Tetrahedron Letters 54 (2013) 3167–3170

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Metal-free C–N bond-forming reaction: straightforward synthesis of anilines, through cleavage of aryl C–O bond and amide C–N bond

Jianzhong Yu [a], Peizhi Zhang [b], Jun Wu [a,*], Zhicai Shang [a,*]

[a] Department of Chemistry, Zhejiang University, Hangzhou 310027, PR China
[b] School of Biological and Chemical Engineering, Zhejiang University of Science and Technology, Hangzhou 310012, PR China

ARTICLE INFO

Article history:
Received 23 January 2013
Revised 21 March 2013
Accepted 8 April 2013
Available online 15 April 2013

Keywords:
C–N bond formation
Metal-free
Anilines
Aryl C–O bond

ABSTRACT

An efficient metal-free C–N bond forming reaction through cleavage of aryl C–O bond and amide C–N bond has been developed. This process represents a practical method for the facile construction of anilines with a broad substrate scope and wide functional group tolerance in moderate to excellent yields.

Anilines are important intermediates for the synthesis of agrochemicals, pharmaceuticals, dyes, and pigments. Traditionally, the manufacturing processes for anilines are based on aromatic nitration and the continuous catalytic hydrogenation of nitroaromatic compounds. Both of them are limited to the preparation of those molecules containing sensitive functional groups. In addition, these processes generate a large amount of waste liquid in the use of sulfuric acid and nitric acid and cause environmental pollution.[1,2] Recent progresses of aniline synthesis via transition-metal-catalyzed cross-coupling reaction of aryl halides with ammonia or ammonia surrogates have been reported.[3] The palladium-catalyzed synthesis of anilines has been developed through couplings of aryl halides (X= I, Br, Cl) or phenol derivatives with ammonia.[4] Similarly, the copper-catalyzed coupling reaction of ammonia with aryl iodides or aryl bromides is available, while the coupling with less reactive but more economically attractive aryl chlorides does not occur.[5] Also, the copper-catalyzed reaction of aromatic boronic acids with ammonia enables direct access to anilines.[6] Despite remarkable advances, there are some notable limitations. Particularly, the presence of heavy transition-metal impurities in the final products remains a major problem. A wide variety of functional groups, including iodo and bromo moieties are typically sensitive in palladium- and copper-catalyzed coupling reactions. For these reasons, the development of metal-free methods will probably provide new ways for constructing anilines.[7]

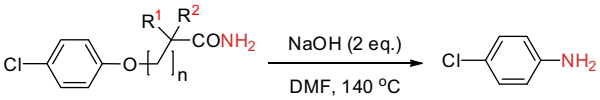
Phenols and their derivatives are common reagents.[8] The aryl C–O bond is generally 'inert' so that the cleavage of aryl C–O bond is very difficult.[9] Only very few examples have been reported for the construction of anilines starting from phenol-derived compounds under metal-free conditions.[10] For example, the alkylation-Smiles rearrangement-hydrolysis sequence has been used for the preparation of anilines, but this method requires harsh reaction conditions and has limited substrate scope.[10b] Herein, we report the example of metal-free cleavage of aryl C–O bond and amide C–N in aryloxyamides, which leads to the formation of new C–N bond. Use of this type reaction provides an efficient and straightforward access to anilines. This general method has highly appreciated qualities of a chemical transformation, including simple operation, high selectivity, and affordable starting materials.

Initially, we selected aryloxyamides **1**–**7** as our model system for the investigation of C–N bond-forming reaction. We treated aryloxyamides with sodium hydroxide as base (2.0 equiv) in *N*,*N*-dimethylformamide solvent at 140 °C (Table 1). No expected C–N bond-forming reactions were observed with **1**, **2**, and **3** (Table 1, entries 1–3, yields <5%). To our delight, the desired C–N bond-forming reaction was observed with **4** (Table 1, entry 4), albeit in low yield. Then, we tested the variation of R^1 groups (R^2=H). Compared with aryloxyamides **5** and **6**, the use of aryloxyamide **7** performed much better in the C–N bond-forming reactions, producing the highest yield up to 55% (Table 1, entries 5–7). As a result, we found that carbon chain length (n) and substituents (R^1 and R^2) had a large effect on the C–N bond formation and aryloxyamide **7** (n = 0, R^1 = CH_3, R^2 = H) was identified as the best substrate in the synthesis of anilines.

* Corresponding authors. Tel.: +86 571 87951352; fax: +86 571 87951895 (J.W.); tel.: +86 571 87952379; fax: +86 571 87951895 (Z.S.).
E-mail addresses: wujunwu@zju.edu.cn (J. Wu), shangzc@zju.edu.cn (Z. Shang).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.04.028

Table 1
Optimization studies for aryloxyamides **1**–**7** as substrates for C–N bond-forming reactions[a]

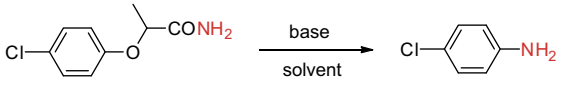


1-7 **8**

Entry	Aryloxyamides	*n*	R^1	R^2	Yield[b] (%)
1	**1**	0	CH_3	CH_3	<5
2	**2**	0	$COCH_3$	H	nr
3	**3**	1	H	H	nr
4	**4**	0	H	H	32
5	**5**	0	Ph	H	50
6	**6**	0	$CONH_2$	H	47
7	**7**	0	CH_3	H	55

[a] Reaction conditions: **1** (1.0 mmol), NaOH (2.0 mmol), DMF (4.0 mL), 140 °C, 3 h.
[b] Isolated yield after column chromatography.

Table 2
Optimization studies for reaction conditions[a]



7 **8**

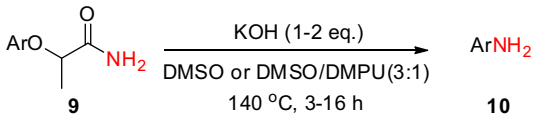
Entry	Base (equiv)	Solvent	Temp/Time	Yield[b] (%)
1	K_2CO_3 (2.0)	CH_3CN	Reflux/16 h	n.r.
2	K_2CO_3 (2.0)	DMF	Reflux/16 h	n.r.
3	Cs_2CO_3 (2.0)	DMF	Reflux/16 h	n.r.
4	NaH (2.0)	DMF	Reflux/16 h	13
5	NaOH (2.0)	DMF	120 °C/3 h	9
6	NaOH (2.0)	DMF	140 °C/3 h	55
7	KOH (2.0)	DMF	140 °C/3 h	60
8	KOH (2.0)	DMAC	140 °C/3 h	55
9	KOH (2.0)	DMSO	140 °C/3 h	65
10	KOH (2.0)	DMSO	160 °C/3 h	63
11	KOH (2.0)	DMSO/DMPU (3:1)	140 °C/3 h	65
12	KOH (2.0)	DMPU	140 °C/3 h	64
13	KOH (1.0)	DMSO	140 °C/3 h	48

[a] Reaction conditions: **7** (1.0 mmol), base (1.0–2.0 mmol), solvent (4.0 mL).
[b] Isolated yield after column chromatography.

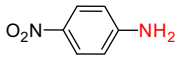
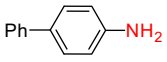
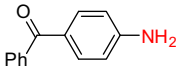
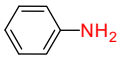
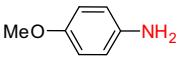
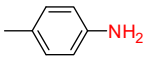
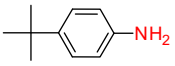
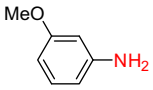
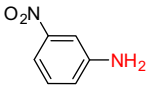
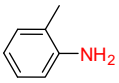
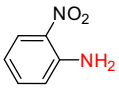
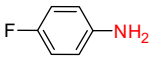
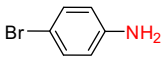
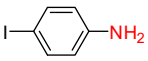
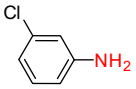
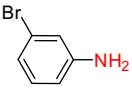
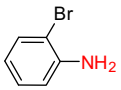
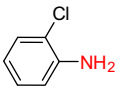
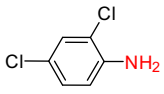
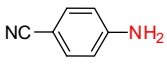
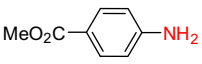
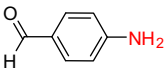
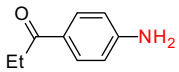
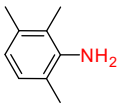
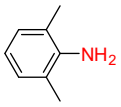
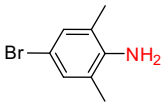
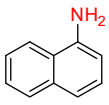
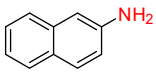
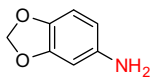
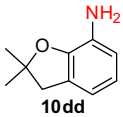
Next, aryloxyamide **7** was chosen as the model substrate to optimize the reaction conditions. Bases, solvents, and co-solvent were investigated at varied temperature (Table 2). We observed that the C–N bond-forming reaction proceeded to afford the product **8** in the presence of a variety of bases, and KOH was the best choice in the formation (Table 2, entry 7). Different solvents were also investigated, and dimethyl sulfoxide (DMSO) was the optimal solvent (Table 2, entry 9). 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyramidinone (DMPU) is often used as a co-solvent,[11] and the same activity was shown with DMSO/DMPU (3:1 ratio; Table 2, entry 11). We were pleased to find that the reaction also proceeded to give **8** even in the presence of 1.0 equiv of KOH, albeit in a decrease in isolated yield (Table 2, entry 13). After the screening, the optimum conditions for C–N bond-forming reaction were as follows: KOH as base, DMSO as solvent, DMPU as co-solvent, and the reaction was carried out at 140 °C.

We then explored the scope of this novel method. As shown in Table 3, all the substrates **9** derived quite easily from the corresponding phenols were examined under the standard reaction conditions. We found that the substrates containing electron-deficient, electron-neutral, and electron-rich groups at the *para*-, *meta*-, or *ortho*-positions provided moderate to excellent yields. Some substrates containing electron-neutral and electron-rich groups in DMSO as reaction solvent were found with very low yields (Table 3, **10d**–**f**). Delightedly, we found that the use of DMPU as co-solvent could dramatically increase the reactivity for the formation (**10d**–**f**). The method showed a wide substrate scope with good functional group tolerance. The aryloxyamides containing halogen substituted groups, such as F, Cl, Br, and I (**10l**–**s**), showed good reactivity, which offered an opportunity for further derivatizations through transition-metal-catalyzed techniques. Moreover, the substrates containing base-sensitive groups including the nitro, ester, aldehyde, and ketone groups were obtained successfully in the presence of only 1.0 equiv of KOH in moderate to high yields (**10t–w**). The 2-(2,3,6-trimethylphenoxy) propanamide, 2-(2,6-dimethyl phenoxy) propanamide, and 2-(4-bromo-2,6-dimethyl phenoxy) propanamide, which are more sterically hindered with two methyl groups at the **C**2 and **C**6 positions, also led to moderate yields (**10x**–**z**). Polycyclic-based substrates could be transformed to the corresponding anilines (**10aa**–**bb**). It is noteworthy that heteroaryl substrates could also be successfully converted into the corresponding anilines (**10cc**–**dd**).

Table 3
Scope of metal-free synthesis of anilines[a]



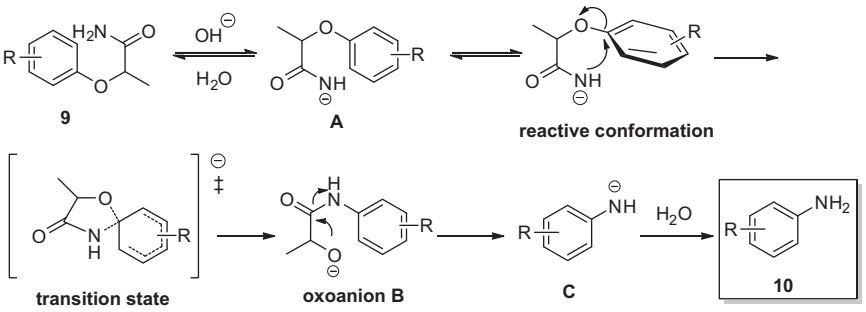
9 **10**

 **10a** 6h 48%[b]	 **10b** 3h 76%	 **10c** 4h 90%	 **10d** 16h 5%[a], 41%[b]
 **10e** 16h 0%,38%[b]	 **10f** 6h 5%[a], 56%[b]	 **10g** 6h 62%	 **10h** 8h 87%
 **10i** 3h 53%	 **10j** 16h 39%[b]	 **10k** 3h 95%	 **10l** 16h 35%[b]
 **10m** 3h 86%	 **10n** 3h 85%	 **10o** 6h 71%	 **10p** 4h 65%
 **10q** 4h 60%	 **10r** 4h 52%	 **10s** 3h 77%	 **10t** 3h 83%[c]
 **10u** 8h 48%[c]	 **10v** 8h 56%[c]	 **10w** 6h 81%[c]	 **10x** 16h 45%[b]
 **10y** 16h 50%[b]	 **10z** 8h 64%[b]	 **10aa** 6h 56%	 **10bb** 6h 81%
 **10cc** 8h 48%	 **10dd** 8h 79%[b]		

[a]Reaction conditions: **9** (1.0 mmol), KOH (2.0 mmol), DMSO (4 mL), 140 °C.
[b]Reaction conditions: **9** (1.0 mmol), KOH (2.0 mmol), DMSO (3 mL) and DMPU (1 mL), 140 °C.
[c]Reaction conditions: **9** (1.0 mmol), KOH (1.0 mmol), DMSO (4 mL), 140 °C.

Our proposed mechanism for the reaction is shown in Scheme 1. The first step of the reaction is the formation of the aryloxyamide anion **A**, a nucleophile by deprotonation of **9** in the presence of hydroxide ion.[12] The nucleophile attacks the aromatic nucleus in an *ipso* fashion to form a five-membered transition state.[13] Breaking of the C–N bond in the transition state regenerates aryloxyamide anion **A** in an unproductive process. Breaking of the C–O bond in the transition state leads to the formation of oxoanion **B** in a productive process. Oxoanion **B** attacks carbonyl carbon via an intramolecular nucleophilic addition to break the C–N bond, releasing the anilinium ion **C**.[14] This anilinium ion **C** captures proton from water to give the final product aniline **10**.

In conclusion, an efficient and metal-free method for constructing anilines from aryloxyamides through cleavage of aryl C–O bond and amide C–N bond has been developed. This transformation is an extremely simple way and offers anilines in moderate to excellent



Scheme 1. Plausible reaction mechanism.

yields via more environmentally benign processes. The reaction displays a broad scope of substrates and tolerates a number of functional groups, including halogen and base-sensitive groups. We believe that the method should have potential to become a widely used transformation in many applications and further researches are going on in our laboratory.

Acknowledgment

Funding from the National Natural Science Foundation of China (No. 31071720) is greatly acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.04.028.

References and notes

1. Downing, R. S.; Kunkeler, P. J.; VanBekkum, H. *Catal. Today* **1997**, *37*, 121–126.
2. Blaser, H. U.; Steiner, H.; Studer, M. *ChemCatChem* **2009**, *1*, 210–221.
3. (a) Lee, S.; Jorgensen, M. *Org. Lett.* **2001**, *3*, 2729–2732; (b) Huang, X. H.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3417–3419; (c) Lee, D. Y.; Hartwig, J. F. *Org. Lett.* **2005**, *7*, 1169–1172; (d) Gao, X.-T.; Fu, H.; Qiao, R.-Z.; Jiang, Y.-Y.; Zhao, Y.-F. *J. Org. Chem.* **2008**, *73*, 6864–6866; (e) Aubin, Y.; Fischmeister, C.; Thomas, C. M.; Renaud, J. L. *Chem. Soc. Rev.* **2010**, *39*, 4130–4135; (f) Klinkenberg, J. L.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 86–95.
4. (a) Shen, Q. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 10028–10029; (b) Surry, D. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 10354–10355; (c) Willis, M. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 3402–3404; (d) Lundgren, R. J.; Peters, B. D.; Alsabeh, P. G.; Stradiotto, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 4071–4074; (e) Klinkenberg, J. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 11830–11833; (f) Vo, G. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 11049–11061; (g) Schulz, T.; Torborg, C.; Enthaler, S.; Schaffner, B.; Dumrath, A.; Spannenberg, A.; Neumann, H.; Borner, A.; Beller, M. *Chem. Eur. J.* **2009**, *15*, 4528–4533; (h) Lee, B. K.; Biscoe, M. R.; Buchwald, S. L. *Tetrahedron Lett.* **2009**, *50*, 3672–3674; (i) Lundgren, R. J.; Sappong-Kumankumah, A.; Stradiotto, M. *Chem. Eur. J.* **2010**, *16*, 1983–1991.
5. (a) Kim, J.; Chang, S. *Chem. Commun.* **2008**, *26*, 3052–3054; (b) Xu, H.; Wolf, C. *Chem. Commun.* **2009**, *35*, 3035–3037; (c) Wu, X.-F.; Darcel, C. *Eur. J. Org. Chem.* **2009**, *28*, 4753–4756; (d) Wang, D.-P.; Cai, Q.; Ding, K. *Adv. Synth. Catal.* **2009**, *351*, 1722–1726; (e) Jiang, L.-Q.; Lu, X.; Zhang, H.; Jiang, Y.-W.; Ma, D.-W. *J. Org. Chem.* **2009**, *74*, 4542–4546; (f) Xia, N.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 337–339; (g) Yang, C.-T.; Fu, Y.; Huang, Y.-B.; Yi, J.; Guo, Q.-X.; Liu, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 7398–7401; (h) Wu, Z.-Q.; Jiang, Z.-Q.; Wu, D.; Xiang, H.-F.; Zhou, X.-G. *Eur. J. Org. Chem.* **2010**, *10*, 1854–1857; (i) Meng, F.; Zhu, X.-H.; Li, Y.; Xie, J.-W.; Wang, B.; Yao, J.-H.; Wan, Y.-Q. *Eur. J. Org. Chem.* **2010**, *32*, 6149–6152; (j) Xu, H.-J.; Liang, Y.-F.; Cai, Z. Y.; Qi, H.-X.; Yang, C.-Y.; Feng, Y.-S. *J. Org. Chem.* **2011**, *76*, 2296–2300; (k) Jiao, J.; Zhang, X.-R.; Chang, N.-H.; Wang, J.; Wei, J.-F.; Shi, X.-Y.; Chen, Z.-G. *J. Org. Chem.* **2011**, *76*, 1180–1183; (l) Siddegowda, M. S.; Yathirajan, H. S.; Ramakrishna, R. A. *Tetrahedron Lett.* **2012**, *53*, 5219–5222.
6. Rao, H.-H.; Fu, H.; Jiang, Y.-Y.; Zhao, Y.-F. *Angew. Chem., Int. Ed.* **2009**, *48*, 1114–1116.
7. Zhu, C.; Li, G.-Q.; Ess, D. H.; Falck, J. R.; Kurti, L. *J. Am. Chem. Soc.* **2012**, *134*, 18253–18256.
8. Izawa, Y.; Pun, D.; Stahl, S. S. *Science* **2011**, *333*, 209–213.
9. Li, B.-J.; Yu, D.-G.; Sun, C.-L.; Shi, Z.-J. *Chem. Eur. J.* **2011**, *17*, 1728–1759.
10. (a) Coutts, I. G. C.; Southcott, M. R. *J. Chem. Soc., Perkin Trans. 1* **1990**, *3*, 767–771; (b) Mizuno, M.; Yamano, M. *Org. Lett.* **2005**, *7*, 3629–3631; (c) Chen, X.; Wu, J.; Shang, Z.-C.; Chen, M.-F.; Sun, Y.-P.; Lv, J.; Lei, M.-K.; Zhang, P.-Z. *Tetrahedron Lett.* **2008**, *49*, 495–499; (d) Zhou, Y.-P.; Pan, Y.-J.; Cao, X.-J.; Wu, J.; Jiang, K.-Z. *J. Am. Soc. Mass. Spectrom.* **2007**, *18*, 1813–1820.
11. Barker, B. J.; Rosenfarb, J.; Caruso, J. A. *Angew. Chem., Int. Ed.* **1979**, *18*, 503–507.
12. Breugst, M.; Tokuyasu, T.; Mayr, H. *J. Org. Chem.* **2010**, *75*, 5250–5258.
13. Newman, M. S. *Acc. Chem. Res.* **1972**, *5*, 354–360.
14. Taagepera, M.; Summerhays, K. D.; Hehre, W. J.; Topsom, R. D.; Pross, A.; Radom, L.; Taft, R. W. *J. Org. Chem.* **1981**, *46*, 891–903.