Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 6517–6521
Tetrahedron Letters

Microwave enhanced reduction of nitro and azido arenes to *N*-arylformamides employing Zn–$HCOONH_4$: synthesis of 4(3*H*)-quinazolinones and pyrrolo[2,1-*c*][1,4]benzodiazepines

Ahmed Kamal,* K. Srinivasa Reddy, B. Rajendra Prasad, A. Hari Babu and A. Venkata Ramana

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India

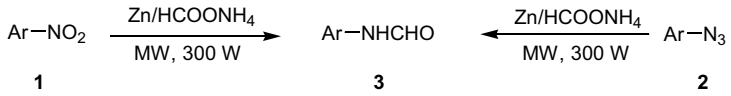
Received 31 March 2004; revised 8 June 2004; accepted 18 June 2004
Available online 20 July 2004

Abstract—Microwave mediated reduction of nitro and azido arenes to *N*-arylformamides using Zn–$HCOONH_4$ is described. In the absence of microwave conditions, this methodology affords amines. This protocol has been extended to the synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepines and 4(3*H*)-quinazolinones.

N-Arylformamides have been widely used in the synthesis of biologically active compounds, such as chemotherapeutic and antibacterial agents[1,2] and precursors for the synthesis of isocyanides.[3] They are also found to catalyze the allylation of carbonyl compounds in solution phase[4a] as well as in the solid phase.[4b] Several methods have been reported for the synthesis of *N*-arylformamides including the formylation of anilines[5a] or direct conversion of nitroarenes with Pd/C and ammonium formate,[5b] tin in the presence of toluene/formic acid,[5c] iron/formic acid[5d] and reductive *N*-formylation of azido arenes under catalytic transfer hydrogenation conditions.[5e] Despite their usefulness, most of these methods have some drawbacks with regard to their long reaction times, vigorous reaction conditions and the expensive and sensitive nature of the reagent system. Hence, there is a continuing requirement to explore practical methodologies for the preparation of *N*-arylformamides. In continuation of our interest in the total synthesis of natural products, we wish to report an efficient and solvent-free reductive *N*-formylation of nitro and azido arenes (**1**, **2**) to *N*-arylformamides **3** with zinc and ammonium formate under microwave irradiation conditions (Scheme 1).

Microwave-assisted organic synthesis has recently gained importance in synthetic organic chemistry[6] and is known to provide several advantages such as reduction in reaction times, improved yields and cleaner work up.[7] As observed from the results in Table 1, the nitro and azido arenes have been converted to their corresponding *N*-arylformamides by employing zinc and ammonium formate under microwave irradiation. Other functional groups such as hydroxyl and halogens were not affected under these reaction conditions.

Employing this procedure, 2-substituted azido- or nitrobenzoic acids were converted to pharmaceutically

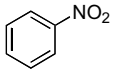
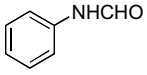
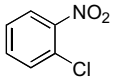
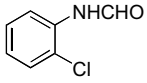
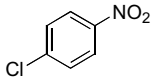
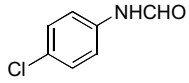
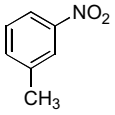
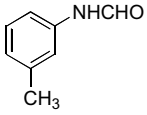
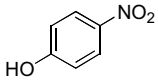
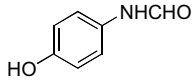
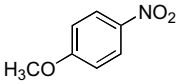
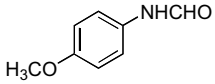
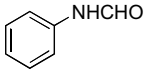
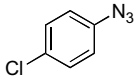
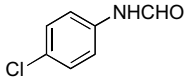
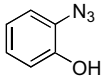
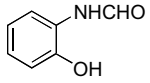
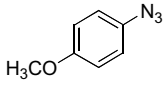
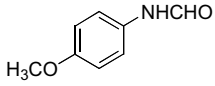
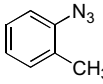
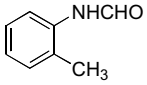


Scheme 1.

Keywords: Zinc; Ammonium formate; Azides; Nitroarenes; *N*-Arylformamides; Microwave; 4(3*H*)-Quinazolinones; Pyrrolo[2,1-*c*][1,4]benzodiazepines.
* Corresponding author. Tel.: +91-40-27193157; fax: +91-40-27193189; e-mail addresses: ahmedkamal@iict.res.in; ahmedkamal@ins.iictnet.com

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.06.112

Table 1. Conversion of azides and nitroarenes to *N*-arylformamides under microwave irradiation

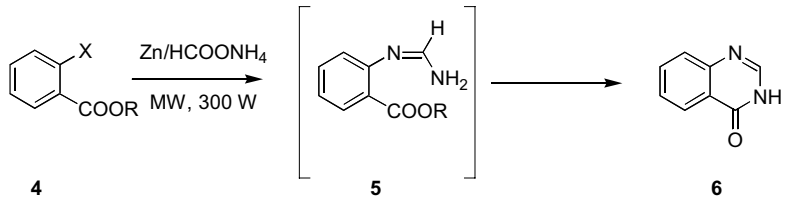
Entry	Substrate (**1**, **2**)	Product **3**[a,b]	Time[c] (min)	Yield[d] (%)
a			3.0	80
b			3.5	75
c			3.0	80
d			3.0	80
e			3.0	75
f			2.0	84
g			2.5	85
h			2.5	90
i			3.0	75
j			2.5	90
k			3.0	77

[a] Mixture of rotamers.
[b] Products gave satisfactory spectroscopic data (^{1}H NMR, mass).
[c] Microwave irradiation was performed at 300 W with 1 min 20 s intervals.
[d] Isolated yields.

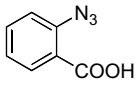
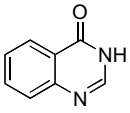
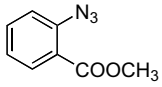
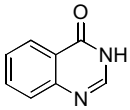
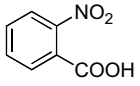
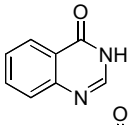
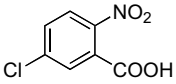
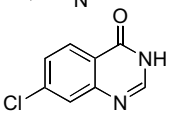
important 4(3*H*)-quinazolinones **6** as shown in Table 2. The formation of quinazolinones is probably due to the decomposition of ammonium formate to formamide, which in turn can condense with the anthranilic acid (or its ester), which is produced upon reduction. Different metals such as Fe and Sn can be used but, amongst these, Zn has showed remarkable efficiency and has proved to be an efficient and inexpensive catalyst for these transformations.[8] Recently, **6** has been prepared from anthranilic acid and formamide under microwave conditions.[9] However, the present study describes, for the first time, the reductive cyclization of 2-azido/2-nitrobenzoic acids for the synthesis of **6** under microwave conditions.

In the absence of microwave irradiation, this reagent system provides a method for the transformation of azides into amines. This conversion is an important chemical transformation in synthetic organic chemistry, especially for the preparation of nitrogen-containing heterocycles,[10] carbohydrates,[11] and in nucleoside chemistry. A wide variety of reagents including tetrathio-molybdate,[12a] $Sm/NiCl_2{\cdot}6H_2O$,[12b] $NaBH_4/CoCl_2{\cdot}6H_2O$,[12c] Zn/NH_4Cl,[12d] MCM–silyl amine Pd(II) complex,[12e] decaborane/Pd/C,[12f] $FeCl_3$–Zn,[12g] modified Staudinger conditions using trimethylphosphine,[12h] and $NaBH_4$/tin-bis(1,2-benzenethiolate)[12i] have been recently reported. Many of these methods have their own disadvantages in terms of general applicability, commercial availability, selectivity, toxicity, and reaction conditions. As a result, there is a continuing demand to explore simple, efficient, and more convenient methodologies. In our related research programmes, we have developed some new methodologies

Table 2. Conversion of 2-azido/2-nitrobenzoic acids to 4(3*H*)-quinazolinones **6** under microwave irradiation



4 **5** **6**

Entry	Substrate (**4**)	Product **6**[a]	Time[b] (min)	Yield[c] (%)
a			4.0	80
b			5.0	75
c			6.0	75
d			6.5	70

[a] Products were characterized by ^{1}H NMR and mass spectroscopy.
[b] Microwave irradiation was performed at 300 W with 2 min intervals.
[c] Yield of isolated products.

towards the synthesis of natural products that involve azide reduction by employing HI,[13a] $FeCl_3$–NaI,[13b] or TMSCl–NaI.[13c] In continuation of this effort, herein we report a simple, mild, and efficient method for the reduction of arylazides **2** to the corresponding arylamines **8** with zinc and ammonium formate. This system has been investigated for the reduction of aliphatic and aromatic nitro compounds to amines,[14a] for the reductive cleavage of azo compounds,[14b] for the deoxygenation of heteroaromatic-*N*-oxides[14c] and for the chemoselective reduction of aromatic nitro and azo compounds in ionic liquids.[14d] After completing this work, we came across one report on the reduction of azides to the corresponding amines[14e] with this system. However this methodology was not applied to the DNA interactive pyrrolobenzodiazepine chemistry.

The results in Table 3 show that this method offers excellent selectivity in the presence of other functionalities such as halogens, acids, esters, and carbonyl groups. Moreover, this process is simple and affords various amines in excellent yields without the use of toxic or expensive materials under near neutral conditions.

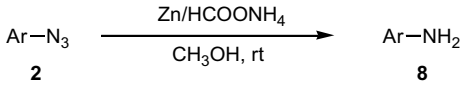
Furthermore, this method has been extended towards the preparation of the DNA-binding pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) ring system. These compounds covalently bind to DNA in a sequence selective manner and as such have potential as antitumor agents and gene targeting drugs.[15] A variety of methods have been investigated for the preparation of this ring system, but most of these have met with varying degrees of success having different limitations.[16] Recently, we have been exploring methods based on an azido reductive cyclization process and in conjunction with these studies, the present methodology has been explored. This process provides PBD imines and dilactams in high yields (Scheme 2).

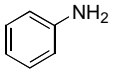
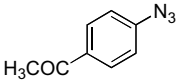
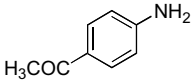
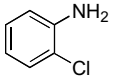
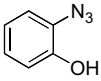
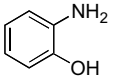
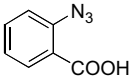
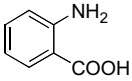
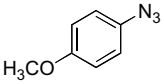
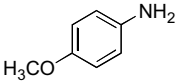
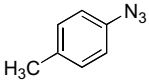
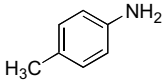
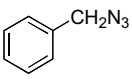
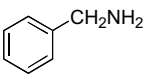
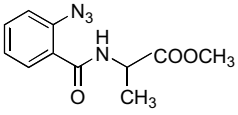
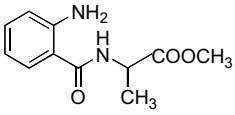
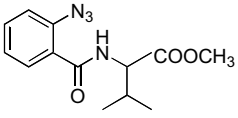
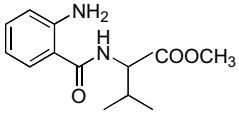
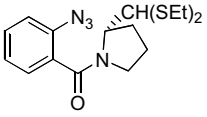
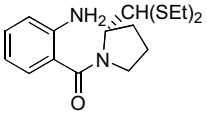
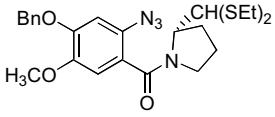
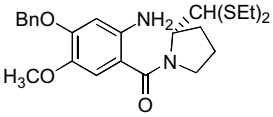
In conclusion, we have developed a simple, mild, and solvent-free method for the synthesis of *N*-arylformamides and 4(3*H*)-quinazolinones by employing Zn and ammonium formate under microwave irradiation. Further, this reagent system has also been employed for the reduction of the azide functionality and for the synthesis of DNA interactive pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs).

Typical procedures—**12a**: To a stirred solution of **11a** (1 mmol) in methanol (10 mL) was added zinc (1.5 mmol), followed by ammonium formate (3 mmol). The resulting mixture was stirred at room temperature until completion of the reaction as indicated by TLC. The reaction mixture was then filtered through a Celite pad and diluted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography on silica gel (60–120) using ethyl acetate/hexane (9:1) to afford pure **12a** (80% yield).

Spectral data for compound **12a**—^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.92–2.35 (m, 4H), 3.52–3.95 (m, 3H),

Table 3. Conversion of azides to amines



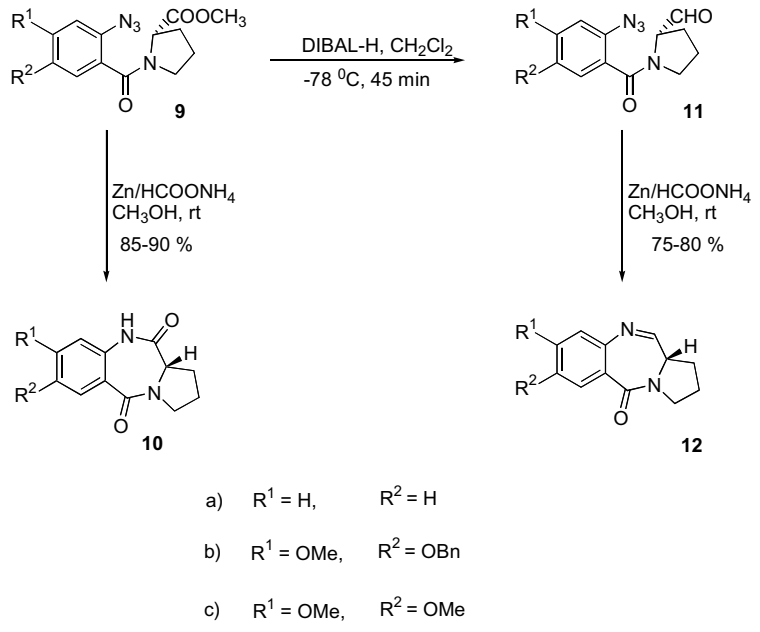
Entry	Substrate (**2**)	Product **8**[a]	Time (min)	Yield[b] (%)
a			15	90
b			20	85
c			20	85
d			18	85
e			20	85
f			15	90
g			15	90
h			25	80
i			30	87
j			30	85
k			25	90
l			30	85

[a] Characterized by spectroscopic data (IR, ^{1}H NMR, mass) and by comparison with authentic samples.
[b] Isolated yields.

7.22–7.58 (m, 3H), 7.78 (d, 1H, $J=4.5$ Hz), 8.05 (d, 1H, $J=5.2$ Hz); EIMS: *m/z* 200 (M^+, 100).

6a: 2-Azido benzoic acid (**4a**) (1 mmol), zinc (2 mmol) and ammonium formate (10 mmol) were taken into a reaction tube and thoroughly mixed with a glass rod. The resulting mixture was placed in a domestic microwave oven (SANYO, model no. BMO 800 TS, 800 W, at 2450 MHz) and irradiated for 4 min at 300 W (see Table 2). The reaction mixture was cooled and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography on silica gel (100–200 mesh) with ethyl acetate/hexane (6:4) to afford pure **6a** (70% yield).

Spectral data for compound **6a**—^{1}H NMR ($CDCl_3$+DMSO-d_6, 300 MHz): δ 7.38 (dt, 1H, $J=8.2$ Hz, 1.5 Hz), 7.58 (d, 1H, $J=8.2$ Hz), 7.66 (dt, 1H, $J=8.2$ Hz, 1.5 Hz), 7.84 (br s, 1H), 8.15 (dd, 1H,



Scheme 2.

$J = 8.2$ Hz, 1.5 Hz), 12.05 (br s, 1H); EIMS: *m/z* 146 (M^+, 100).

Acknowledgements

We (K.S.R., B.R.P., A.H.B., and A.V.R.) thank CSIR (New Delhi) for the award of research fellowships.

References and notes

1. Petit, G. R.; Kalnins, M. V.; Liu, T. M. H.; Thomas, E. G.; Parent, K. *J. Org. Chem.* **1961**, *26*, 2563–2566.
2. Jackson, A.; Meth-Cohn, O. *J. Chem. Soc., Chem. Commun.* **1995**, 1319.
3. Barton, D. H. R.; Bringman, G.; Motherwell, W. B. *Synthesis* **1980**, 68–70.
4. (a) Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, *59*, 6620–6628; (b) Ogawa, C.; Sugiura, M.; Kobayashi, S. *Chem. Commun.* **2003**, 192–193.
5. (a) Jung, S. H.; Ahn, J. H.; Park, S. K.; Choi, J.-K. *Bull. Korean Chem. Soc.* **2002**, *23*, 149–150; (b) Pratap, T. V.; Baskaran, S. *Tetrahedron Lett.* **2001**, *42*, 1983–1985; (c) Hrvatin, P.; Sykes, A. G. *Synlett* **1997**, 1069–1070; (d) Lee, K. Y.; Kim, J. M.; Kim, J. N. *Bull. Korean Chem. Soc.* **2002**, *23*, 1359–1360; (e) Reddy, P. G.; Baskaran, S. *Tetrahedron Lett.* **2002**, *23*, 1919–1922.
6. (a) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283; (b) *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2002.
7. (a) Varma, R. S. *Green Chem.* **1999**, *1*, 43–55; (b) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacqualt, P.; Mathé, D. *Synthesis* **1998**, 1213–1234; (c) Varma, R. S. *Pure Appl. Chem.* **2001**, *73*, 193–198.
8. Paul, S.; Nanda, P.; Gupta, R.; Loupy, A. *Synthesis* **2003**, 2877–2881.
9. (a) Alexandre, F.-R.; Berecibar, A.; Besson, T. *Tetrahedron Lett.* **2002**, *43*, 3911–3913; (b) Balalaie, S.; Sharifi, A.; Ahangarian, B.; Kowsari, E. *Heterocycl. Commun.* **2001**, *7*, 337–340; (c) Rad-Moghadam, K.; Khajavi, M. S. *J. Chem. Res. (S)*, **1998**, 702–703.
10. Smith, S. C.; Heathcock, C. H. *J. Org. Chem.* **1992**, *57*, 6379–6380.
11. McDonald, F. E.; Danishefsky, S. J. *J. Org. Chem.* **1992**, *57*, 7001–7002.
12. (a) Sridhar, P. R.; Prabhu, K. R.; Chandrasekaran, S. *J. Org. Chem.* **2003**, *68*, 5261–5264; (b) Wu, H.; Chen, R.; Zhang, Y. *Synth. Commun.* **2002**, *32*, 189–193; (c) Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Synthesis* **2000**, 646–650; (d) Lin, W.; Zhang, X.; He, Z.; Jin, Y.; Gong, L.; Mi, A. *Synth. Commun.* **2002**, *32*, 3279–3284; (e) Kantam, M. L.; Chowadari, N. S.; Rahaman, A.; Choudary, B. M. *Synlett* **1999**, 1413–1414; (f) Jung, Y. J.; Chang, Y. M.; Lee, J. H.; Yoon, C. M. *Tetrahedron Lett.* **2002**, *43*, 8735–8739; (g) Pathak, D.; Laskar, D. D.; Prajapati, D.; Sandhu, S. J. *Chem. Lett.* **2000**, 816–817; (h) Nyffeler, P. T.; Liang, C.-H.; Koeller, M. K.; Wong, C.-H. *J. Am. Chem. Soc.* **2002**, *124*, 10773–10778; (i) Bosch, I.; Costa, A. M.; Martín, M.; Urpí, F.; Vilarrasa, J. *Org. Lett.* **2000**, *2*, 397–400.
13. (a) Kamal, A.; Reddy, P. S. M. M.; Reddy, D. R. *Tetrahedron Lett.* **2002**, *43*, 6629–6631; (b) Kamal, A.; Ramana, K. V.; Ankati, H. B.; Ramana, A. V. *Tetrahedron Lett.* **2002**, *43*, 6861–6863; (c) Kamal, A.; Laxman, E.; Ariffuddin, M. *Tetrahedron Lett.* **2000**, *41*, 7743–7746.
14. (a) Gowda, D. C.; Mahesh, B.; Gowda, S. *Indian J. Chem.* **2001**, *40B*, 75–77; (b) Gowda, S.; Abiraj, K.; Gowda, D. C. *Tetrahedron Lett.* **2002**, *43*, 1329–1331; (c) Balicki, R.; Cybulski, M.; Maciejewski, G. *Synth. Commun.* **2003**, *33*, 4137–4141; (d) Khan, F. A.; Dash, J.; Sudheer, Ch.; Gupta, R. K. *Tetrahedron Lett.* **2003**, *44*, 7783–7787; (e) Srinivasa, G. R.; Nalina, L.; Abiraj, K.; Gowda, D. C. *J. Chem. Res. (S)*, **2003**, 630–631.
15. Gregson, S. J.; Howard, P. W.; Hartley, J. A.; Brooks, N. A.; Adams, L. J.; Jenkins, T. C.; Kelland, L. R.; Thurston, D. E. *J. Med. Chem.* **2001**, *44*, 737–748.
16. (a) Kamal, A.; Rao, M. V.; Laxman, N.; Ramesh, G.; Reddy, G. S. K. *Curr. Med. Chem. Anti-Cancer Agents* **2002**, *2*, 215–254; (b) Thurston, D. E.; Bose, D. S. *Chem. Rev.* **1994**, *94*, 433–465.