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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 1861–1864

One-step reductive amidation of nitro arenes: application in the synthesis of Acetaminophen™

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Received 1 September 2005; revised 16 September 2005; accepted 16 September 2005
Available online 30 January 2006

Abstract—A novel thioacetate mediated one-step reductive acetamidation of aryl nitro compounds was developed and applied to an efficient synthesis of acetaminophen. The reaction also proceeds well without a solvent in the presence of a catalytic amount of surfactant.
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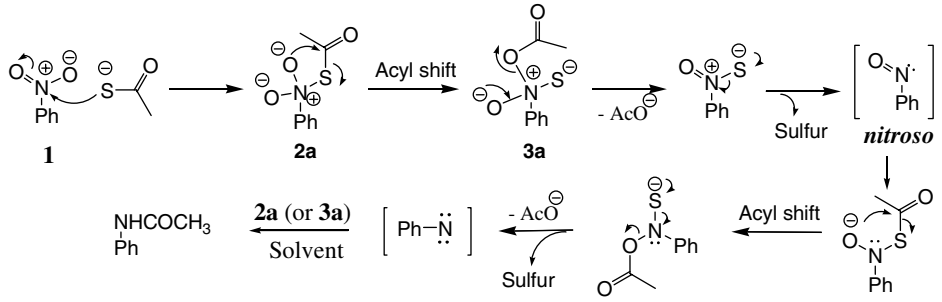
1. Introduction

Aryl amides are versatile synthetic intermediates, and are important structural elements of several drug candidates.[1] Traditional two-step syntheses of *N*-arylacetamides involving reduction of nitroarenes followed by acylation via activated carboxylic acids are well documented.[2] However, direct, one-step conversions of nitro group to acetamides without the intermediacy of the amine and the obligatory activation of carboxylic acid are nontrivial and suffer from unwanted by-product formation such as N,O-diacetylated derivatives.[3] A solution to this problem originated from an earlier report describing an efficient reduction of aromatic nitro compounds to the corresponding amines employing sodium trimethylsilanethiolate (NaSTMS). The proposed mechanism involved a nucleophilic attack by TMS–$S^{(-)}$ on the $-NO_2$ group followed by energetically favorable intramolecular TMS shift from S to O and eventual expulsion of sulfur.[4] Conceptually, the strategy could be extended to reductive amidation of NO_2 by replacing TMS–$S^{(-)}$ with $CH_3COS^{(-)}$, with the acetyl group acting as a TMS surrogate. Thus, sequential nucleophilic attack of the thioacetate anion producing the acyl intermediate **2a** would be followed by an energetically favorable intramolecular acetyl shift from sulfur to oxygen (analogous to the TMS shift) 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).[5]



Scheme 1. Proposed mechanism of thioacetate mediated reductive amidation.

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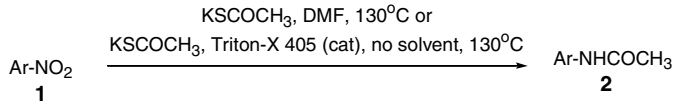
doi:10.1016/j.tetlet.2005.09.196

Table 1. Thioacetate mediated acetamidation of arylnitro compounds



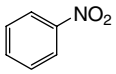
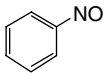
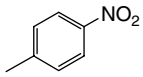
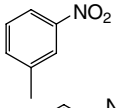
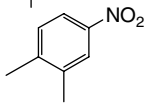
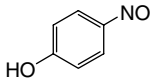
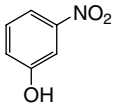
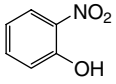
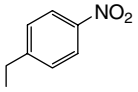
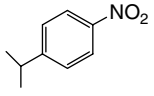
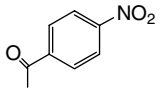
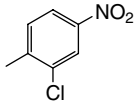
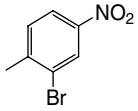
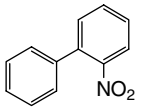
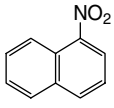
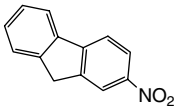
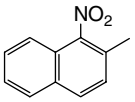
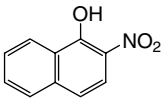
Entry	1	Time (h)	% Conversion[a] (% yield)[b]	
			DMF	Solvent free
1		2	97 (83)	96 (78)
2		1	98 (85)	95 (75)
3		2	94 (85)	95 (77)
4		2	94 (86)	94 (73)
5		2	95 (88)	95 (78)
6		1	90 (60)	90 (55)
7		1	90 (62)	88 (58)
8		1	90 (65)	85 (60)
9		2	95 (85)	94 (76)
10		2	95 (88)	93 (79)
11		1	80 (65)	70 (60)
12		2	92 (85)	88 (75)
13		2	95 (85)	90 (78)
14		3	85 (75)	75 (68)
15		3	90 (87)	88 (75)

Table 1 (*continued*)

Entry	1	Time (h)	% Conversion[a] (% yield)[b]	
			DMF	Solvent free
16		2	80 (75)	77 (64)
17		3	98 (87)	95 (78)
18		3	95 (70)[c]	93 (65)[c]

[a] Conversion based on GC and HPLC.
[b] All products exhibited satisfactory spectral properties (^{1}H NMR and ^{13}C NMR) fully in accord with known or expected values.[9]
[c] The isolated product was a 1:1 mixture of the expected amide and the oxazole derivative namely, 2-methyl-1-oxa-3-aza-cyclopenta[*a*]-naphthalene  .

These expectations were fully realized, resulting in a simple and efficient potassium thioacetate-mediated one-step acetamidation of various aryl nitro compounds under essentially neutral conditions. Representative examples are summarized in Table 1. A typical experimental procedure is as follows: Under nitrogen, a stirred mixture of potassium thioacetate (3.71 g, 32.5 mmol), nitrobenzene (1 g, 8.1 mmol), and DMF (2.0 ml) was heated at 130 °C. The progress of the reaction was monitored by HPLC and GC. After 2 h, the reaction mixture was cooled to room temperature, brine (2 ml) was added, and the resulting mixture was extracted with *tert*-butyl methyl ether (2×15 ml). The combined organic layers were washed with brine (2×4 ml) to remove residual DMF and filtered through a pad of charcoal and Celite to remove any residual sulfur. Evaporation of the solvent in vacuo produced 0.9 g of acetanilide (83%). Although the hypothetical pathway depicted in Scheme 1 served as a guide for designing the acetamidation protocol, the mechanistic course is undoubtedly complicated and is speculative, at best, at this point. Preliminary results indicated the formation of S_8 (fingerprint GC–MS) in the reaction as depicted in Scheme 1. Under the reaction conditions, nitrosobenzene, a proposed intermediate, also produced acetanilide in >95% conversion.[6] The reductive amidation of nitrobenzene failed to proceed in thioacetic acid itself. Remarkably, 1-hydroxy-2-nitronaphthalene, when subjected to the acetamidation conditions, afforded a mixture of the expected amide and the corresponding oxazole-derivative, produced via cyclization of the –OH and the amide group.

2. Synthesis of Acetaminophen™

The one-step acetamidation technology was successfully utilized to convert *p*-nitrophenol in a single step to *p*-hydroxyacetamide (Acetaminophen™) in >95% conversion. Interestingly, *p*-nitroanisole, when treated with $KSCOCH_3$ (4 equiv) in DMF under otherwise identical conditions, was also converted to acetaminophen as a result of the concomitant methoxy-cleavage followed by acetamidation of the $-NO_2$ group; *p*-nitrophenol was produced as an intermediate in this process as evidenced by HPLC and GC–MS analysis, and *p*-nitrophenol was the major product when 1 equiv of potassium thioacetate was utilized.

3. Solvent-free acetamidation

Earlier, we described an efficient solvent-free synthesis of nitroalcohols utilizing a novel dual catalytic system consisting of a mineral base (e.g., KOH) and polyethylene glycol (PEG) type Triton-X surfactant under homogeneous conditions.[7] The crown ether-like complementary nature of the various types of Triton-X and their differential solubilization tendencies for specific counter-ions was demonstrated.[8] Surfactant-mediated protocols were also successfully extended to the conversion of aryl nitro compounds to aryl acetamides. Thus, solvent-free acetamidation reactions involved treating a mixture of the aryl nitro compound (1 equiv) with potassium thioacetate (4 equiv) in the presence of Triton-X 405 (cat) at 130 °C for 3 h producing the corresponding arylacetamide in good to excellent yields (Table 1).

In summary, we have developed a novel, one-step acetamidation of aryl nitro compounds. The reaction could be performed without solvent in the presence of a catalytic amount of surfactant. The acetamidation chemistry was successfully utilized to convert *p*-nitrophenol in a single step to *p*-hydroxyacetamide (Acetaminophen™) in approximately 90% conversion. Further extension of this technology for the synthesis of various heterocycles starting from suitably substituted aryl 2-nitro derivative is in progress.

Acknowledgements

Financial support provided by the Petroleum Research Fund (PRF), National Institute of Health (NIH), Welch Foundation, and Bristol Myers Squibb Corporation is gratefully acknowledged.

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1. (a) Zhang, Z.; Yin, A.; Kadow, J. F.; Meanwell, N. A.; Wang, T. J. *J. Org. Chem.* **2004**, *69*, 1360; (b) Lidocaine. In *Merck Index*, 12th ed.; Budavari, S., Ed.; Merck, 1996; Vol. 5505, p 936; (c) Ballini, R.; Bosica, G.; Fiorini, D. *Tetrahedron* **1998**, *59*, 1143; (d) Katritzky, A. R.; He, H.-Y.; Suzuki, K. *J. Org. Chem.* **2000**, *65*, 8210.
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3. Kim, B. H.; Han, R.; Piao, F.; Jun, Y. M.; Baik, W.; Lee, B. M. *Tetrahedron Lett.* **2003**, *44*, 77, and references cited therein.
4. (a) Hwuk, J. R.; Wong, F. F.; Shiao, M.-J. *J. Org. Chem.* **1992**, *57*, 5254; (b) Shiao, J.-J.; Long-Li, L.; Wei-Shan, K.; Lin, P.-Y.; Hwu, J. R. *J. Org. Chem.* **1993**, *58*, 4742; (c) The formation of nitrosobenzene via an alternate pathway involving the nucleophilic attack of *RS*(−) on the oxygen of the nitro functionality can not be ruled out.
5. (a) Average bond energy of C–S is 65 kcal/mol, C–C is 83 kcal/mol and C–Si is 83 kcal/mol; data obtained from Michigan State University–Organic home page website (http://www.cem.msu.edu/~reusch/OrgPage/bndenrgy.htm); For analogous O- to C-acyl migration, see Baker–Venkataraman rearrangement: (b) Bowden, K.; Chehel-Amiran, M. *J. Chem. Soc., Perkin Trans. 2* **1986**, 2039.
6. An alternate mechanism could involve S–S bond formation thereby delivering two electrons in the form of a hydride (H^-). The S–S bond formation has precedence in peptide chemistry of cysteine. The resulting dithiane can act as an effective acylating agent.
7. Bhattacharya, A.; Purohit, V. C.; Rinaldi, F. *Org. Proc. Res. Dev.* **2003**, *7*, 254.
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9. (a) All of the compounds gave a ^{13}C resonance of 169 ± 2 ppm, indicative of the amide carbon and a resonance at 24 ± 2 ppm indicative of the acetamide methyl. The ^{13}C and ^{1}H NMR spectra were consistent with the products in coupling and chemical shift data; (b) For all the compounds GC–MS analysis (Shimadzu QP5050A) in the EI mode provided similarity index match of >90% compared to the authentic samples in the NIST-98 database.