of new dinitro compounds 4 and 7.



Scheme 2. Nitration of compound **5** by acetyl nitrate and synthesis of compound **8**: by deprotection of **7** and the historical method.

ever, even when challenged with ten equivalents of nitrating agent, dinitro **7** was the product isolated in good yield. The X-ray crystal structure of **7** is shown in Figure 1.¹¹ The careful control of temperature during aqueous work-up of these nitrations may have been unnecessary based on the results described below.

As an acid-labile protecting group, Boc has been cleaved by a plethora of different acidic conditions.⁶ The nitro groups of **7**, through an electron inductive effect, were expected to make the adjacent Boc groups more susceptible to reaction with acid, Scheme 2. Thus, it was surprising that even refluxing **7** in acetic acid ($pK_a 4.76$)¹³ did not result in deprotection. Therefore, concentrated hydrochloric acid ($pK_a -8$; four equivalents)¹³ was added to the acetic acid solution and deprotection occurred smoothly.¹⁴ The initial product isolated was the hydrochloride salt (**8**·HCl) which was freebased by washing with triethylamine and compound **8** was obtained in 63% yield over the two steps from **5**. This methodology compares favorably to the only ever preparation of **8** by Borsche and Trautner,¹⁵ owing to the difficulty in preparing the trihalodinitrobenzene.

In summary, acetyl nitrate in acetic anhydride is a viable method for aromatic nitration in the presence of the acid sensitive Nprotecting group, Boc. Further research into the generality of this method with more complicated anilines and amine-substituted heterocycles as well as employing stronger nitrating agents will be the subject of a future communication.

Acknowledgments

Financial support through an In-house Laboratory Independent Research award from the Office of Naval Research is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/ j.tetlet.2012.05.139.

References and notes

- (a) Holleman, A. F.; Hartogs, J. C.; van der Linden, T. Ber. Dtsch. Chem. Ges. 1911, 44, 704–728; (b) Blanck, F.C. Ph.D. Dissertation, University of Michigan, 1908;; (c) Brickman, M.; Ridd, J. H. J. Chem. Soc. 1965, 6845–6851; (d) Zhang, P.; Cedilote, M.; Cleary, T. P.; Pierce, M. E. Tetrahedron Lett. 2007, 48, 8659–8664; (e) Rosevear, J.; Wilshire, J. F. K. Aust. J. Chem. 1985, 38, 723–733.
- (a) Sánchez-Viesca, F.; Gómez Gómez, M. R.; Berros, M. J. Chem. Educ. 2011, 88, 944–946; (b) Rondestvedt, C. S., Jr. Ind. Eng. Chem., Proc. Res. Dev. 1977, 16, 177– 179.
- 3. (a) Hanson, J. R.; Saberi, H. *J. Chem. Res.* **2004**, *7*, 460–462; (b) Cheeseman, G. W. H. *J. Chem. Soc.* **1962**, 1170–1176.
- (a) Curry, H. M.; Mason, J. P. J. Am. Chem. Soc. 1951, 73, 5043–5046; (b) Davis, M. C. Synth. Commun. 2007, 37, 1457–1462.
- (a) Siri, O.; Braunstein, P. New. J. Chem. 2005, 29, 75–79; (b) O'Keefe, D. M. U.S. Patent 4 833 265, 1989; Chem. Abstr. 1989, 111, 194324.
- Greene, T. W.; Wuts, P. G. M. Protecting Groups in Organic Synthesis, 2nd ed.; Wiley: New York, 1991.
- (a) Carpino, L. A. J. Am. Chem. Soc. 1957, 79, 98–101; (b) Carpino, L. A. Acc. Chem. Res. 1973, 6, 191–198.
- (a) Pagoria, P. F.; Mitchell, A. R.; Schmidt, R. D.; Coon, C. L.; Jessop, E. S. In Nitration: Recent Laboratory and Industrial Developments; Albright, L. F., Carr, R. V. C., Schmitt, R. J., Eds.; ACS Symposium Series, American Chemical Society: Washington, DC, 1996; Vol. 623, pp 151–164; (b) Papageorgiou, G.; Corrie, J. E. T. Synth. Commun. 2002, 32, 1571–1577; (c) Rodenko, B.; Koch, M.; van der Burg, A. M.; Wanner, M. J.; Koomen, G. –J. J. Am. Chem. Soc. 2005, 127, 5957– 5963; (d) Fedoryak, O.; Sul, J. –Y.; Haydon, P. G.; Ellis-Davies, G. J. R. Chem. Comm. 2005, 3664–3666; (e) Wang, X.; Gao, Y.; Li, L.; Zhang, Z.; Liu, J. Synth. Commun. 2009, 39, 4030–4038.
- (a) Schofield, K. Aromatic Nitration, Cambridge University Press, Cambridge, UK,1980, pp. 54-71.; (b) Andreozzi, R.; Marotta, R.; Sanchirico, R. J. Hazard. Mater. 2002, 90, 111-121; (c) Bak, R. R.; Smallridge, A. J. Tetrahedron Lett. 2001, 42, 6767-6769; (d) Olah, G. A.; Narang, S. C.; Olah, J. A.; Pearson, R. L.; Cupas, C. A. J. Am. Chem. Soc. 1980, 102, 3507-3510.
- 10. Lynch, B. M.; Chen, C. M.; Wigfield, Y. -Y. Can. J. Chem. 1968, 46, 1141-1152.
- 11. Crystallographic data (without structure factors) for compounds **4** and **7** has been deposited with Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 862521 and 862520, respectively.
- 12. Davis, M. C. Synth. Commun. 2007, 37, 2079-2089.
- 13. Moran, M. J. J. Chem. Educ. 2006, 83, 800-803.
- 14. Ashworth, I. W.; Cox, B. G.; Meyrick, B. J. Org. Chem. 2010, 75, 8117-8125.
- 15. Borsche, W.; Trautner, W. Justus Liebigs Ann. Chem. 1926, 447, 1-18.