Nitration of N-acetyl anilides using silver(I) nitrate/persulfate combination

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ABSTRACT
Nitration of N-acetyl anilides using a simple combination of AgNO₃ and K₂S₂O₈ as a stable nitro source and an oxidant, respectively, was explored. The reaction was practical to operate and proceeded under considerably mild reaction conditions (reflux in acetonitrile) within acceptable reaction time (6 h). The para-substituted N-acetyl anilides gave only ortho-nitrated products in moderate to good yields (30–63% yields). The ortho-, meta-, or non-substituted N-acetyl anilides gave a mixture of nitrated products (30–72% combined yields) with preferentially at the para- over the ortho-position (ortho:para; 1.0:1.1–1.0:2.8).

GRAPHICAL ABSTRACT

Introduction
Nitroanilide is a member of nitroarene derivatives[1] which is an important building block for the synthesis of pharmaceuticals, dyes, explosives, and polymers and has been found in various biologically active compounds. As a result, numerous synthetic methods for the synthesis of nitroanilides have been developed and particular attention has been focused on regioselective introduction of a nitro group into the desired position, i.e., ortho-, meta-, or para-, on aromatic ring of anilide precursors. To this end, various directing groups (DGs), a variety of nitro sources as well as the additives and conditions have been developed and reported (Scheme 1).[2] Based on metal-catalyzed nitration, the directing groups, such as azo groups,[3] pyrimidine,[4] pyridine, pyrazine, pyridazine, quinoline, isoquinoline, and benzothiazole,[5] were revealed to assist highly regioselective...
ortho-nitration of aniline derivatives (Scheme 1a). Regioselective para-nitration of aniline derivatives could be obtained using oxazoline, for example, as a directing group.[6] Recently, the most challenging meta-nitration of arenes was also successfully developed.[7] Notably, metal-catalyzed nitration of naphthylamine derivatives and 8-aminoquinolines was also established.[8] Without the directing group, on the other hand, nitration of anilines protected with the protecting groups (PGs) also received considerable attention during the past decade (Scheme 1b).[9] In 2013, nitration of aromatic sulfonamides was reported by Arns using tert-butyl nitrite (TBN) as a nitro source.[10] Carretero[11] and Jiang[12] reported copper-catalyzed nitration of anilides using nitric acid or TBN as a nitrating reagent. Using riboflavin tetraacetate (RFTA) as an organic photoredox catalyst with NaNO2 was explored by König.[13] Without a catalyst, Chandrasekhararam employed Fe(NO3)3·9H2O for nitration of anilides and aromatic sulfonamides.[14] In the presence of N-hydroxyphthalimide (NHPI) or CuCl2·2H2O as a catalyst, nitration using Fe(NO3)3·9H2O gave selective ortho-nitration as reported by Gao[15] and Sun.[16] The silver-catalyzed regioselective ortho-nitration of anilides using NaNO2 in the presence of K2S2O8 as the oxidant was reported by Kianmehr.[17] Using

**Scheme 1.** Nitration of anilides and selected examples of bioactive nitroanilides and nitroanilide intermediates.
NaNO₂ or Cu(NO₃)₂·3H₂O as a nitro source, the reactions in the presence of the oxidant, i.e., PhI(TFA)₂, oxone, or K₂S₂O₈ were independently reported by Nachtsheim,¹⁸ Liang,¹⁹ Liang²⁰ and Jadhav and Vidavalur.²¹ In the presence of dioxygen, N-nitroso anilines served as a self-providing nitro group source to promote the direct nitration of N-alkylanilines as reported by Yuan and Jia.²² Silver(I) nitrate (AgNO₃) is among stable and readily available silver species that have been widely used in metal-catalyzed nitration of aromatic derivatives.²³ However, using AgNO₃ as a nitrating reagent for nitration of protected anilines especially in the absence of a catalyst has not been reported. Herein, we report our results on nitration of N-acetyl anilides using AgNO₃/K₂S₂O₈ combination. The nitro products could be useful for the synthesis of pharmaceuticals and biologically active compounds. Selected structures of important nitroanilides are presented in Scheme 1c, including L-γ-glutamyl-p-nitroanilide (GPNA),²⁴ flutamide,²⁵ niclosamide,²⁶ Schiff bases of glycine o-nitroanilides,²⁷ and 2-nitro-N-acylanilines.²⁸

### Results and discussion

To begin with, non-substituted N-phenylacetamide (1a) was used as a model substrate to find the reaction conditions to perform nitration using AgNO₃ as a nitro source (Table 1). Initially, treatment of 1a with AgNO₃ (1 equiv.) and K₂S₂O₈ (2 equiv.) in acetonitrile (open-flask) at 50 °C for 6 h failed to give the desired nitro products; 1a was

| Entry | AgNO₃ (equiv.) | K₂S₂O₈ (equiv.) | Time (h) | 1a | 2a | 3a |
|-------|---------------|-----------------|----------|----|----|----|
| 1     | 1             | 2               | 6        | 99 | –  | –  |
| 2     | 1             | 1               | 16       | 34 | 19 | 24 |
| 3     | 2             | 1.5             | 6        | 0  | 34 | 38 |
| 4     | 1             | 2               | 6        | 0  | 20 | 27 |
| 5     | 2             | 1.5             | 12       | 0  | 29 | 32 |
| 6     | 3             | 1.5             | 6        | 0  | 20 | 26 |
| 7     | 5             | 3               | 6        | 0  | 10 | 10 |
| 8     | 4             | 3               | 12       | 0  | 9  | 6  |
| 9     | 2 / TEMPO (2) | 1.5             | 6        | 99 | –  | –  |
| 10    | 2 / BHT (2)   | 1.5             | 6        | 97 | –  | –  |

⁰Unless stated otherwise, the reaction was carried out using 0.5 mmol of 1a in acetonitrile (analytical grade) at reflux for 6 h (open-flask). For more detail, see the Supporting Information.

¹Yield of product isolated by column chromatography (SiO₂).

²The reaction was carried out at 50 °C.

³94% Combined yield of crude 2a (o-p-, ratio = 1.0:1.2) was obtained.

⁴The reaction was carried out under an argon atmosphere.

⁵Only o,p-3a was obtained.

⁶AgNO₃ (2 equiv.) and K₂S₂O₈ (1.5 equiv.) were added portion-wise after 6 h.
recovered in 99% yield (Entry 1). When the reaction temperature was increased to reflux (16 h), \( o-2a \) and \( p-2a \) could be isolated in 19% and 24% yields, respectively (Entry 2). Next, the amount and ratio of AgNO₃ and K₂S₂O₈ were carefully screened and it was found that using AgNO₃ (2 equiv.) and K₂S₂O₈ (1.5 equiv.) in acetonitrile at reflux (6 h) gave \( o-2a \) and \( p-2a \) in 34% and 38% isolated yields (Entry 3). The reaction under an argon atmosphere did not give the superior results (Entry 4). Along with \( 2a \), a mixture of dinitro products \( 3a \) could also be obtained in up to 24% yield (\( o,p-3a:o,o-3a \) ratio = 8:1) using a large excess of AgNO₃ and K₂S₂O₈ at prolonged reaction time (Entries 5–8). Using AgNO₃ (2 equiv.) with other oxidants [Na₂S₂O₈, (NH₄)₂S₂O₈, PhI(OAc)₂, PhI(TFA)₂, oxone, and Cu(OAc)₂] gave the inferior results compared to those obtained from using K₂S₂O₈ (see Supporting Information for more detail). Finally, among the nitro sources tested in this study [AgNO₃, AgNO₂, NaNO₂, NaNO₃, t-BuNO₂, Fe(NO₃)₃·9H₂O, and Zn(NO₃)₂·6H₂O], AgNO₃ was found to be the most effective nitro source. It should be mentioned here that a variety of solvents was also screened. While using AgNO₃/K₂S₂O₈ combination in MeCN:H₂O (1:1), DME, and DCE at reflux led to the recovery of \( 1a \) in good to quantitative yields, the reactions in toluene, dimethylformamide, and dimethyl sulfoxide at 90 °C gave the degradation of \( 1a \). To gain insights into the mechanism, the reactions in the presence of radical scavengers, (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) or butylated hydroxytoluene (BHT), were performed (Entries 9–10). It was found that the reactions were completely inhibited when TEMPO (2 equiv.) or BHT (2 equiv.) were added. Based on the above-observed results and previous reports,[23] a plausible mechanism for nitration of \( 1a \) using a combination of AgNO₃/K₂S₂O₈ is proposed to occur through the radical pathway (Scheme 2). The reaction between AgNO₃ and K₂S₂O₈ generated nitrogen dioxide radical that would react with \( 1a \) to provide radical intermediate A. Subsequently, oxidation of A followed by deprotonation of the corresponding cation B should give the desired nitro products \( o-2a \) and \( p-2a \). At this stage, the reaction conditions in Entry 3 \([1a \ (0.5 \text{ mmol)}, \text{AgNO}\text{₃} (2 \text{ equiv.}), \text{K}_2\text{S}_2\text{O}_8 \ (1.5 \text{ equiv.}), \text{MeCN, reflux, 6 h}] \) was chosen as the optimized reaction conditions in this study.

Using the optimized conditions, the scope of the protecting group of anilines was also investigated (Scheme 3). Compared to the reaction of \( 1a \) that produced \( 2a \) in 72% combined yield (\( o:p \) ratio = 1.0:1.1), nitration of anilines protected with pivaloyl (\( 1b \)) and benzoyl (\( 1c \)) groups gave lower combined yields of \( 2b \) (64% yield) and \( 2c \) (55%
yield) with slightly higher ratio ($o:p$ ratio = 1.0:1.9 and 1.0:1.6, respectively) preferentially at the $para$-position over the $ortho$-position of 1. It should be mentioned here that the ratio of the $ortho$- to $para$-regioselectivity based on $^1$H NMR analysis of the crude reaction mixtures of 2a, 2b, and 2c was 1.0:1.2, 1.0:1.6, and 1.0:1.4, respectively (see Supporting Information). These results suggested that the steric effect of the $N$-protecting group did not play a significant role in the regioselectivity of the reaction. In addition, aniline protected with a strong withdrawing tosyl group (1d) and unprotected aniline (1e) are not suitable under these nitration conditions. While 1d gave a mixture of $o$-$2d$ and $p$-$2d$ (11% combined yield) and dinitro products $o,p$-$3d$ and $o,o$-$3d$ (18% 

Scheme 3. Substrate scope. $^a$Using AgNO$_3$ (4 equiv.) at reflux for 8 h. $^b$Yield of the corresponding aniline.
combined yield), 1e was found to decompose and gave a complex mixture without the detection of 2e. Based on the observed efficiency of the reaction, anilines protected with acetyl group were used for further exploration in this work. A variety of N-acetyl anilides 1 possessing different electronic property and substituents were subjected to the optimized reaction conditions and the results are summarized in Scheme 3. N-Acetyl anilides possessing para-substituents such as MeO–, AcO–, and Me– provided the corresponding ortho-nitro products 2f–2h in acceptable yields (30–51% yields). Notably, using a substrate containing a strong donating MeO– group at a para-position as a substrate, dinitro product 3f was also obtained in 30% yield along with mono-nitro product 2f. Nitration of N-acetyl anilides having biaryl motif also proceeded regioselectively to provide nitro products 2i–2l each as a single product in good yields (50–63% yields). Nitration of N-acetyl anilides bearing di-MeO– and p-NO2– groups gave 2m (41% yield) and o,p-3a (38% yield), respectively. N-Acetyl anilides containing ortho (NO2–, Ph–, CN–, and MeSO2–) and meta (Me– and NO2–) substituents proceeded to give the corresponding nitro products o,p-3a, o,o-3a, and both o- and p-derivatives of 2n–2r in 30–57% yields with preferentially at the para-position over the ortho-position of 1.

The ratio of the ortho- to para-regioselectivity based on 1H NMR analysis of the crude reaction mixtures of 2p and 3a was 1.0:2.5 and 1.0:3.8, respectively. The observed regioselectivity was possibly governed by the steric effect of the protecting group. In addition, the electronic property and the steric hindrance of the substituents on aromatic ring of anilides could also influence the regioselectivity of the reaction. It should also be
pointed out here that N-acetyl anilides possessing a strong withdrawing groups (NO₂−, CN−, and MeSO₂−) also proceeded providing the corresponding nitro products (2o, 2p, 2r, and 3a, respectively) in acceptable yields (30–48% yields).

As synthetic applications, a gram scale reaction of 1a was performed as summarized in Scheme 4. In addition, bromination of p-2a leading to products 4 and 5 could be achieved based on the modified procedure as reported by Das and Kapur using a palladium-mediated reaction with NBS.[29] Finally, selective transformations of NO₂− or N-acetyl group of o-2a was demonstrated. Hydrolysis of o-2a (NaOH, EtOH, reflux, 2 h) gave ortho-nitro aniline 6 in 84% yield. Reduction of nitro group could be accomplished using either Et₃SiH as a reducing agent or a catalytic hydrogenation process leading to the corresponding aniline derivative 7 in 76% and 98% yields, respectively.

**Conclusions**

In conclusion, we reported nitration of N-acetyl anilides using a simple combination of AgNO₃/K₂S₂O₈. The advantages of the present procedure include the practical operation in an open-flask, considerably mild reaction conditions, and acceptable reaction time (6 h) without additional catalyst. Scale-up synthesis could also be performed in this study. Although both para- and ortho-nitroanilides were formed, they could be readily separable by using a simple chromatographic technique. Additionally, the synthetic entry to both para- and ortho-nitroanilides, especially those possessing interesting chemical and biological activities, should be attractive where the structure-activity relationship (SAR) study are required.

**Experimental**

All reagents and solvents were purchased and used without further purification. Column chromatography was performed by using Merck silica gel 60 (Art 7734). NMR spectra were recorded on a Bruker-400 (¹H NMR at 400 MHz and ¹³C NMR at 100 MHz), a Bruker-500 (¹H NMR at 500 MHz and ¹³C NMR at 125 MHz), and a JNM-ECZS (¹H NMR at 400 MHz and ¹³C NMR at 100 MHz) spectrometer in CDCl₃, CD₃OD, or (CD₃)₂SO using TMS as an internal standard. Melting points were obtained on a Büchi M-565 Melting Point apparatus and uncorrected. IR spectra were recorded on an ALPHA FTIR spectrometer. The high-resolution mass spectra were recorded on an HR-TOF-MS Micromass model VQ-TOF2 mass spectrometer. Mass spectra were recorded with a Thermo Finnigan Polaris Q mass spectrometer.

**Nitration of 1 using AgNO₃/K₂S₂O₈ combination: General procedure**

Anilide 1a (67.8 mg, 0.5 mmol, 1.0 equiv.), AgNO₃ (170.0 mg, 1.0 mmol, 2.0 equiv.), and K₂S₂O₈ (203.1 mg, 0.75 mmol, 1.5 equiv.) were placed in a 10 mL round-bottom flask equipped with a condenser and dissolved by acetonitrile (3 mL). The reaction flask was placed in a pre-heated oil bath and stirred at reflux for 6 h. After cooling to room temperature, the reaction mixture was quenched with water (3 mL) and extracted with
EtOAc (3 × 10 mL). The combined organic layer was dried (anh. Na2SO4), filtered, and evaporated. Purification by column chromatography (SiO2, 40% EtOAc/hexanes) gave o-2a (31.0 mg, 34% yield) and p-2a (33.8 mg, 38% yield). o-2a: yellow solid; Rf 0.50 (40% EtOAc/hexanes); 1H NMR (400 MHz, CDCl3): δ 10.32 (br s, 1H, N H), 8.76 (dd, J = 1.0, 8.6 Hz, 1H, ArH), 8.20 (dd, J = 1.4, 8.6 Hz, 1H, ArH), 7.64 (ddd, J = 1.5, 7.3, 8.5 Hz, 1H, ArH), 7.17 (ddd, J = 1.4, 7.4, 8.6 Hz, 1H, ArH), 2.29 (s, 3H, CH3) ppm. 13C NMR (100 MHz, CDCl3): δ 169.2 (CO), 136.5 (C), 136.1 (CH), 135.0 (C), 125.9 (CH), 123.4 (CH), 122.3 (CH), 25.8 (CH3) ppm. MS: m/z (%) 181 (100) [M + H]+, 180 (43) [M]+, 138 (77). HRMS (ESI-TOF): calcd. for C8H8N2O3Na [M + Na]+ 203.0427; found 203.0425.

p-2a: pale-yellow solid; Rf 0.19 (40% EtOAc/hexanes); 1H NMR (400 MHz, CDCl3 + CD3OD): δ 8.11–8.06 (m, 2H, ArH), 7.69–7.64 (m, 2H, ArH), 2.09 (s, 3H, CH3) ppm. 13C NMR (100 MHz, CDCl3 + CD3OD): δ 170.5 (CO), 144.7 (C), 143.0 (C), 124.8 (2 × CH), 119.0 (2 × CH), 23.8 (CH3) ppm. MS: m/z (%) 181 (39) [M + H]+, 180 (41) [M]+, 138 (100), 108 (65). HRMS (ESI-TOF): calcd. for C8H8N2O3Na [M + Na]+ 203.0427; found 203.0424.

Copies of 1H and 13C NMR spectra of all compounds are available in the Supporting Information associated with this manuscript.

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