ORGANIC LETTERS

2013
Vol. 15, No. 24
6218–6221

Cobalt- and Iron-Catalyzed Redox Condensation of *o*-Substituted Nitrobenzenes with Alkylamines: A Step- and Redox-Economical Synthesis of Diazaheterocycles

Thanh Binh Nguyen,* Julie Le Bescont, Ludmila Ermolenko, and Ali Al-Mourabit

Centre de Recherche de Gif-sur-Yvette, Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette Cedex, France

nguyen@icsn.cnrs-gif.fr

Received October 24, 2013

ABSTRACT

A wide variety of functionalized 2-aryl benzimidazoles can be prepared by a solvent-free cobalt- or iron-catalyzed redox condensation of 2-nitroanilines and benzylamines. The cascade including benzylamine oxidation, nitro reduction, condensation, and aromatization occurs without any added reducing or oxidizing agent. The method can be extended to other alkylamines as reducing components or 2-nitrobenzamides as oxidizing components when using an iron/sulfur catalyst to afford various diazaheterocycles.

Redox condensation of the nitro group with other reducing components provides a direct, step-, atom-, and redox-economical approach to nitrogen containing compounds, including amides and aza-heterocycles. Most of the reported methods for redox condensation of the nitro group employ expensive metals and/or ligands[1] with a large excess of the reducing components or external oxidizing agents.[2] In this context, we are interested in developing such methods using low-cost and readily available simple salts of the first-row transition metals in association with ligands within reach. Recently, we reported iron−sulfur catalyzed methods for redox condensation between *o*-nitroanilines and 2- or 4-methylhetarenes[3] or 2-phenethylamines[4] as an efficient route to aza-heterocycles. In continuing our study, we report here a general method for iron- and cobalt-catalyzed redox condensation between *o*-substituted nitrobenzenes and amines.

Our initial efforts were focused on identifying the catalytic activity of the first row transition metal salts. For this

(1) Pd/XantPhos: (a) Xie, Y.; Liu, S.; Liu, Y.; Wen, Y.; Deng, G. *Org. Lett.* **2012**, *14*, 1692. Ru(acac)$_3$/dppe: (b) Liu, Y.; Chen, W.; Feng, C.; Deng, G. J. *Chem.—Asian J.* **2011**, *6*, 1142. Au: (c) Tang, C. H.; He, L.; Liu, Y. M.; Cao, Y.; He, H. Y.; Fan, K. N. *Chem.—Eur. J.* **2011**, *17*, 7172. dppf: (d) Wang, H.; Cao, X.; Xiao, F.; Liu, S.; Deng, G. *Org. Lett.* **2013**, *15*, 4900. (e) Wu, M.; Hu, X.; Liu, J.; Liao, Y.; Deng, G. *Org. Lett.* **2012**, *14*, 2722. Ir/Pd complex: (f) Zanardi, A.; Mata, J. A.; Peris, E. *Chem.—Eur. J.* **2010**, *16*, 10502.

(2) (a) Xiao, F.; Liu, Y.; Tang, C.; Deng, G. *Org. Lett.* **2012**, *14*, 984.

(3) Nguyen, T. B.; Ermolenko, L.; Al-Mourabit, A. *J. Am. Chem. Soc.* **2013**, *135*, 118.

(4) Nguyen, T. B.; Retailleau, P.; Al-Mourabit, A. *Org. Lett.* **2013**, *15*, 5238.

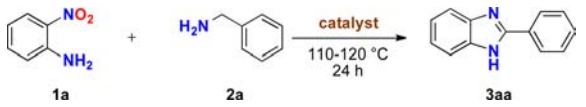
(5) For some selected recent examples, see: (a) Li, J.; Benard, S.; Neuville, L.; Zhu, J. *Org. Lett.* **2012**, *14*, 5980. (b) Bastug, G.; Eviolitte, C.; Marko, I. E. *Org. Lett.* **2012**, *14*, 3502. (d) Pizzetti, M.; De Luca, E.; Petricci, E.; Porcheddu, A.; Taddei, M. *Adv. Synth. Catal.* **2012**, *354*, 2453. (e) Cano, R.; Ramon, D. J.; Yus, M. *J. Org. Chem.* **2011**, *76*, 654. (f) Matsushita, H.; Lee, S.; Joung, M.; Clapham, B.; Janda, K. D. *Tetrahedron Lett.* **2004**, *45*, 313. (g) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932. (h) Nguyen, T. B.; Ermolenko, L.; Al-Mourabit, A. *Heterocycles* **2012**, *86*, 555. (i) Huang, J.; He, Y.; Wang, Y.; Zhu, Q. *Chem.—Eur. J.* **2012**, *18*, 13964. (j) Peng, J.; Ye, M.; Zong, C.; Hu, F.; Feng, L.; Wang, X.; Wang, Y.; Chen, C. *J. Org. Chem.* **2011**, *76*, 716. (k) Lewis, J. C.; Berman, A. M.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 2493. (l) Shen, M.; Driver, T. G. *Org. Lett.* **2008**, *10*, 3367. (m) Hubbard, J. W.; Piegols, A. M.; Soederberg, B. C. G. *Tetrahedron* **2007**, *63*, 7077. (n) Nguyen, T. B.; Ermolenko, L.; Dean, W. A.; Al-Mourabit, A. *Org. Lett.* **2012**, *14*, 5948. (o) Nguyen, T. B.; Ermolenko, L.; Al-Mourabit, A. *Green Chem.* **2013**, *15*, 2713.

10.1021/ol403064z
Published on Web 11/14/2013

purpose, the redox condensation of *o*-nitroaniline with benzylamine was chosen as a model reaction. This reaction has been reported under uncatalyzed conditions at high reaction temperatures (>210 °C) to furnish 2-phenylbenzimidazole[5] in low yields.[6]

All the screened reactions were carried out at 120 °C, with 3 equiv of benzylamine under solvent-free conditions and an argon atmosphere. As can be seen from the data shown in Table 1, in the absence of catalysts, no trace of the condensed product **3aa** could be detected and both starting materials were recovered unchanged. In the presence of a catalyst (2 mol %), while the reaction catalyzed by manganese- (entry 2), nickel- (entry 7), and copper- (entry 8) halides proceeded sluggishly, cobalt- (entries 5–6) and iron- (entries 3–4) halides were all competent to provide cleanly the desired 2-phenylbenzimidazole **3aa** product.

Table 1. Redox Condensation of *o*-Nitroaniline **1a** with Benzylamine **2a**[a]



1a **2a** **3aa**

entry	catalyst	conversion (%)[c]
1	–	0
2	$MnCl_2 \cdot 4H_2O$	20
3	$FeCl_2 \cdot 4H_2O$	85
4	**$FeCl_3 \cdot 6H_2O$**	**92**
5	$CoCl_2 \cdot 6H_2O$	85
6	**$CoBr_2 \cdot xH_2O$**[b]	**95**
7	$NiCl_2 \cdot 6H_2O$	5
8	CuCl	15

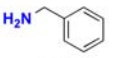
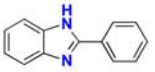
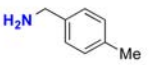
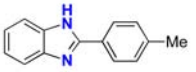
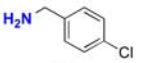
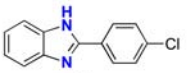
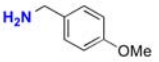
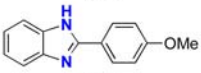
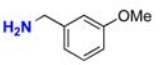
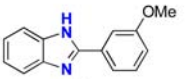
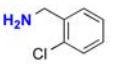
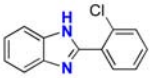
[a] Reaction conditions: **1a** (5 mmol), **2a** (15 mmol), metal salt (2 mol %, 0.1 mmol). [b] 18.5% Co. [c] Deteremined by ^{1}H NMR.

We then investigated the scope of the redox condensation between *o*-nitroaniline **1a** and various primary benzylamines **2**. The results are summarized in Table 2. All the benzylamines examined gave the condensed products in moderate-to-good yields (entries 1–6). No significant difference in catalytic activity between Co and Fe was found. In the case where benzylamine is *o*-substituted by a chlorine atom, the yield is somewhat lower, possibly due to the steric hindrance (entry 6).

Next, a series of *o*-nitroanilines were then subjected to the selected optimized conditions with benzylamine **2a** (Table 3). *o*-Nitroanilines bearing methyl, chlorine, bromine, and methoxy substituents at different positions are all effective substrates although a lower yield was observed for **1g** (entry 6) wherein a methoxy group at the *para* position to the nitro group could probably strongly influence the redox property of the nitro group. The reaction with *N*-substituted *o*-nitroanilines **1h–i** (entries 7–8) proceeded also efficiently despite the higher reaction temperatures required to afford good yields. It should be noted that the *N*-debenzylation was not observed for the case of **1i**.

Table 2. Cobalt- or Iron-Catalyzed Redox Condensation of *o*-Nitroaniline **1a** with Benzylamine **2**[a]

1a 5 mmol **2** 3 equiv **3**

entry	benzylamine **2**	benzimidazole **3**	yield (%)
1	 **2a**	 **3aa**	88[b] 85[c]
2	 **2b**	 **3ab**	92[b] 87[c]
3	 **2c**	 **3ac**	79[b] 81[c]
4	 **2d**	 **3ad**	67[b] 65[c]
5	 **2e**	 **3ae**	69[b] 71[c]
6	 **2f**	 **3af**	65[b] 58[c]

[a] Reaction conditions: *o*-nitroaniline **1a** (5 mmol), benzylamine **2** (15 mmol), metal salt (2 mol %, 0.1 mmol). [b] Catalyst $CoBr_2 \cdot xH_2O$ (18.5% Co). [c] Catalyst $FeCl_3 \cdot 6H_2O$.

A plausible mechanism for the present transformation shown in Scheme 1 could involve the following steps: (a) the initial oxidation of benzylamine **2a** into benzaldimine which is rapidly transformed into *N*-benzylbenzaldimine **4** via a transamination reaction.[7] This step also yielded the metal complex in reduced form that could participate in the next reduction step, (b) the nitro group.

Although the reduction of a nitro group into an amino group is a complex six-electron transfer cascade process, under no circumstances could we observe the formation of partially reduced intermediates but fully reduced product **5** is readily detected in trace quantities in the crude reaction mixture. The process was achieved by step (c) which

(6) (a) Nishioka, H.; Ohmori, Y.; Iba, Y.; Tsuda, E.; Harayama, T. *Heterocycles* **2004**, *64*, 193. (b) Rao, C. V. C.; Reddy, K. K.; Rao, N. V. S. *Indian J. Chem. B* **1980**, *19*, 655.

(7) For selected examples of oxidation of benzylamines into *N*-benzylbenzaldimines, see: (a) Hu, Z.; Kerton, F. M. *Org. Biomol. Chem.* **2012**, *10*, 1618. (b) Huang, B.; Tian, H.; Lin, S.; Xie, M.; Yu, X.; Xu, Q. *Tetrahedron Lett.* **2013**, *54*, 2861. (c) Aschwanden, L.; Mallat, T.; Krumeich, F.; Baiker, A. *J. Mol. Catal. A: Chem.* **2009**, *309*, 57. (d) Zhu, B.; Lazar, M.; Trewyna, B. G.; Angelici, R. J. *J. Catal.* **2008**, 260. (e) Grirrane, A.; Corma, A.; Garcia, H. *J. Catal.* **2009**, *264*, 138. (f) Guo, H.; Kemell, M.; Al-Hunaiti, A.; Rautiainen, S.; Leskelä, M.; Repo, T. *Catal. Commun.* **2011**, *12*, 1260. (g) Wendlandt, A. E; Stahl, S. S. *Org. Lett.* **2012**, *14*, 2850. (h) Zhang, E.; Tian, H.; Xu, S.; Yu, X.; Xu, Q. *Org. Lett.* **2013**, *15*, 2704.

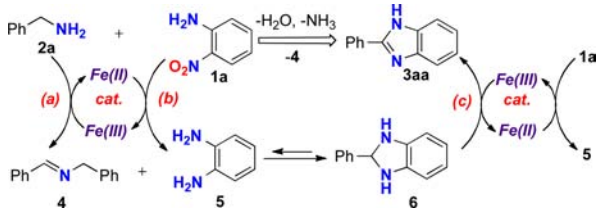
Table 3. Cobalt- or Iron-Catalyzed Redox Condensation of *o*-Nitroaniline **1** with Benzylamine **2a**[a]

entry	*o*-nitroaniline **1**	benzimidazole **3**	temp (°C)	yield (%)
1	**1b**	**3ba**	120 120	77[b] 75[c]
2	**1c**	**3ca**	120 120	65[b] 70[c]
3	**1d**	**3da**	120 120	78[b] 80[c]
4	**1e**	**3ea**	120 120	65[b] 66[c]
5	**1f**	**3fa**	120 120	62[b] 65[c]
6	**1g**	**3ga**	120 140	30[d] 71[d]
7	**1h**	**3ha**	130	70[d]
8	**1i**	**3ia**	140	72[d]

[a] Reaction conditions: *o*-nitroaniline **1** (5 mmol), benzylamine **2a** (15 mmol), metal salt (2−5 mol %). [b] Catalyst $CoBr_2 \cdot xH_2O$ (Co assay 18.5% Co) (2 mol %). [c] Catalyst $FeCl_3 \cdot 6H_2O$ (2 mol %). [d] Catalyst $FeCl_3 \cdot 6H_2O$ (5 mol %).

includes formation of the final benzimidazole **3aa** product by a cascade condensation **4** + **5** → **6**, oxidation–aromatization **6** → **3aa**.

Scheme 1. Proposed Mechanism



It is noteworthy that both hydrated $CoBr_2$ and $FeCl_3$ failed to promote efficiently the redox condensation of *o*-nitroaniline **1a** with amines other than primary

Table 4. Fe/S-Catalyzed Redox Condensation of *o*-Nitroaniline **1a** with Amines and *o*-Nitrobenzamides **1j**,**k** with Benzylamines[a]

entry	nitrobenzene **1**	amine **2**	temp (°C)	product, yield (%)
1	**1a**	**2a**, $R^1 = R^2 = H$	120	**3aa**, 87
2	**1a**	**2a'**, $R^1 = H$, $R^2 = Me$	120	**3aa**, 90
3[b]	**1a**	**2a''**, $R^1 = H$, $R^2 = Bn$	130	**3aa**, 76
4	**1a**	**2a'''**, $R^1 = R^2 = Me$	120	**3aa**, 10
5	**1a**	**2a'''**, $R^1 = R^2 = Me$	140	**3aa**, 65
				3ag, 25[c]
6[b]	**1a**	**2g**	120	**3ag'**, 48
7[b]	**1a**	**2h**	120	**3ah**, 65
8[b]	**1a**	**2i**	120	**3ai**, 72
9[b]	**1a**	**2j**	130	**3aj**, 67
10	**1j**	**2a**, $R^1 = R^2 = H$	140	**3ja**, 73
11	**1j**	**2a'**, $R^1 = H$, $R^2 = Me$	140	**3ja**, 75
12	**1j**	R' = *p*-Me, **2b**	140	R' = *p*-Me, **3jb**, 71
13	**1j**	R' = *p*-MeO, **2d**	140	R' = *p*-MeO, **3jd**, 70
14	**1j**	R' = *m*-MeO, **2e**	140	R' = *m*-MeO, **3je**, 69
15	**1j**	R' = *o*-Cl, **2f**	140	R' = *o*-Cl, **3jf**, 72
16	**1k**	**2a**	150	**3ka**, 68

[a] Reaction conditions: **1a**,**j**,**k** (5 mmol), amine **2** (15 mmol), $FeCl_3 \cdot 6H_2O$ (5 mol %, 0.25 mmol), S (20 mol %, 1 mmol, 32 mg) unless otherwise noted. [b] **1a** (2.5 mmol), **2g** (5 mmol). [c] Conversion by ^1H NMR.

benzylamines (Table 4). To solve this handicap and in connection with our previous results obtained with the Fe/S catalyst,[3,4] we decided to study the applicability of the present methodology using the iron/sulfur catalyst generated *in situ* from hexahydrated ferric chloride (5 mol %) and elemental sulfur (20 mol %).[8]

To our delight, this catalyst displayed a high efficiency in promoting the reaction not only with unsubstituted benzylamine **2a** (entry 1) but also with various amines (entries 2−8). The condensed product **3aa** could be formed from different *N*-substituted benzylamines.

While the reaction with *N*-methylbenzylamine **2a′** proceeded smoothly, the condensation with more hindered analogues **2a″** and **2a‴** required higher temperatures (entries 3, 5). Amines other than benzylamines such as *n*-octylamine (**2g**, entry 6), di-*n*-butylamine (**2h**, entry 7), triethylamine (**2i**, entry 8), and tri-*n*-propylamine (**2j**, entry 9) could also condense with **1a** to provide the corresponding benzimidazoles **3ag**−**3aj**. Although the formation of quinoxaline product **3ag′** was the major reaction pathway in the reaction of **2g** (entry 6), this type of condensation remained only a minor side reaction in the cases of secondary and tertiary amines **2h**−**j**. While the explanation for this observation remained unknown, some factors could strongly modify the product distribution, including steric hindrance of amines **2**, molar ratio of the starting materials, and reaction temperature. An investigation of these parameters is underway in our laboratory.

As final trials to establish the scope of *o*-substituted nitrobenzene using the Fe/S catalyst, we condensed *o*-nitrobenzamide **1j,k** with benzylamines to furnish the corresponding quinazolin-4(3*H*)-ones.[9] Representative examples given in entries 12−16 showed that the reaction could be applied successfully to a wide range of benzylamines with high functional group tolerance. As a general trend, reaction with the *N*-substitued substrate **1k** required a higher temperature.

The differences in catalytic activity observed with the two Co and Fe halides and Fe/S can be attributed to the differences in their electrochemical properties. As clusters with multiple iron and sulfur atoms in different oxidation states, the Fe/S catalyst is expected to behave as an electronically more flexible capacitor which is capable of storing and releasing electrons for redox reactions with a wide range of redox potentials.

In conclusion, we have demonstrated that the redox condensation reaction between *o*-nitroanilines and benzylamines can be achieved smoothly by using iron- and cobalt-halide salts. The scope of the reaction can be extended to other alkylamines as reducing reaction components or 2-nitrobenzamides as oxidizing components when using an iron/sulfur catalyst. Overall, our procedure is highlighted by its simple, straightforward, step- and redox-economical nature combined with the use of readily available, inexpensive, and nontoxic catalysts. Our future study will focus on the mechanistic understanding and on the application of this redox condensation methodology to the synthesis of biologically interesting molecules.

Supporting Information Available. Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

(8) Control experiments using only elemetal sulfur as a catalyst (20 mol %) resulted in less than 5% of the condensed heterocyclic products **3**.

(9) Hydrated $CoBr_2$ or $FeCl_3$ or elemental sulfur failed to promote this redox condensation.

The authors declare no competing financial interest.