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# Eco-friendly reductive acetamidation of arylnitro compounds by thioacetate anion through in situ catalytic regeneration: application in the synthesis of Acetaminophen™

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**Abstract**—A novel one-step reductive acetamidation of arylnitro compounds mediated by thioacetate anion in thioacetic acid via in situ catalytic regeneration was developed and applied to an efficient synthesis of Acetaminophen™.


Earlier we reported a simple and highly efficient potassium thioacetate mediated one-pot conversion of aryl nitro compounds to aryl acetamides.[1] The reactions are conducted by employing potassium thioacetate (4 equiv) as a nucleophile in dipolar aprotic solvents or in a solvent-free environment in the presence of catalytic amounts of polyethylene glycol (PEG) type surfactants such as Triton-X.[2] Although the acetamidation proceeds well with useful levels of conversion and efficiency, its utility is limited by the use of a large amount of relatively expensive potassium thioacetate. The process is also encumbered by excessive amounts of environmentally unacceptable salt-waste formation, leading to complex isolation as well as high disposal cost. Furthermore, use of stoichiometric amounts of the highly nucleophilic thioacetate anion results in unwanted nucleophilic displacement of halogens as well as dealkylative methoxy cleavage in electron-poor aromatic systems. This report describes a facile and cost-effective surfactant-mediated one-pot reductive acetamidation of aryl nitro derivatives utilizing inexpensive thioacetic acid in conjunction with catalytic amounts of base such as potassium carbonate through in situ catalytic regeneration of thioacetate anion as the nucleophile. The presence of catalytic potassium carbonate is essential; no reductive acetamidation was observed in its absence in thioacetic acid under otherwise identical conditions.[3] The need for such methodology originated from our Industry–University collaborative research program directed towards developing efficient and environmentally friendly pharmaceutical processes.[4]

The mechanism proposed for the reductive acetamidation involves a sequential nucleophilic attack of the thioacetate anion on the nitro function producing the acyl intermediate **2a** followed by an energetically favorable intramolecular acetyl shift from S to oxygen producing the second acyl intermediate **3a**. Both **2a** and **3a** could potentially act as in situ acetyl donor equivalents and lead directly to the desired acetanilide after sulfur expulsion (Scheme 1).[1,5] Since thioacetic acid is a stronger acid ($pK_a = 3.33$) than acetic acid ($pK_a = 4.76$), it occurred to us that the acetate anion generated in the scheme should deprotonate thioacetic acid, regenerating the thioacetate anion thereby rendering the process catalytic with respect to thioacetate anion. Thus, conceptually, the process could be carried out in thioacetic acid itself in the presence of catalytic amount of a base such as potassium carbonate. These expectations were fully realized resulting in an efficient, solvent-free, one-pot acetamidation of aryl nitro compounds utilizing a unique acid–base system consisting of thioacetic acid in conjunction with catalytic amounts of potassium carbonate under essentially salt-free conditions.

The catalytic nitroamidation protocol involves treating a mixture of the aryl nitro compound (1 equiv) with thioacetic acid (4–8 equiv) and potassium carbonate

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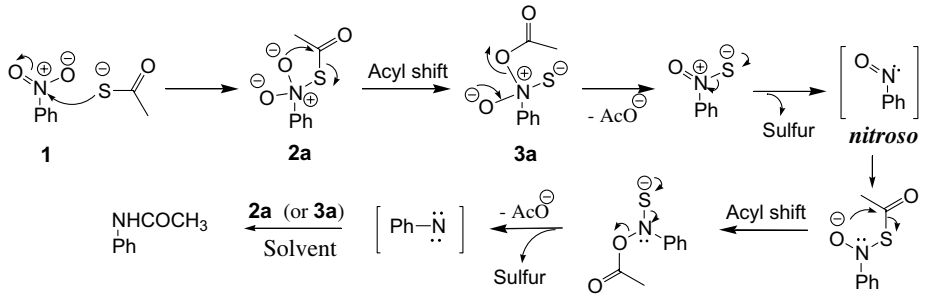
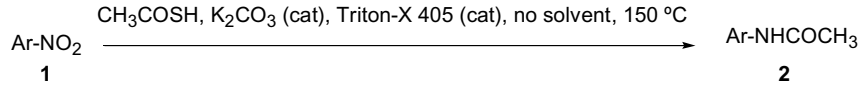



**Scheme 1.** Proposed mechanism of thioacetate mediated reductive amidation.

(5 mol %) at 150 °C. The reaction was monitored by HPLC until completion. Since the reaction is conducted in the absence of a large amount of a strong sulfur nucleophile, it obviates the shortcomings associated with the undesired nucleophilic displacement of aryl halides or dealkylative methoxy cleavage by thioacetate anion (Table 1, entries 4, 5, 6 and 9) thereby essentially complementing the nucleophilic protocol reported earlier.[1] The presence of Triton-X is imperative; the reactions conducted without Triton-X 405 was considerably slower (three to five times) under otherwise identical conditions.[2] The process is essentially salt-free and is performed neat; the product is directly obtained by distillative removal of thioacetic acid. No exhaustive workup to remove the large amounts of salt was necessary, thus leading to significant process simplicity. These conditions were successfully applied to prepare various arylacetamides from a representative group of aryl nitro compounds in good yields (Table 1). The one-step acetamidation technology was successfully utilized to convert *p*-nitrophenol in a single step to *p*-hydroxyacetamide (Acetaminophen™ or Tylenol®) in 78% yield. A typical experimental procedure is as follows: Under nitrogen, a stirred mixture of 4-chloro-1-nitrobenzene (1 g, 6.35 mmol), thioacetic acid (1.93 g, 25.39 mmol), $K_2CO_3$ (0.050 g, 0.36 mmol), and dry Triton-X 405 (0.010 g) was heated at 150 °C. The progress of the reaction was monitored by HPLC and GC. After 4 h the reaction was cooled to room temperature, and acetone (8 mL) was added and filtered through a sintered glass funnel. Evaporation of the acetone in vacuo produced 0.975 g of *N*-(4-chloro-phenyl)-acetamide (91%). It needs to be stressed that the mechanism depicted in Scheme 1 although served as a guide for designing the salt-free protocol, is hypothetical at best, and the mechanistic course is undoubtedly complicated and is yet to be established. Preliminary results indicated the formation of $S_8$ (fingerprint GCMS) in the reaction as depicted in the scheme. When nitrosobenzene (a proposed intermediate in the reaction) was subjected under the reaction conditions, acetanilide was produced in 80% yield providing indirect support for the hypothesis (entry 13).

In conclusion, we have developed an efficient, salt-free environmentally friendly one-pot acetamidation of aryl nitro compounds under essentially non-nucleophilic conditions. The reaction is performed without solvent in the presence of catalytic amounts of surfactant and base. The acetamidation chemistry was successfully utilized to convert *p*-nitrophenol in a single step to *p*-hydroxyacetamide (Acetaminophen™ or Tylenol®) in good yield. The fact that the reactions proceed to high conversions, selectivity and vessel efficiency renders the process practical and economically attractive and demonstrates yet another facet

**Table 1.** Thioacetate anion promoted acetamidation of arylnitro compounds via in situ catalytic regeneration[6]




| Entry | Substrate (Ar) | Product | Time (h) | Yield (%) |
|---|---|---|---|---|
| 1 | 1-Isopropyl-4-nitrobenzene | *N*-(4-Isopropyl-phenyl)-acetamide | 114 | 77 |
| 2 | 1-Ethyl-4-nitrobenzene | *N*-(4-Ethyl-phenyl)-acetamide | 67 | 84 |
| 3 | 4-Nitrotoluene | *N*-*p*-Tolyl-acetamide | 67 | 69 |
| 4 | 2-Bromo-4-nitrotoluene | *N*-(3-Bromo-4-methyl-phenyl)-acetamide | 5 | 99 |
| 5 | 4-Chloro-1-nitrobenzene | *N*-(4-Chloro-phenyl)-acetamide | 4 | 93 |
| 6 | 1-Bromo-2-nitrobenzene | *N*-(2-Bromo-phenyl)-acetamide | 13 | 81 |
| 7 | Nitrobenzene | *N*-Phenyl acetamide | 14 | 76 |
| 8 | 4-Nitrophenol | *N*-(4-Hydroxy-phenyl)-acetamide | 18 | 78 |
| 9 | 4-Nitroanisole | *N*-(4-Methoxy-phenyl)-acetamide | 67 | 67 |
| 10 | 2,3-Dichloro-1-nitrobenzene | *N*-(2,3-Dichloro-phenyl)-acetamide | 14 | 78 |
| 11 | 2-Nitrophenol | *N*-(2-Hydroxy-phenyl)-acetamide | 18 | 73 |
| 12 | 2-Nitroaniline | *N*-(2-Amino-phenyl)-acetamide | 10 | 28 |
| 13 | Nitrosobenzene | *N*-Phenyl acetamide | 1 | 80 |

of the utility of the surfactant-mediated solvent-free technology in organic synthesis.

## Acknowledgements

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6. (a) All of the compounds gave a $^{13}C$ resonance of $169 \pm 2$ ppm, indicative of the amide carbon and a resonance at $24 \pm 2$ ppm indicative of the acetamide methyl. The $^{13}C$ and $^{1}H$ NMR spectra were consistent with the predictions made by CNMR and HNMR programs (ACD/Labs,V8.0); (b) For all the compounds GCMS analysis (Shimadzu QP5050A) in EI mode provided similarity index match of >90% compared to the authentic samples in the NIST-98 database.