Published in final edited form as:

Tetrahedron Lett. 2012 March 1; 53(13): 1592–1594. doi:10.1016/j.tetlet.2012.01.066.

Facile synthesis of 2,3,5,6-tetrabromo-4-methyl-nitrocyclohexa-2,5-dien-1-one, a mild nitration reagent

Christopher K. Arnatt^a and Yan Zhang^a

Yan Zhang: yzhang2@vcu.edu

^aDepartment of Medicinal Chemistry, Virginia Commonwealth University, Richmond, VA 2329, USA, Fax: 804-282-7625; Tel: 804-828-7625

Abstract

Nitrocyclohexadienones have been applied as nitration reagents for mild, mono-nitrating reactions. The original synthesis of 2,3,5,6-tetrabromo-4-methyl-4-nitrocyclohexa-2,5-dien-1-one appeared to be difficult to pursue due to both the solvent system and reaction conditions. Therefore, we applied a modified solvent system and optimized the reaction conditions to prepare the dienone at 0°C, eventually overcome the difficulties.

Keywords

Nitrocyclohexadienone; mono-nitration; reaction condition modification

The ubiquitous nature of aromatic nitration has shown the reaction's simplicity, versatility, and usefulness in both the chemical and pharmaceutical industries.¹ The addition of a nitro group into an aromatic system can be used for a variety of reasons; such as to tune the electronic properties of a molecule or to be reduced to an amine which can be utilized in an abundant amount of reactions. However, there are several conundrums that exist with this type of reaction: oxidation of starting material, poly-nitration, regioselectivity, and general safety concerns. Therefore, a large amount of nitration reagents and methods have been investigated in an attempt to alleviate these difficulties.^{2–4}

Nitrocyclohexadienones have been used as selective and mild nitration reagents under a variety of conditions and unlike using nitric acid for nitration, they lead to less oxidative and poly-nitro byproducts.⁴ First reported by Lemaire et al., perhalo-nitrocyclohexadienones were shown to mono-nitrate a variety of naphthols and phenols while avoiding problems with oxidation and regioselectivity.⁴ Several nitrocyclohexadienones were explored with varying substituents, while 2,3,5,6-tetrabromo-4-methyl-4-nitrocyclohexa-2,5-dien-1-one (**1**) was chosen for its stability and ability to react with 1-naphthol and afford mono-nitrated products at appreciable yields. Additionally, **1** has been shown to selectively mono-nitrate highly activated organic compounds such as aromatic amines.⁵

Scheme 1 illustrates the general reaction mechanism that **1** has been shown to undergo. Studies utilizing ¹⁵N NMR have shown that ¹⁵N-labeled **1** undergoes homolytic fission of the C-N bond to form a radical pair.⁶ This radical pair can subsequently mono-nitrate

Correspondence to: Yan Zhang, yzhang2@vcu.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

various aromatic substrates and in the process, a phenol byproduct, 4-methyl-2,3,5,6-tetrabromophenol (**2**) is formed which can be separated out and recycled to reform **1**.^{6–7}

One aspect of its robustness is its selectivity and mild reaction conditions: as seen with the mono-nitrate products **3–5**, even though the substrate and reaction conditions are varied significantly, **1** was able to afford the mono-nitrate adduct as the major one (Scheme 2). The three mono-nitrated products represented, **3–5**, are intermediates in the synthesis of various pharmacologically active compounds.^{8–10} Interestingly, all three utilized **1** under different solvent systems which range from non-polar to polar. Of the three, the synthesis of **5** proved to be difficult under acidic conditions using routine nitration conditions (i.e. HNO₃ in H₂SO₄) because the 3-position is nitrated over the 4-position due to the protonation of the amine.^{10–11} However, when **1** was adopted in the reaction, reasonable yields of the 4-nitro product **5** were achieved.

In context of our lab's continuing studies to make pharmacologically active compounds, we were interested in synthesizing an intermediate **6** (Scheme 3). First attempts to form the mono-nitrate product using a system of HNO₃ and AcOH yielded 2,6-di-nitro and oxidative by-products only. Different solvent systems and temperatures were attempted, but no mono-nitrate product was observed. However, when **1** was adopted, the mono-nitrate product **6** was selectively synthesized in relatively high yields. While this synthetic route selectively afforded the aim product we ran into difficulties in synthesizing the critical nitration agent **1**.

Typically, **1** is synthesized from nitration of 4-methyl-2,3,5,6-tetrabromophenol (**2**)¹¹ in acetic acid utilizing 100% HNO₃ (d 1.52) at 10°C and then consequently stirring at 5°C for 2 hours (Scheme 4).⁴ However, several difficulties were encountered while following the original method. First, 100% HNO₃ must be used which is both hard to handle and readily decomposes. Second, the reaction temperature is very crucial and difficult to maintain; it was found that above 5°C the starting material **2** decomposed and below that temperature the reaction would not proceed but freeze, making mechanical mixing of the reaction components difficult. Lastly, **2** is sparingly soluble in acetic acid. Altogether, these factors made yields and reaction times vary widely.

We sought to change the reaction conditions to prepare **1** in order to overcome the above difficulties. First, 100% HNO₃ was replaced with 70% HNO₃ (d 1.42) which proved to be easier to handle and readily available (Scheme 5). It was then found that controlling the reaction temperature, solubility of the starting material, and reaction time were still major problems. The reaction times ranged from 2 to 72 hours and yields ranged from 10 to 75% in most cases.

In order to overcome these setbacks, the acetic acid, the solvent of the reaction, was replaced with acetic anhydride (Scheme 5). It was speculated that similar to typical nitration reactions, acetic anhydride would allow for a possible wider range of reaction temperatures, while a different mechanism of reaction may be followed. Upon reacting with nitric acid, acetic anhydride rapidly forms acetyl nitrate (a milder nitrating reagent than HNO₃), which directly forms a nitronium ions in solution (Scheme 6).^{12–13}

Several reaction conditions were then explored and the results were summarized in Table 1. In all, the synthesis of **1** became more reproducible, and efficient. First of all, the concentration of HOAc and **2** were kept constant while the final concentration of HNO₃ changed. Concentrations of HNO₃ above 6 M lead to the formation of mainly oxidative by-products whereas concentrations below that gave fairly consistent yields. However, the concentration of 4 M HNO₃ (Table 1, entry 2) gave the highest yield. Second, acetic acid was first kept in the system (Entry 1 to 4) to prevent oxidative byproducts from forming due to excess acetyl nitrate in solution,^{12–13} but either reaction time or yield was unaffected with

or without the acetic acid (Entry 2 and 5). Third, when the reaction was scaled up from 1.17 mmol (Entry 5) of the substrate **2** to 9.35 mmol (Entry 6) a significant increase of yield was observed.¹⁴ Most significantly, for all the conditions we tried, the reaction substrate **2** was consumed completely within 5 to 10 min after the addition of nitric acid.

In summary, nitrocyclohexadienones represent mild and selective nitration reagents that have seen a variety of applications in the synthesis of complex pharmacological compounds. We developed a new procedure for the facile synthesis of 2,3,5,6-tetrabromo-4-methyl-4-nitrocyclohexa-2,5-dien-1-one (**1**) using an acetic anhydride and 70% HNO₃ system at 0°C. Compared to the original synthesis, our method provides a practical approach with efficiency and reliable yields.

Acknowledgments

We are grateful to the funding support from NIH/NIAID AI69975 and AI074461. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of AIDS and Infectious Diseases or the National Institutes of Health.

References

1. Olah, GA.; Malhotra, R.; Narang, SC. Nitration: Methods and Mechanisms. VCH; New York: 1989. p. 1-7.
2. Ridd JH. Acta Chem Scand. 1998; 52:11.
3. Olah GA, Narang SC, Olah JA, Lammertsma K. Proc Natl Acad Sci USA. 1982; 79:4487.
4. Lemaire M, Guy A, Roussel J, Guette JP. Tetrahedron. 1987; 43:835.
5. Lemaire M, Guy A, Boutin P, Guette JP. Synthesis. 1989:761.
6. Coombes RG, Ridd JH. J Chem Soc, Chem Commun. 1992:174.
7. Coombes RG, Hadjigeorgiou P, Jensen DGJ, Morris DL. ACS Symposium Series. 1996; 623:19.
8. Parker DL, Meng D, Ratcliffe RW, Wilkening RR, Sperbeck DM, Greenlee ML, Colwell LF, Lambert S, Birzin ET, Frisch K, Rohrer SP, Nilsson S, Torsell AG, Hammond ML. Bioorg Med Chem Lett. 2006; 16:4652. [PubMed: 16777408]
9. Yu Y, Singh SK, Liu A, Li TK, Liu LF, LaVoie EJ. Bioorg Med Chem. 2003; 11:1475. [PubMed: 12628673]
10. Ban H, Muraoka M, Ohashi N. Tetrahedron. 2005; 61:10081.
11. For example synthesis, see reference 4.
12. Hoggett, JG.; Moodie, RB.; Penton, JR.; Schofield, K. Nitration and Aromatic Reactivity. University Press; Cambridge: 1971. p. 79-106.
13. Fischer A, Read AJ, Vaughan J. J Chem Soc. 1964:3691.
14. Optimized procedure: To a solution of 4.0 g (9.35 mmol) of **2** in 28 mL of acetic anhydride was added, drop-wise, 6 mL (135 mmol) HNO₃ (d 1.42) at 0°C. The suspension was stirred at that temperature for 10 min and the product was precipitated out with the addition of 40 mL H₂O. The product, **1**, was filtered out and the resultant pale yellow crystals were washed with H₂O and hexane and dried under vacuum giving a yield of 4.15 g (95%). ¹H NMR (400 MHz, CDCl₃) δ 2.26 (s, 3H); mp: decomposed 80°C, IR Vmax (ATR): 1682 cm⁻¹.

Scheme 1.

General reaction scheme for 2,3,5,6-tetrabromo-4-methyl-4-nitrocyclohexa-2,5-dien-1-one (**1**).

Scheme 2.

Example reactions that utilize **1** to prepare selectively and mildly nitrate products.

Scheme 3.

Synthesis of 1-(trifluoromethyl)-4-(4-isopropoxy-3-nitrophenyl)piperazine.

Scheme 4.

Synthesis of 2,3,5,6-tetrabromo-4-methyl-4-nitrocyclohexa-2,5-dien-1-one **1**.

Scheme 5.
Conditions to optimize the synthesis of **1**.

Scheme 6.

a) Nitration mechanism for HNO₃ b) Putative nitration mechanism for acetyl nitrate.

Table 1

Screening different conditions to carry out the nitration at 0°C. The amount of **2** was kept constant at 0.5 g, 1.17 mmol (unless noted otherwise) and the amounts of HNO₃ and AcOH were varied. The volume of acetic anhydride used varied in each reaction to achieve a final reaction volume of 4.25 mL.

Entry	Amount of 2 (g)	Acetic anhydride (mL)	[HNO ₃] (M)	[AcOH] (M)	Yield(%) ^a
1	0.5	2.6	6	2	68
2	0.5	3.0	4	2	77
3	0.5	3.4	2	2	66
4	0.5	3.5	1.5	2	70
5	0.5	3.5	4	0	79
6	4.0	28	4	0	95

^a Separation yields.