Tetrahedron Letters 53 (2012) 1511–1513

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Copper catalyzed *ipso*-nitration of iodoarenes, bromoarenes and heterocyclic haloarenes under ligand-free conditions

P.J. Amal Joseph, S. Priyadarshini, M. Lakshmi Kantam *, H. Maheswaran

Inorganic and Physical Chemistry Division, Indian Institute of Chemical Technology, Hyderabad 500607, India

ARTICLE INFO

Article history:
Received 10 December 2011
Revised 13 January 2012
Accepted 14 January 2012
Available online 21 January 2012

Keywords:
Copper salts
ipso-Nitration
Haloarenes
Potassium nitrite
Homogeneous catalysis

ABSTRACT

A catalytic protocol for the conversion of haloarenes into the corresponding nitroarenes is presented using copper salts under ligand-free conditions. The method was effectively utilized for the *ipso*-nitration of a broad variety of haloarenes that includes iodoarenes, bromoarenes, and heterocyclic haloarenes.

Nitroarenes are important constituents in natural products, biologically active compounds, pharmaceuticals, agrochemicals, dyes, explosives, and material chemistry.[1] The nitro group possesses an indispensable significance in organic synthesis attributed to the ease with which it can undergo Nef reaction, reduction, and nucleophilic displacement reactions.[2] Traditionally, nitro groups are introduced into the aromatic framework by electrophilic substitution of electron rich arenes with in situ generated nitronium ion under various conditions.[3] However, this method suffers drawbacks such as poor regioselectivity, requirement of harsh reaction conditions that are not often compatible with many functional groups, and also the dependency of the reaction on the nature and orientation of the functional groups present. Many of these persistent problems were resolved by the development of *ipso*-nitration protocols via nitrodemetallation route. These efforts include *ipso*-nitration of aryllithium,[4] heteroaryl stannanes,[5] and arylboronic acids.[6] Nonetheless, these directed methods are not atom economical and their limitations include poor substrate scope, high cost, and complications involved in the preparation of starting materials. Therefore, it is very important to develop catalytic process to synthesize nitroarenes from relatively cheap and readily available haloarenes.

Earlier, Saito demonstrated a protocol for the conversion of iodoarenes into corresponding nitroarenes using copper powder/DMEDA based catalytic system.[7,8] Subsequently, Buchwald et al. disclosed a promising protocol for the conversion of chloroarenes, triflates, and nonaflates into the respective nitroarenes using tris(dibenzylideneacetone)dipalladium(0)/*t*-BuBrettPhos catalyst.[9] These methods have made substantial impact in this field; however, it is of high interest to develop *ipso*-nitration protocols for bromoarenes.[10] Furthermore, the use of ligands and palladium demands high cost and toxicity; therefore, it is desirable to develop a catalytic process using relatively cheap and less toxic metal salts. In this respect, herein we report copper catalyzed *ipso*-nitration of haloarenes under ligand-free conditions. This protocol circumvents the need of a phase transfer catalyst and is applicable for a wide variety of haloarenes such as iodoarenes, bromoarenes, and heterocyclic haloarenes. In addition, the reaction is carried out in weakly basic conditions that tolerate many functional groups. Notably, several structurally divergent nitroarenes were synthesized in moderate to good yields with complete regioselectivity.

At first, 4-bromothioanisole was selected as the model substrate for carrying out the optimization studies and was subjected to various reaction conditions on a 0.5 mmol scale using 25 mol % copper salts and 3 equiv of potassium nitrite as catalyst and nucleophile, respectively in 0.6 mL DMSO at 130 °C for 48 h. The results of these studies are summarized in Table 1. As depicted in Table 1, different copper salts such as CuI, CuBr, $CuBr_2$, $CuSO_4$, and $Cu(OSO_2CF_3)_2$ (Table 1, entries 1, 2 and 9–11) promoted the *ipso*-nitration to furnish the product 4-nitrothioanisole in decent yields, whereas only moderate yields were obtained using CuOAc, copper powder, and $Cu(OAc)_2$ (Table 1, entries 3, 5 and 8). In contrast, the reaction failed with CuO nanoparticles (Table 1, entry 6) and further very low yield was obtained when Cu_2O and $Cu(O_2C_5H_7)_2$ (Table 1,

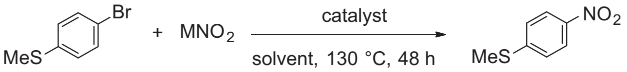
---

* Corresponding author. Tel.: +91 40 27193510; fax: +91 40 27160921.
E-mail address: mlakshmi@iict.res.in (M. Lakshmi Kantam).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2012.01.056

Table 1

Screening of reaction parameters for copper catalyzed direct *ipso*-nitration of 4-bromothioanisole[a]



Entry	Catalyst	Solvent	Nitrite salt (MNO_2)	Yield[f] (%)
1	CuI	DMSO	KNO_2	69
2	CuBr	DMSO	KNO_2	67
3	Cu(OAc)	DMSO	KNO_2	49
4	Cu_2O	DMSO	KNO_2	18
5	Cu powder	DMSO	KNO_2	38
6	Nano CuO	DMSO	KNO_2	0
7	$Cu(acac)_2$	DMSO	KNO_2	15
8	$Cu(OAc)_2$	DMSO	KNO_2	58
9	$CuBr_2$	DMSO	KNO_2	72
10	$CuSO_4$	DMSO	KNO_2	75
11	$Cu(OSO_2CF_3)_2$	DMSO	KNO_2	84, 87[b]
12	$Cu(OSO_2CF_3)_2$	DMSO	KNO_2	41[c]
13	$Cu(OSO_2CF_3)_2$	DMSO	KNO_2	85[d]
14	None	DMSO	KNO_2	Trace[e]
15	$Cu(OSO_2CF_3)_2$	DMF	KNO_2	Trace
16	$Cu(OSO_2CF_3)_2$	NMP	KNO_2	5
17	$Cu(OSO_2CF_3)_2$	Glycol	KNO_2	4
18	$Cu(OSO_2CF_3)_2$	Toluene	KNO_2	0
19	$Cu(OSO_2CF_3)_2$	EtOH	KNO_2	0
20	$Cu(OSO_2CF_3)_2$	H_2O	KNO_2	0
21	$Cu(OSO_2CF_3)_2$	DMSO	$NaNO_2$	42
22	$Cu(OSO_2CF_3)_2$	DMSO	$AgNO_2$	20

[a] Unless otherwise stated, reactions were performed on a 0.5 mmol scale with 4-bromothioanisole (0.5 mmol), catalyst (0.125 mmol, 25 mol %) and MNO_2 (1.5 mmol) in 0.6 mL of solvent at 130 °C for 48 h under N_2 atmosphere.

[b] Reaction continued for 60 h.

[c] Reaction performed with 10 mol % of catalyst.

[d] Reaction performed with 30 mol % of catalyst.

[e] Reaction performed without catalyst.

[f] Isolated yield.

entries 4 and 7) were used as the catalysts. Thus, among the various copper precursors screened for the reaction, the best result was obtained with $Cu(OSO_2CF_3)_2$. Thereafter, a trial reaction was performed employing KNO_2 in the absence of copper catalyst. The reaction was sluggish and insignificant amount of product was obtained, thereby proving that copper catalyst is a prerequisite for the reaction[11,12] (Table 1, entry 14). Next, the solvent screening revealed that it has a profound effect, as the reaction was sluggish and furnished very poor yields in DMF, NMP, and ethylene glycol (Table 1, entries 15–17). Besides that, the reaction failed in toluene (Table 1, entry 18), and in polar protic solvents such as ethanol and water (Table 1, entries 19 and 20). On the other hand, very good results were obtained when DMSO was used as the solvent. These observations can be partly explained by considering the solubility of KNO_2 and copper salts in the above aprotic solvents, as KNO_2 and $Cu(OSO_2CF_3)_2$ are rather soluble in hot DMSO. Later, the screening of different nitrite salts proved KNO_2 to be superior to other nucleophiles like $NaNO_2$ and $AgNO_2$ (Table 1, entries 11, 21 and 22). Thus, among the various optimization studies listed in Table 1 for the *ipso*-nitration of 4-bromothioanisole, the most promising result (84% yield, Table 1, entry 11) was obtained using 25 mol % of $Cu(OSO_2CF_3)_2$ and 3 equiv of KNO_2 in 0.6 mL of DMSO at 130 °C.

Thereafter, the above optimized reaction conditions[13] were explored for the *ipso*-nitration of various haloarenes, and the results are summarized in Table 2. As exemplified in Table 2, this protocol is rather general for a wide variety of electron-rich as well as electron-deficient iodoarenes and bromoarenes. It is noteworthy that several electron-rich haloarenes reacted smoothly irrespective of the nature and orientation of the functional groups present to

Table 2

Copper catalyzed *ipso*-nitration of haloarenes[a]

$$ArX + KNO_2 \xrightarrow[\text{DMSO, 48 h}]{Cu(OSO_2CF_3)_2} ArNO_2$$

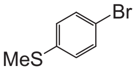
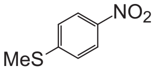
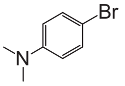
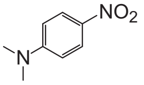
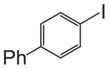
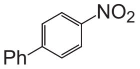
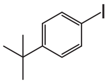
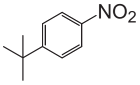
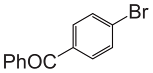
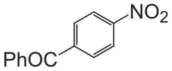
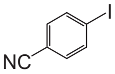
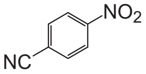
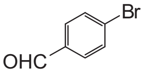
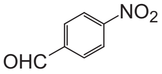
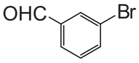
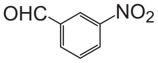
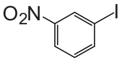
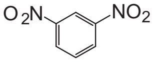
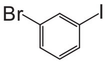
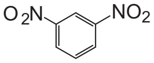
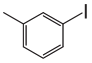
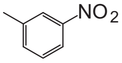
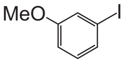
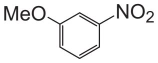
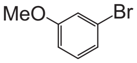
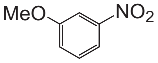
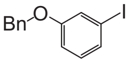
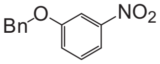
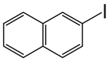
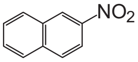
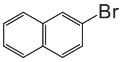
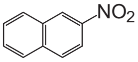
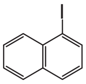
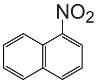
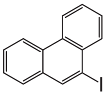
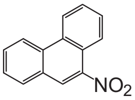
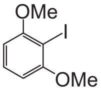
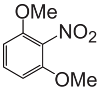
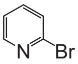
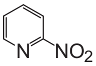
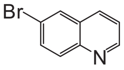
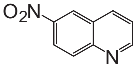
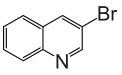
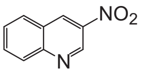
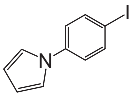
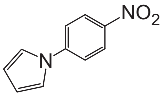
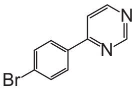
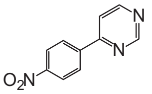
Entry	ArX	$ArNO_2$	Yield[f] (%)
1			84
2			73
3			73
4			66
5			54
6[b]			45
7[c]			61
8			55
9			68
10[d]			65
11			67
12			72
13			58
14			81
15			82
16			71
17[d]			70
18[d]			73
19[d,e]			32
20[b]			48
21			82

Table 2 (*continued*)

Entry	ArX	$ArNO_2$	Yield[f] (%)
22			62
23			78
24			70

[a] Unless otherwise stated, reactions were performed on a 0.5 mmol scale with haloarene (0.5 mmol), $Cu(OSO_2CF_3)_2$ (25 mol %) and KNO_2 (1.5 mmol) in dry DMSO (0.6 mL) at 130 °C for 48 h under N_2 atmosphere.

[b] Reactions performed at 120 °C.

[c] Reaction performed at 125 °C.

[d] Reactions performed with 30 mol % $Cu(OSO_2CF_3)_2$ for 60 h.

[e] Reaction performed at 135 °C.

[f] Isolated yield.

afford the corresponding products in good yields (Table 2, entries 1–4, 10, 11, 15 & 16). On the other hand, the reaction of electron-deficient haloarenes like 4-bromobenzophenone, 4-iodobenzonitrile, 4-bromobenzaldehyde, 3-bromobenzaldehyde, and 1-iodo-3-nitrobenzene provided respective products in modest yields (Table 2, entries 5–9). The reactions of *ortho*-substituted haloarenes like 1-iodonaphthalene and 9-iodophenanthrene took prolonged time to furnish the corresponding products in good yields (60 h, Table 2, entries 17 & 18). Similarly, the reaction of sterically hindered 2-iodo-1,3-dimethoxybenzene also afforded the product in moderate yield, albeit at slightly higher temperature (135 °C, Table 2, entry 19). It is important to note that several functional groups including NO_2, CHO, CN, COPh, NMe_2, OCH_2Ph, OMe, SMe, Ph, and Me were tolerated in this method. However, the reaction failed to yield the desired products for 4-bromoaniline and 4-iodophenol substrates. Later, the scope of this method was effectively utilized for the *ipso*-nitration of heterocycles like 2-bromopyridine, 3-bromoquinoline, 6-bromoquinoline, 1-(4-iodophenyl)-1*H*-pyrrole, and 4-(4-bromophenyl)pyrimidine with good outputs (Table 2, entries 20–24).

To demonstrate the application of this procedure in gram scale, a reaction was performed using 10 mmol (2.030 g) of 4-bromothioanisole, 2.5 mmol of $Cu(OSO_2CF_3)_2$ and 30 mmol of KNO_2 in 10 mL of dry DMSO at 130 °C for 48 h under nitrogen atmosphere. The reaction proceeded smoothly to afford the corresponding product 4-nitrothioanisole in a good yield (80%, 1.352 g) and the unreacted starting material recovered was found to be 19% (0.386 g).

In summary a very handy and efficient catalytic *ipso*-nitration protocol that may find widespread applications in synthetic chemistry is presented. This procedure circumvents the use of expensive ligands and phase transfer catalyst for the reaction. The protocol merits complete regioselectivity, excellent functional group tolerance, and broad substrate scope. Several nitroarenes were synthesized in moderate to good yields from various structurally divergent haloarenes that includes iodoarenes, bromoarenes, and heterocyclic haloarenes.

Acknowledgments

P.J.A.J. thanks UGC New Delhi for the award of research fellowship. S.P. thanks CSIR India for the award of fellowship.

Supplementary data

Supplementary data (general procedure for synthesis, characterization data and copies of ^1H and ^{13}C NMR spectra of all the compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.056.

References and notes

1. (a) Parry, R.; Nishinob, S.; Spain, J. *Nat. Prod. Rep.* **2011**, *28*, 152; (b) Li, H.; Huang, H.; Zhang, X.; Luo, X.; Lin, L.; Jiang, H.; Ding, J.; Chen, K.; Liu, H. *Acta Pharmacol. Sin* **2008**, *12*, 1529; (c) Muller, W. E. *The Benzodiazepine Receptor*; Cambridge University Press: New York, 1988; (d) Belciug, M.; Ananthanarayanan, V. S. *J. Med. Chem.* **1994**, *37*, 4392; (e) Zollinger, H. *Color Chemistry*; Wiley-VCH: New York, 1987. p 161; (f) Agrawal, J. P. *Prop. Explos. Pyrotech. 30* **2005**, *5*, 316; (g) Fan, F.-R. F.; Yao, Y.; Cai, L.; Cheng, L.; Tour, J. M.; Bard, A. J. *J. Am. Chem. Soc.* **2004**, *126*, 4035.
2. (a) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001; (b) Vlasov, V. M. *Russ. Chem. Rev.* **2003**, *8*, 681; (c) Ballini, R.; Petrini, M. *Tetrahedron* **2004**, *60*, 1017; (d) Tafesh, A. M.; Weiguny, J. *Chem. Rev.* **1996**, *96*, 2035.
3. (a) Shiri, M.; Zolfigol, M. A.; Kruger, H. G.; Tanbakouchian, Z. *Tetrahedron* **2010**, *66*, 9077; (b) Olah, G. A.; Malhotra, R.; Narang, S. C. *Nitration: Methods and Mechanisms*; VCH: Weinheim, 1989.
4. Tani, K.; Lukin, K.; Eaton, P. E. *J. Am. Chem. Soc.* **1997**, *119*, 1476.
5. (a) Favresse, F.; Fargeas, V.; Charrue, P.; Lebret, B.; Piteau, M.; Quintard, J. *J. Organomet. Chem.* **2000**, 187; (b) Fargeas, V.; Favresse, F.; Mathieu, D.; Beaudet, I.; Charrue, P.; Lebret, B.; Piteau, M.; Quintard, J. *Eur. J. Org. Chem.* **2003**, 1711.
6. (a) Prakash, G. K. S.; Panja, C.; Mathew, T.; Surampudi, V.; Petasis, N. A.; Olah, G. A. *Org. Lett.* **2004**, *6*, 2205; (b) Salzbrunn, S.; Simon, J.; Prakash, G. K. S.; Petasis, N. A.; Olah, G. A. *Synlett* **2000**, 1485; (c) Yang, H.; Li, Y.; Jiang, M.; Wang, J.; Fu, H. *Chem. Eur. J.* **2011**, *17*, 5652; (d) Wu, X. F.; Schranck, J.; Neumann, H.; Beller, M. *Chem. Commun.* **2011**, *47*, 12462.
7. For copper catalyzed *ipso*-nitration of iodoarenes and 4-bromoanisole; For reference, see: Saito, S.; Koizumi, Y. *Tetrahedron Lett.* **2005**, *46*, 4715.
8. Very good yields were obtained by the application of microwave, albeit at high catalyst and ligand loading; For reference, see: LaBeaume, P.; Placzek, M.; Daniels, M.; Kendrick, I.; Ng, P.; McNeel, M.; Afroze, R.; Alexander, A.; Thomas, R.; Kallmerten, A. E.; Jones, G. B. *Tetrahedron Lett.* **1906**, *2010*, 51.
9. (a) Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 12898; (b) Prakash, G. K. S.; Mathew, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 1726.
10. Bromoarenes are relatively cheaper than iodoarenes, and are practically unexplored for *ipso*-nitration reaction; For reference, see:7–9.
11. This observation clearly confirms the absence of uncatalyzed SNAr mechanistic pathway in this protocol.
12. A free radical mechanism is less likely in this protocol, because the reaction proceeded in the presence of free radical inhibitor (3 equiv of TEMPO was used as free radical inhibitor) for substrates such as 4-bromothioanisole and 1-iodo-3-nitrobenzene under optimal conditions.
13. An oven dried pressure tube was charged with haloarenes (0.5 mmol), copper(II) triflate (45 mg, 0.125 mmol), KNO_2 (128 mg, 1.5 mmol) and anhydrous DMSO (0.6 mL) under N_2 atmosphere. The tube was sealed with a Teflon screw cap having mininert valve and nitrogen is purged through it for 5 min. It is stirred at room temperature for 10 min and then the temperature was gradually increased to 130 °C and is maintained at the same for 48 h. The reaction mixture was then cooled to room temperature, washed with excess ice cold water and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product which was purified by column chromatography using silica gel and a mixture of ethyl acetate and hexane as the eluent to afford the desired products in good yields. For detailed procedure; see Supplementary data.