Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 47 (2006) 1861–1864
Tetrahedron Letters

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

Apurba Bhattacharya,[a,*] Vikram C. Purohit,[a] Victor Suarez,[a] Ritesh Tichkule,[a] Gaurang Parmer[a] and Frank Rinaldi[b]

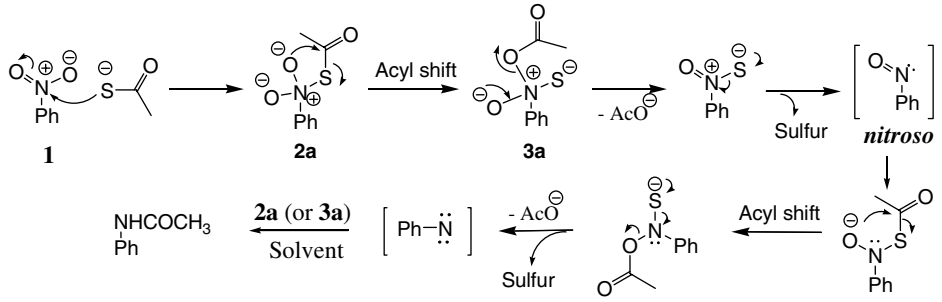
[a]*Department of Chemistry, Texas A&M University-Kingsville, Kingsville, TX 78363, USA*
[b]*Department of Process Research, Bristol-Myers Squibb, Pharmaceutical Research Institute, One Squibb Drive, PO Box 191, New Brunswick, NJ 08903-0191, USA*

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.
© 2006 Elsevier Ltd. All rights reserved.

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]

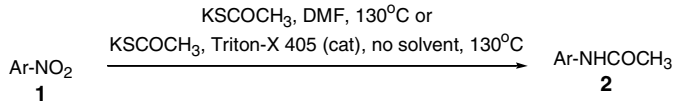


Scheme 1. Proposed mechanism of thioacetate mediated reductive amidation.

* Corresponding author. Tel.: +1 361 593 2664; fax: +1 361 593 3597; e-mail: kfab002@tamuk.edu

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.09.196

Table 1. Thioacetate mediated acetamidation of arylnitro compounds



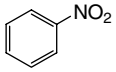
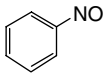
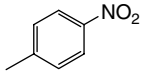
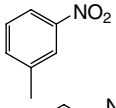
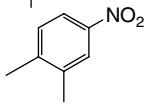
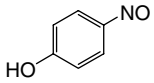
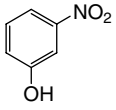
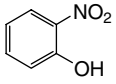
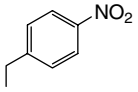
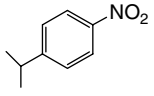
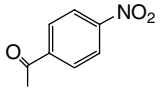
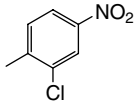
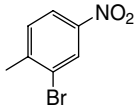
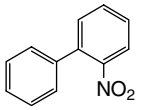
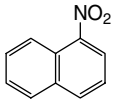
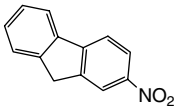
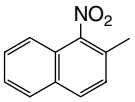
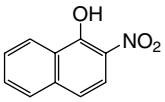
Entry	1	Time (h)	% Conversion[a] (% yield)[b]	
			DMF	Solvent free
1		2	97 (83)	96 (78)
2		1	98 (85)	95 (75)
3		2	94 (85)	95 (77)
4		2	94 (86)	94 (73)
5		2	95 (88)	95 (78)
6		1	90 (60)	90 (55)
7		1	90 (62)	88 (58)
8		1	90 (65)	85 (60)
9		2	95 (85)	94 (76)
10		2	95 (88)	93 (79)
11		1	80 (65)	70 (60)
12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

References and notes

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.
2. (a) Nishimura, S. *Bull. Chem. Soc. Jpn.* **1961**, *34*, 32; (b) Adams, R.; Cohen, F. L. *Org. Synth. Coll.* **1932**, *1*, 240; (c) Mendennhall, G. D.; Smith, P. A. S. *Org. Synth. Coll.* **1973**, *5*, 829; (d) Adkins, H.; Connar, R. *J. Am. Chem. Soc.* **1931**, *53*, 1091; (e) Davies, R. R.; Hodgson, H. H. *J. Chem. Soc.* **1943**, 281; (f) Broadbent, H. S.; Slaugh, L. H.; Jarvis, N. L. *J. Am. Chem. Soc.* **1954**, *76*, 1519; (g) Tsukinoki, T.; Tsuzuki, H. *Green. Chem.* **2001**, *3*, 37–38; (h) Hodgson, H. H.; Whitehurst, J. S. *J. Am. Chem. Soc.* **1945**, 202; (i) Wang, L.; Zhou, L.; Zhang *Synlett* **1999**, 1065; (j) Pitts, M. R.; Harrison, J. R.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 955; (k) Blackie, J. A.; Turner, N. J.; Wells, A. S. *Tetrahedron Lett.* **1997**, *38*, 3043.
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.
8. (a) Rebeck, J. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 245; (b) March, J. In *Adv. Org. Chem.*, 4th ed.; John Wiley, 1992; pp 82–93; and references cited therein.
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.