Tetrahedron Letters 53 (2012) 4841-4842

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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



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Aromatic nitration under neutral conditions using N-bromosuccinimide/silver(I) nitrate

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ARTICLE INFO

ABSTRACT

Article history: Received 18 April 2012 Revised 24 May 2012 Accepted 27 June 2012 Available online 4 July 2012

Keywords: N-Bromosuccinimide (NBS) Silver nitrate (AgNO₃) Nitration Aromatic compounds

Aromatic nitro compounds are key intermediates in organic synthesis. This important class of industrial chemicals is widely used in the synthesis of many diverse products, including dyes, polymers, pesticides, and explosives. Aromatic nitration is commonly achieved using a mixture of nitric and sulfuric acids, called 'mixed acid', which is expensive to treat, creates pollution, and is hazardous to the environment. These disadvantages have encouraged researchers to develop procedures using solid acid catalysts,¹ metal nitrates,² organic nitrating agents,³ inorganic acidic salts,⁴ and other sources of NO₂^{+,5}

However, many of these reactions have been carried out in the presence of protic and Lewis acids, and most suffer from drawbacks, such as regioselectivity issues, over nitration, and competitive oxidation of substrates. Hence, there is still a need for the design and execution of mild methods for aromatic nitration.

In continuation of our recent work on aromatic nitration,⁶ herein, we report the application of NBS/AgNO₃ as a novel reagent system for the efficient and selective nitration of aromatic compounds under essentially neutral conditions. This method minimizes waste products compared to traditional methods and gives the corresponding mononitro derivatives in good to excellent yields.

Initially, *N*,*N*-dimethylaniline was chosen as the substrate for model reactions and several common solvents were tested in the presence of different amounts of N-bromosuccinimide and silver nitrate. We found that the reaction afforded high yields of the corresponding nitro derivatives after three hours, when using a



The use of N-bromosuccinimide and silver nitrate as a convenient reagent system for the nitration of

aromatic compounds under neutral and environmentally safer reaction conditions is described.

molar ratio of NBS/AgNO₃/*N*,*N*-dimethylaniline of 1:1:1 in refluxing CH₃CN (Scheme 1).

Having established optimized reaction conditions, various aromatic compounds with electron-donating and electron-withdrawing groups were examined and the results are summarized in Table 1.

In the case of reactive aromatic compounds nitrated products were obtained in high yields. The reactions were selective, and no dinitro or side-chain substitution products were detected. Deac-tivated aromatic compounds failed to undergo nitration with this reagent system, even after prolonged reaction times under reflux (Table 1, entries 13–16).

Nitrophenols are important intermediates for the manufacture of drugs and pharmaceuticals.⁷ Phenols are highly reactive, therefore the nitration of phenols by mixed acids is always associated with the formation of dinitro compounds, oxidized products, and unspecified resinous materials. Thus, many mild nitration processes for phenols have been developed to overcome these shortcomings.⁸ However, some of the nitrating reagents are poorly regioselective and uneconomical.



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^{0040-4039/\$ -} see front matter @ 2012 Elsevier Ltd. All rights reserved. http://dx.doi.org/10.1016/j.tetlet.2012.06.126

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Nitration of aromatic compounds using NBS/AgNO₃ in refluxing CH₃CN

1N,N-Dimethylaniline3 hortho: para: 62Anisole3.5 hortho: para: 73Toluene4.5 hortho: para: 6	16 59 15 74 20
2 Anisole 3.5 h ortho: para: 7 3 Toluene 4.5 h ortho: para: 6	59 15 74 20
2 Anisole 3.5 h ortho: para: 7 3 Toluene 4.5 h ortho: para: 6	15 74 20
para: 7 3 Toluene 4.5 h ortho: para: 6	74 20 36
3 Toluene 4.5 h ortho: para: 6	20 36
para: 6	36
4 4-Iodoanisole 5 h 2-Nitro	o: 88
5 Indole 2 h 3-Nitro	o: 91
6 2-Methylindole 1.5 h 3-Nitro	o: 87
7 Naphthalene 3.5 h 1-Nitro	o: 80
8 Phenol 2.5 h ortho:	20
para: 6	57
9 4-Bromophenol 4 h 2-Nitro	o: 81
10 4-Methoxyphenol 50 min 2-Nitro	o: 92
11 4-Nitrophenol 7 h 2-Nitro	o: 76
12 2-Nitrophenol 7.5 h 4-Nitro	o: 75
13 Cyanobenzene 24 h –	
14 Chlorobenzene 24 h –	
15 Bromobenzene 24 h –	
16 Iodobenzene 24 h –	

^a Isolated yield.





Here, treatment of phenols under similar conditions to those described above gave the nitro derivatives in good to excellent yields. Phenols with electron-donating or electron-withdrawing groups reacted smoothly under mild conditions, and in all cases, mononitration was observed. For example, 4-methoxy-2-nitrophenol was isolated in 92% yield following nitration of 4-methoxyphenol for 50 min (Table 1, entry 10).

A possible mechanism for the nitration process is shown in Scheme 2. Addition of $AgNO_3$ to N-bromosuccinimide produces the intermediate I which is accompanied by the precipitation of AgBr. This reactive intermediate then reacts with the aromatic ring of the substrate to produce the corresponding nitro aromatic compound along with N-hydroxysuccinimide. N-hydroxysuccinimide can be removed from the organic phase by washing with an aqueous solution of sodium bicarbonate.

The precipitation of AgBr and formation of N-hydroxysuccinimide during the reaction are considered strong evidence for the proposed mechanism. In this reaction, the silver salt is recovered as AgBr by filtration of the reaction mixture.

In summary, we have described a simple and convenient method for the nitration of aromatic compounds using NBS/AgNO₃.⁹ The reactions occur under mild and environmentally safer conditions and can be applied to a wide range of acid-sensitive substrates in comparison to traditional methods. Further, the absence of dinitrated and polynitrated products is another advantage of our system.

Acknowledgement

We thank the Persian Gulf University Research Council for generous partial financial support of this study.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06. 126. These data include MOL files and InChiKeys of the most important compounds described in this article.

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- Typical procedure for the nitration of N,N-dimethylaniline: To a stirred mixture of CH_3CN (5 mL) and NBS (1.0 mmol, 0.177 g) at reflux, was added AgNO₃ (1.0 mmol, 0.169 g). N,N-Dimethylaniline (1 mmol, 0.126 mL) was then added to the mixture. After 3 h, the mixture was filtered to remove AgBr. The solvent was evaporated and the residue dissolved in CH2Cl2 (10 mL) and washed with aqueous 4% NaHCO₃ (2×5 mL) to remove N-hydroxysuccinimide from the organic phase. The aqueous phase was separated and the organic phase dried and concentrated. The residue was subjected to column chromatography over silica gel using n-hexane/EtOAc (4:1) as eluent to give 4-nitro- and 2-nitro-N,Ndimethylaniline in 69% and 16% yields, respectively. 4-Nitro-NNdimethylaniline (Table 1, entry 1): Yellow powder; mp 162-165 °C (Lit10 163-165 °C); IR (KBr) 800, 1300, 1350, 1500, 1525, 1600, 2900–3000 cm⁻¹; ¹H NMR (250 MHz, CDCl₃): δ (ppm) 2.89 (6H, s), 6.32 (2H, d, J = 5.49 Hz), 7.8 (2H, d, J = 5.5 Hz; ¹³C NMR (62.9 MHz, CDCl₃): δ (ppm) 30.2, 110.5, 126.4, 138.0, 154.4. The aqueous phase was treated with 4% HCl solution and extracted with CH₂Cl₂ (10 mL). The organic layer was separated and evaporated. The melting point of the obtained product (colourless crystals) was 93-95 °C, which was in accordance with the melting point of N-hydroxysuccinimide (mp 95 °C).
- 10. (a) www.sigmaaldrich.com.; (b) www.chemexper.com.