One-pot reductive conversion of nitroarenes to *N*-arylacetamides mediated by metallic samarium

Yandong Zhang[a] and Yongmin Zhang[a,b,*]

[a]*Department of Chemistry, Zhejiang University, Xixi Campus, Hangzhou, Zhejiang, 310028, P.R. China*

[b]*State Key Laboratory of Organometallic Chemistry, Chinese Academy of Sciences, Shanghai, 200032, P. R. China*

Nitroarenes can be reduced and then converted to *N*-arylacetamides by metallic samarium in the presence of acetic anhydride, acetic acid and methanol in excellent yields by a one pot-procedure.

As an excellent single electron transfer and ether soluble reagent, samarium diiodide has been widely used in organic synthesis since Kagan had shown a simple method for the preparation of samarium diiodide from samarium metal and 1,2-diiodoethane.[1,2] Recently direct using of metallic samarium as a reducing agent in organic transformations has also drawn the attention of many organic chemists.[3]

Amides are important constitutuents of many biologically significant materials and the preparation of amides in organic synthesis is significant. Generally, the preparation of *N*-arylacetamides involves two steps, *i.e.* reduction of nitroarenes to *N*-arylamines[4] followed by the acylation of *N*-arylamines to the corresponding *N*-arylacetamides. Although other metal reagents have been employed to convert nitroarenes to arylacetamides in one-pot procedures[5] and various samarium reagents are often used to reduce nitroarenes to the corresponding aminoarenes,[6] reports on one-pot conversion of nitroarenes to arylacetamides using a samarium reagent have never been seen. Compared with other metal reagents such as indium, tellurium, low valent titanium and Pd/C, samarium is much cheaper and more readily available. This application of metal samarium in organic synthesis may therefore be valuable.

Here we report that mediated by metallic samarium, nitroarenes can be reduced and then converted to *N*-arylacetamides in the presence of acetic anhydride, acetic acid and methanol in excellent yields by a one pot-procedure (Scheme 1).

In order to get the optimum reaction conditions, various reaction conditions have been examined for this one-pot conversion of nitroarenes to *N*-arylacetamides. After a series of trials, we found that the best results are obtained when nitrobenzene (1 equiv.) was subjected to Ac₂O (2.25 equiv.), AcOH (9 equiv.) and samarium (4.5 equiv.). The amount of samarium cannot be decreased; otherwise substrates cannot be fully reduced. For example, 3 equiv. or 2.25 equiv. samarium were used, however, yields of *N*-arylacetamides are poor. Under the optimum conditions we found that substituted nitroarenes are converted to the corresponding *N*-arylacetamides and the results are listed in Table 1.

As shown in Table 1, the reaction proceeds smoothly and good to excellent yields are obtained from various substituted nitroarenes. As far as some of the nitroarenes are concerned, yields are moderate and we found that by-products are *N*-arylamines. In view of this, an extra amount of Ac₂O is added to guarantee the high yields (Entries 3, 7, 8).

Dinitroarenes can also be reacted under conditions using double the amount of metallic samarium, acetic anhydride and acetic acid. The reaction of 2,4-dinitro-phenol gives *N*-(3-acetylamino-4-hydroxy-phenyl)-acetamide (**2i**) in excellent yields (Entry 9). However, products of 1-chloro-2,4-dinitro-benzene and 1-fluoro-2,4-dinitro-benzene under these reaction

* Correspondence. E-mail: yongminzhang@css.zju.edu.cn
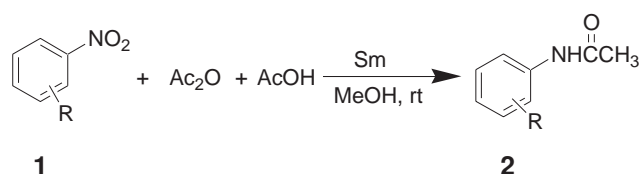
Scheme 1

conditions are unexpected (Entries 10, 11). Take 1-chloro-2,4-dinitro-benzene for example, the major product was *N*-(3-amino-4-chloro-phenyl)-acetamide (**2j**) while a by-products were *N*-(3-acetylamino-4-chloro-phenyl)-acetamide (**2j'**) and a small amount of 4-chloro-benzene-1,3-diamine. The result of reaction using 1-fluoro-2,4-dinitro-benzene as substrate was similar to that with 1-chloro-2,4-dinitro-benzene (Scheme 2). Many trials were made to investigate this reaction under different conditions. The results indicate that the amount of samarium cannot be reduced; otherwise, products will be complicated. If the amount of acetic anhydride is reduced to less than 4.5 equiv, the yield of by-product a 4-halo-benzene-1, 3-diamine will be increased. Although increasing the amount of acetic anhydride improved the yield of compound **5**, the effect is not conspicuous. For example, the reaction was conducted with 9 equiv. anhydride under the same condition, the yield of compound **5** is increased to 15%.

This high selectivity is meaningful, because there are few reports on the synthesis of *N*-(3-amino-4-chloro-phenyl)-

**Table 1** One-pot reductive conversion of nitroarenes to N-arylacetamides mediated by metallic samarium

Entry	R	The amount of Ac₂O/equiv	Reaction time/h	Products 2	Yield/ %[a]
1	*o*-OH	2.25	1.5	**2a**	90
2	*p*-CH₃	2.25	1.5	**2b**	89
3	*p*-Cl	3.25	1.5	**2c**	89
4	*o*-CH₃	2.25	1.5	**2d**	88
5	H	2.25	1.5	**2e**	85
6	*o*-Cl	2.25	1.5	**2f**	80
7	*p*-OH	3.25	1.5	**2g**	80
8	(1-nitronaphthalene)	3.25	1.5	**2h**	80
9[b]	(2,4-dinitrophenol)	4.5	2	**2i**	90
10[b]	(1-chloro-2,4-dinitrobenzene)	4.5	10	**2j**	85
				2j'	10
11[b]	(1-fluoro-2,4-dinitrobenzene)	4.5	10	**2k**	70
				2k'	20

[a]Yield of isolated products. [b]The amount of samarium, acetic anhydride and acetic acid are all doubled when dinitroarenes are reacted as the substrates.

Table 2 One-pot reductive conversion of nitroarenes to arylamides mediated by metallic samarium, acid and anhydride.

Nitroarene	Acid	Anhydride	Reaction time	Yield/%[a]
p-CH$_3$C$_6$H$_4$NO$_2$	Benzoic acid	Benzoic anhydride	24	25
p-ClC$_6$H$_4$NO$_2$	Benzoic acid	Benzoic anhydride	24	24
p-CH$_3$C$_6$H$_4$NO$_2$	Propionic acid	Propionic anhydride	24	32
p-ClC$_6$H$_4$NO$_2$	Propionic acid	Propionic anhydride	24	34
p-CH$_3$C$_6$H$_4$NO$_2$	Hexanoic acid	Hexanoic anhydride	24	35
p-ClC$_6$H$_4$NO$_2$	Hexanoic acid	Hexanoic anhydride	24	33

[a]Products were corresponding arylamides
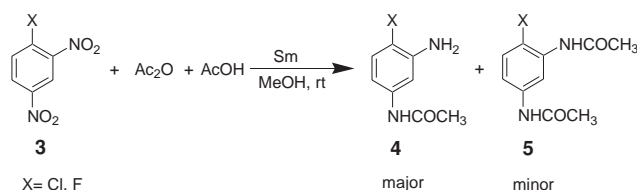
Scheme 2

acetamide (**2j**).[7] Furthermore, *N*-(3-amino-4-chloro-phenyl)-acetamide (**2j**) and *N*-(3-amino-4-fluoro-phenyl)-acetamide (**2k**) are important materials in the chemical industry and have been widely used to synthesise dyestuffs, pigments, herbicides and so on.[8]

Other acids and anhydrides can also be used for this kind of reaction instead of acetic acid and acetic anhydride; however, yields of the corresponding amides are poor. The results are listed in Table 2. We observed that many substrates are recovered and the poor yields are due to low reactivity of these acids and anhydrides.

In conclusion, nitroarenes can be reduced and then converted to *N*-arylacetamides mediated by metallic samarium in the presence of acetic anhydride, acetic acid and methanol in excellent yields by one pot-procedure. The reaction can be easily operated and the reaction conditions are mild. It is a good way to synthesise *N*-arylacetamides using metallic samarium.

Experimental

General: Melting points were uncorrected. Infrared spectra were recorded on an IR-408 spectrometer in KBr or film with absorption in cm^{-1}. ^{1}H NMR spectra were determined in a Bruker AC–400 spectrometer as CDCl$_3$ solutions. *J* values are in Hertz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Mass spectra were recorded on a HP 5989B MS spectrometer and Bruker esquire 3000 plus. Microanalysis was carried out on a EA 1110 instrument. Product **2h** and **2i** were further characterised by the H-H NOZY NMR. MeOH was redistilled from magnesium before use. The reaction was monitored by TLC, and products were crystallised from ethanol.

Typical procedure for the synthesis of N-phenyl-acetamide (**2e**): Nitrobenzene (0.123 g, 1 mmol), acetic acid (0.516 ml, 9 mmol) and acetic anhydride (0.213 ml, 2.25 mmol) were dissolved in 5 ml methanol freshly distilled from magnesium. The solution was injected in a three-necked flask to which was added Sm powder (0.675 g, 4.5 mmol) in advance. At room temperature, the reaction proceeded under the protection of nitrogen. After being stirred for a given time (Table 1, the reaction was monitored by TLC), the reaction mixture was extracted with ethyl acetate (3×30 ml). The organic phase was washed with water (20 ml), saturated brine (15 ml), and dried over anhydrous Na$_2$SO$_4$. The solvents were removed under reduced pressure to give the crude product, which was purified by column chromatography. The product was finally recrystallised from ethanol and afforded N-phenyl-acetamide in 85% yield.

N-(2-Hydroxy-phenyl)-acetamide (**2a**): m.p. 210–211 °C (lit. 209 °C)[9a]. ν$_{max}$(KBr)/cm^{-1}: 3404, 3083, 2881, 2743, 1657, 1614, 1594. δ$_H$(CDCl$_3$): 8.66 (1H, s), 7.471–7.476 (1H, broad), 7.11–7.15 (1H, m), 6.98–7.03 (2H, m), 6.84–6.88 (1H, m), 2.27 (3H, s) *m/z*(%): 173.9 (M+Na)$^+$. Anal. C$_8$H$_9$NO$_2$. Calcd. C, 63.56; H, 6.00; N, 9.27. Found C, 63.52; H, 6.03; N, 9.24%.

N-p-Tolyl-acetamide (**2b**): m.p. 147–148 °C (lit. 146 °C)[9a]. ν$_{max}$(KBr)/cm^{-1}: 3291, 3066, 2944, 2919, 1662, 1609. δ$_H$(CDCl$_3$): 7.38–7.40 (2H, m), 7.11–7.16 (3H, m, broad), 2.34 (3H, s), 2.19 (3H, s). *m/z*(%): 150 (M$^+$+1, 3.78), 149 (M$^+$, 33.82), 107 (100), 106 (91.24), 91 (3.63), 77 (18.95), 43 (30.21). Anal. C$_9$H$_{11}$NO$_2$. Calcd. C, 72.46; H, 7.43; N, 9.39. Found C, 72.57; H, 7.33; N, 9.34%.

N-(4-Chloro-phenyl)-acetamide (**2c**): m.p. 180 °C (lit. 178.4 °C)[9a]. ν$_{max}$(KBr)/cm^{-1}: 3304, 3192, 1665, 1608. δ$_H$(CDCl$_3$): 7.46–7.48 (2H, m), 7.28–7.31 (3H, m, broad), 2.19 (3H, s). *m/z*(%): 171 (M$^+$+2, 5.30), 170 (M$^+$+1, 2.78), 169 (M$^+$, 16.23), 129 (33.62), 127 (100), 111(1.54), 92 (13.90), 91(6.74), 43 (76.95). Anal. C$_8$H$_8$ClNO. Calcd. C, 56.65; H, 4.75; N, 8.26. Found C, 56.19; H, 4.72; N, 8.28%.

N-o-Tolyl-acetamide (**2d**): m.p. 108 °C (lit. 110 °C)[9a]. ν$_{max}$(KBr)/cm^{-1}: 3444, 3290, 1650, 1587, 1529. δ$_H$(CDCl$_3$): 7.78–7.80 (1H, m), 7.20–7.26 (2H, m), 7.09–7.13 (1H, m), 6.97 (1H, broad), 2.29 (3H, s), 2.24 (3H, s). *m/z*(%):150 (M$^+$+1, 4.71), 149 (M$^+$, 31.82), 134 (0.9), 107 (100), 106 (80.64), 91 (4.85), 77 (16.99), 43 (58.62). Anal. C$_9$H$_{11}$NO. Calcd. C, 72.46; H, 7.43; N, 9.39. Found C, 72.81; H,7.46; N, 9.90%.

N-Phenyl-acetamide (**2e**): m.p. 114–115 °C (lit. 115–116 °C)[9a]. ν$_{max}$(KBr)/cm^{-1}: 3294, 3136, 1664, 1599, 1557. δ$_H$(CDCl$_3$): 7.50–7.52 (2H, m), 7.31–7.35 (2H, m), 7.21 (1H, broad), 7.10–7.14 (1H, m), 2.2 (3H, s). *m/z*(%):136 (M$^+$+1, 2.37), 135 (M$^+$, 20.21), 93 (100), 77 (3.77), 43 (34.38). Anal. C$_8$H$_9$NO. Calcd. C, 71.09; H, 6.71; N, 10.36. Found C, 71.22; H, 6.78; N, 10.38%.

N-(2-Chloro-phenyl)-acetamide (**2f**): m.p. 87 °C (lit. 87–8 °C)[9a]. ν$_{max}$(KBr)/cm^{-1}: 3242, 3110, 3044, 1664, 1588, 1532. δ$_H$(CDCl$_3$): 8.37–8.39 (1H, m), 7.64 (1H, broad), 7.37–7.39 (1H, m), 7.27–7.31 (1H, m), 7.04–7.08 (1H, m), 2.26 (3H, s). *m/z*(%): 171 (M$^+$+2, 3.33), 170 (M$^+$+1, 1.40), 169 (M$^+$, 10.39), 134 (38.28), 129 (36.73), 127 (100), 92 (15.01), 91(7.02), 43 (62.66). Anal. C$_8$H$_8$ClNO. Calcd. C, 56.65; H, 4.75; N, 8.26. Found C, 56.23; H, 4.77; N, 8.21%.

N-(4-Hydroxy-phenyl)-acetamide (**2g**): m.p. 169 °C (lit. 168–169 °C)[9e]. ν$_{max}$(KBr)/cm^{-1}: 3327, 3201, 3169, 2799, 1656, 1610. δ$_H$(CDCl$_3$): 9.63 (1H, s), 9.12 (1H, s), 7.33–7.35 (2H, m), 6.67–6.69 (2H, m), 1.99 (3H, s). *m/z*(%):173.8 (M+Na)$^+$. Anal. C$_8$H$_9$NO$_2$. Calcd. C, 63.56; H, 6.00; N, 9.27. Found C,63.62; H, 5.98; N, 9.31%.

N-Naphthalen-1-yl-acetamide (**2h**): m.p. 158 °C (lit. 160 °C)[9a]. ν$_{max}$(KBr)/cm^{-1}: 3495, 3271, 3050, 1655, 1598, 1543. δ$_H$(CDCl$_3$): 7.86–7.92 (3H, m), 7.72–7.74 (1H, m), 7.48–7.60 (4H, m), 2.35 (3H, s). *m/z*(%): 207.9 (M+Na)$^+$. Anal. C$_{12}$H$_{11}$NO. Calcd. C, 77.81; H, 5.99; N,7.56. Found C,77.63; H, 5.95; N, 7.59%.

N-(5-Acetylamino-2-hydroxy-phenyl)-acetamide (**2i**): m.p. 222 °C (lit. 220–222 °C)[9b]. ν$_{max}$(KBr)/cm^{-1}: 3442(broad), 1653, 1540. δ$_H$(CDCl$_3$): 9.71 (1H, s), 9.49 (1H, s), 9.34 (1H, s), 7.89 (1H, s), 7.24 (1H, d, *J*=8.6), 6.77 (1H, d, *J*=8.6). *m/z*(%): 230.9 (M+Na)$^+$. Anal. C$_{10}$H$_{12}$N$_2$O$_3$. Calcd. C, 57.68; H, 5.81; N, 13.45. Found C, 57.77; H, 5.83; N, 13.59%.

N-(3-Amino-4-chloro-phenyl)-acetamide (**2j**): m.p. 170 °C (lit. 174 °C)[9c]. ν$_{max}$(KBr)/cm^{-1}: 3409, 3309, 1657, 1631, 1605. δ$_H$(CDCl$_3$): 7.32–7.33 (1H, m), 7.14–7.16 (1H, m), 7.01–7.03 (1H, broad) 6.55–6.57 (1H, m), 4.07 (2H, broad), 2.16 (3H, s). *m/z*(%): 206.9 (M+Na)$^+$. Anal. C$_8$H$_{10}$N$_2$O$_2$. Calcd. C, 52.04; H, 4.91; N, 15.17. Found C, 52.23; H, 4.87; N, 15.11%.

N-(3-Acetylamino-4-chloro-phenyl)-acetamide (**2j'**): m.p. 240 °C (lit. 242–243 °C)[9c]. ν$_{max}$(KBr)/cm^{-1}: 3493, 3235, 3038, 1659, 1593, 1536. δ$_H$(CDCl$_3$): 8.15 (1H, s), 7.75–7.77 (1H, m), 7.63 (1H, broad), 7.46 (1H, broad), 7.27–7.30 (1H, m), 2.25 (3H, s), 2.16 (3H, s). *m/z*(%): 248.9 (M+Na)$^+$. Anal. C$_{10}$H$_{11}$ClN$_2$O$_2$. Calcd. C, 52.99; H, 4.89; N, 12.36. Found C, 52.16; H, 4.81; N, 12.49%.

N-(3-Amino-4-fluoro-phenyl)-acetamide (**2k**): m.p. 165–167 °C. ν$_{max}$(KBr)/cm^{-1}: 3398, 3319, 3222, 1658, 1567. δ$_H$(CDCl$_3$): 9.67 (1H, s), 7.12–7.14 (1H, m), 6.85–6.90 (1H, m), 6.60 (1H, broad), 5.12 (2H, broad), 2.01 (3H, s). *m/z*(%):190.8 (M+Na)$^+$. Anal. C$_8$H$_9$FNO. Calcd. C, 57.14; H, 5.39; N, 16.66. Found C, 57.64; H, 5.37; N, 16.58%.

N-(3-Acetylamino-4-fluoro-phenyl)-acetamide (**2k'**): m.p. 189–190 °C (lit. 190.5 °C)[9d] ν$_{max}$(KBr)/cm^{-1}: 3268, 3079, 2931, 1667, 1618.

δ_H(CDCl$_3$): 9.99 (1H, s), 9.70 (1H, s), 8.06–8.08 (1H, m), 7.41–7.45 (1H, m), 7.14–7.19 (1H, m), 2.10 (3H, s), 2.04 (3H, s). m/z(%): 232.9 (M+Na)$^+$. Anal. C$_{10}$H$_{11}$FN$_2$O$_2$. Calcd. C, 57.14; H, 5.27; N, 13.33. Found C, 57.94; H, 5.24; N, 13.29%.

References

1 P. Girard, J.L. Namy and H.B. Kagan, *J. Am. Chem. Soc.,* 1980, **102**, 2693.
2 For Review to see: (a) A. Krief and A.M. Laval, *Chem Rev.,* 1999, **99**, 745; (b) G.A. Molander, *Acc. Chem. Res.,* 1998, **31**, 603; (c) G.A. Molander and C.R. Harris, *Tetrahedron,* 1998, **54**, 3321; (d) G.A. Molander and C.R. Harris, *Chem Rev.,* 1996, **96**, 307; (e) G.A. Molander, *Chem Rev.,* 1992, **92**, 29; (f) T. Imamoto, *Lanthanides in Organic Synthesis*, Academic Press: London, 1994, Chap. 4.
3 For Review see: B.K. Banik, *Eur. J. Org. Chem.* 2002, **67**, 2431.
4 (a) M.R. Pitts, J.R. Harrison and C.J. Moody, *J.C.S Perkin Trans 1* 2001, 955; (b) R.H. Khan, *J. Chem. Res(s)*, 2000, 290; (c) D.Q. Shi, L.H. Zhou, G.Y. Dai and W.X. Chen, *Youji Huaxue* 1995, **15**, 272.
5 (a) B.H. Kim, Y.M. Jun, S.W. Suh, W. Baik and B.M. Lee, *J. Chem. Res(s)*, 1998, 46; (b) I.D. Entwistle, R.A.W. Johnston and T.J. Povall, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1300; (c) B.H. Kim, J.W. Cheong, R. Han, Y.M. Jun, W. Baik and B.M. Lee, *Synth. Commun.* 2001, **31**, 3577; (d) B.H. Kim, R. Han, F. Piao, Y.M. Jun, W. Baik and B.M. Lee *Tetrahedron Lett.,* 2003, **44**, 77.
6 (a) C. Yu, B. Liu and L. Hu *J. Org. Chem* 2001, **66**, 919; (b) B.K. Banik, C. Mukhopadhyay, M.S. Venkatraman and F.F. Becker, *Tetrahedron Lett.,* 1998, **39**, 7243; (c) X.L. Zheng and Y.M. Zhang, *Chin. J. Chem.,* 2002, **20**, 925; (d) L. Wang, L.H. Zhou and Y.M. Zhang, *Synlett*, 1999, **7**, 1065; (e) M.K. Basu, F.F. Becker and B.K. Banik *Tetrahedron Lett.,* 2000, **41**, 5603; (f) B.K. Banik, C. Mukhopadhyay, M.S. Venkataraman and F.F. Becker *Tetrahedron Lett.,* 1998, **39**, 7243.
7 *Beilsteins Handbuch der Organichen Chemie*, Vier auflage, 13, 53.
8 (a) K. Trauner, K.H. Schuendelhuette and H. Nikel, Ger Offen. 2,242,507 (Cl. C 09b); (b) W. Kunstman and W. Rieper, Ger Offen. 2,338,973 (Cl. C09B, C08k); (c) U.S.J.K. Harrington, D.C. Kvam and A.R. Mendel, 3,920,444 (Cl. 71-103; A01N).
9 (a) *Dictionary of Organic Compounds*, 5th edn; (b) Beilsteins Handbuch der Organichen Chemie, Vier auflage, **13**, 551; (c) *Beilsteins Handbuch der Organichen Chemie*, Vier auflage, **13**, 53; (d) Kogyo Kagaku Zasshi 1969, **72**, 2425; (e) Beilsteins *Handbuch der Organichen Chemie*, Vier auflage, **13**, 460.