



Arylation of benzyl amines with aromatic nitriles†

Cite this: *Chem. Commun.*, 2018, 54, 11881

Received 6th August 2018,
Accepted 24th September 2018

DOI: 10.1039/c8cc06408c

rsc.li/chemcomm

Yingjie Lei, Ju Yang, Rupeng Qi, Shan Wang, Rui Wang * and Zhaoqing Xu *

In the past years, the activations of aromatic nitriles for radical arylations under photoirradiation have been developed. We here report the first example of radical arylations using aromatic nitriles without the assistance of photoirradiation. Importantly, with this method, the direct arylation of C(sp³)-H in benzyl amines provided a practical method for the synthesis of diarylmethylamines without the use of precious transition metal catalysts.

Diarylmethylamines are important structural motifs in medicinal chemistry and often act as central components of pharmaceuticals, bioactive natural products, and agrochemicals.¹ Importantly, recent statistical studies have indicated that the prominence of heteroaromatic rings in marketed oral drugs is increasing (Fig. 1).^{1c} In this context, the synthesis of diarylmethylamines has attracted more and more attention. In the past decades, the transition-metal-catalyzed direct α -C(sp³)-H arylations of benzyl amines with aryl halides have been developed, which provided convenient methods to prepare diarylmethylamines.² The reactions avoid the commonly employed nucleophilic addition of aryl-metal reagents (aryl lithium or Grignard reagent) to imines. In the reactions, precious transition-metal catalysts (mostly Pd) were required (Scheme 1, a).

In the past years, the application of aromatic nitriles for radical C(sp³)-H arylation has been developed.³ The reactions were usually proceeded under photoirradiation, in which the aromatic nitrile received an electron from the photoreductant and formed an aryl radical anion. This intermediate was then subjected to the subsequent radical coupling reactions (Scheme 1, b). For example, the MacMillan group recently realized the first example of photoinduced radical C-H arylation using aromatic nitriles as the arylation reagents.⁴ In these reactions, the sp³ C-H bonds at the allylic, benzylic, and α -positions of

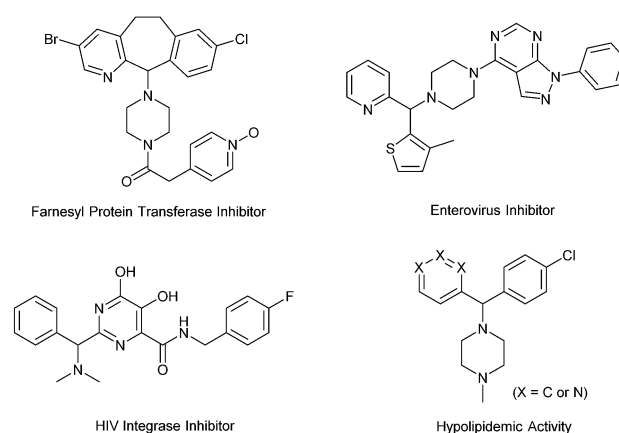


Fig. 1 Pharmacologically active compounds containing diaryl (heteroaryl) methylamines.

alkyl amines were successfully coupled with a variety of (hetero)-aromatic nitriles. With this strategy, the reactions needed to be conducted under UV light irradiation or proceeded under visible light with the assistance of a precious Ir photocatalyst.⁵ In 2013, Inoue and co-workers reported a novel photoinduced transition-metal free arylation reaction with aromatic nitriles. In this reaction, a sub-stoichiometric amount of benzophenone (0.5 equiv.) and 100 W medium pressure mercury lamp irradiation were essentially required to mediate the electron transfer.⁶ So far, the strategy to activate aromatic nitriles and apply to radical arylation without the assistance of photoirradiation has been undeveloped, and is still highly desirable.

In the past years, organic molecule based electron donors have received much attention due to their tunable reduction ability and environmentally benign reaction conditions.⁷ Among them, one class of compounds called super-electron-donors (SEDs) possess reduction potentials as high as -1.50 eV (versus SCE),⁸ which were able to initiate the dissociation of a large variety of chemical bonds.⁹ In the reactions, organic SEDs are capable of spontaneous one- or two-electron transfer from a donor to an organic substrate, while the bond dissociation can take place

Key Laboratory of Preclinical Study for New Drugs of Gansu Province, The Institute of Pharmacology, School of Basic Medical Sciences, Lanzhou University, 199 West Donggang Road, Lanzhou 730000, China.
E-mail: wangrui@lzu.edu.cn, zqxu@lzu.edu.cn

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c8cc06408c



Scheme 1 Research background introductions.

either simultaneously or in a stepwise process under mild and homogeneous conditions. Different ranges of redox potentials and choices of reactivities and selectivities can be achieved by simple modulation of their structure and the reaction parameters. These unique properties are now attracting more and more attention in various original applications like substitutions, addition, cyclization, polymerization initiators, and greenhouse gas reduction.¹⁰ For example, the Walsh group recently developed a novel transition-metal free radical coupling reaction of 2-azaallyl species with vinyl, aryl and alkyl halides.¹¹ The DFT computational studies and EPR experiment suggested that the 2-azaallyl anion served as an SED and mediated the SET (single electron transfer) with organic halides.

As a complementary method to the previously reported photo-induced activation of aromatic nitriles for radical arylations,^{4–6} we were interested in developing an alternative method without the assistance of photoirradiation. We envisioned that an SED, such as the 2-azaallyl anion, could possibly provide an electron to aromatic nitriles and promoted the generation of aryl radicals. Importantly, the direct arylation of 2-azaallyl based ketimines could provide a practical method for C(sp³)-H arylation for the synthesis of diarylmethylamines without the use of precious transition metal catalysts (Scheme 1, c).² In this reaction, the ketimine served not only as the SED to activate the aromatic nitrile but also as the radical coupling partner after SET.

The investigation was initiated using ketimines **1a** and 4-cyanopyridine **2a** (2 equiv.) as model substrates, and the reaction was proceeded at room temperature for 4 h in 1 ml methyl *tert*-butyl ether (MTBE). It was delightful that the desired arylation product **3a** was obtained in 40% yield using 3 equiv. of NaHMDS (NaN(SiMe₃)₂, Table 1, entry 1). Other basic additives were also tested in our reactions, such as LiO^tBu, NaO^tBu, KO^tBu, K₂CO₃, Na₂CO₃, NaOAc, Et₃N, TMEDA, DBU, DMAP, *etc.*; however, only LiHMDS and KHMDS gave the desired products but with lower yields (entries 2 and 3, see the ESI† for details). The solvent screening indicated that dimethoxyethane (DME) was the best choice (entries 4–8). Increasing the amount of NaHMDS to 4 equiv. did not improve the yield (entry 9).

Table 1 Optimization of the reaction conditions^a

Entry	Base	Solvent	Time (h)	Yield (%)
1	NaHMDS	MTBE	4	40
2	LiHMDS	MTBE	4	28
3	KHMDS	MTBE	4	18
4	NaHMDS	THF	4	56
5	NaHMDS	DME	4	72
6	NaHMDS	Toluene	4	21
7	NaHMDS	Dioxane	4	44
8	NaHMDS	Et ₂ O	4	22
9 ^b	NaHMDS	DME	4	68
10 ^c	NaHMDS	DME	4	38
11	NaHMDS	DME	12	95 (88)
12	NaHMDS	DME	24	69

^a Reaction conditions: unless otherwise noted, reactions were conducted using 0.2 mmol of **2a**, 2 equiv. of **1**, 2 equiv. of **1a**, 3 equiv. of base, and 1 ml solvent. NaHMDS 2 M in THF was used. ^b 4 equiv. of NaHMDS used. ^c 2 equiv. of NaHMDS used. Yields were determined by ¹H NMR using mesitylene as the internal standard; the isolated yield indicated in parentheses.

To our satisfaction, upon reducing the loading of NaHMDS to 2 equiv. and extending the time to 12 h, a complete conversion of **1a** was observed with 95% yield (88% isolated yield, entries 10–12).

With the optimized reaction conditions in hand, we first studied the substrate scope with respect to the ketimine with different substituents. The substrates with *-tert*-Bu, -OMe, -OPh, -F, and -Cl at the *para*-position of the aryl ring all gave good results (**3b–3f**). The aromatic ketimines with *-3-CH₃*, *-2-F*, and *-2-Cl* afforded compatible yields (**3g–3i**). It was worth noting that heteroaryl substituted substrates, such as 2-pyridyl, 2-furyl, and 2-thiophenyl ketimines, also underwent the reaction smoothly and afforded the corresponding products in good yields (**3j–3l**). Our attention then turned to the variation of the aromatic nitriles. Cyano-substituted pyridines with halide or phenyl substituents at the 2-position of pyridine were tolerated and afforded the corresponding heteroarylated products with good results (**3m–3q**). Unfortunately, 2-cyanopyridine and 3-cyanopyridine did not give the desired products, which might be attributed to the competing side-reaction under basic conditions.¹² The cyanopyridine substrates were consumed in the system with complex by-products formed. The site specificity of the coupling process can be further exploited through the use of 1,2-dicyanobenzene, efficiently forming diarylmethylamines **3r** and **3s** in 66% and 70% yields respectively. The substrates with the *-F* (**3u**) and *-OMe* (**3v**) groups were also well tolerated. A simple chloride can function equivalently to *-CN* as a suitable leaving group; this enables heteroarylation of ketimines with chloro-substituted benzoxazole (**3t**) (Table 2).

To test the scalability of this protocol, we performed the gram-scale synthesis of a heterocyclic product (**3k**). Ketimine **1k** was prepared from the corresponding furyl amine and benzophenone imine precursors and directly used for the next step without further purification. The radical arylation step was

Table 2 Substrate scope studies^a

^a Reaction conditions: unless otherwise noted, reactions were conducted using 0.2 mmol of **2**, 2 equiv. of **1**, 2 equiv. of NaHMDS, and 1 ml DME, and the mixture was stirred at r.t. for 12 h. Isolated yields. ^b 4 equiv. of NaHMDS, 1 ml DME, and stirred at r.t. for 15 h.

performed with 4-cyanopyridine with a standard process and afforded the desired product (**3k**) in 61% overall yield (1.03 g, Scheme 2, eqn (1)). Hydrolysis of **3s** was conducted to afford 4-(amino(2-chlorophenyl)methyl)benzonitrile (**4**) in 80% yield.

In order to gain some information on the reaction mechanism, radical inhibition experiments were carried out. When 2 equiv. of radical scavenger TEMPO (2,2,6,6-tetromethyl-1-piperidinyloxy) was added under the standard conditions, the reaction was completely suppressed (Scheme 3, eqn (1)). Addition of butylated hydroxytoluene (BHT) led to a dramatic decrease of



Scheme 2 Synthetic applications.



Scheme 3 Mechanistic studies.

the yield (eqn (2)). These results suggested that a radical pathway might be involved in the current reaction.

Although the precise reaction mechanism remains to be clarified, guided by these supporting pieces of evidence and known literature reports,¹¹ a plausible mechanism for the reaction is depicted in Scheme 4. At the beginning, the azaallyl anion **A** was formed after deprotonation of 2-azaallyl by NaHMDS, which could serve as an SED to donate an electron to nitriles and formed the corresponding arene radical anion **C**. In the meantime, 2-azaallyl radical **B** was simultaneously formed during this SET process. The subsequent coupling of the relatively long lived persistent 2-azaallyl radical **B** with the short lived transient aromatic radical provided the desired arylation product owing to the persistent radical effect.¹³



Scheme 4 Proposed mechanism.

In summary, we reported that organic SEDs (2-azaallyl anions) drove SET, which was able to activate aromatic nitriles for radical arylations without the assistance of photoirradiation. The reaction required only commercially available base and proceeded under mild conditions. The azaallyl based ketimine acts not only as an electron donor reagent but also a benzyl amine substrate, which facilitated the C(sp³)-H arylation of benzyl amines for the synthesis of diarylmethylamines under transition metal free conditions.

We are grateful for the grants from the NSFC (No. 21432003) and Fundamental Research Funds for the Central Universities (lzujbky-2017-127 and lzujbky-2018-k09).

Conflicts of interest

There are no conflicts to declare.

Notes and references

- Some selected examples: (a) M. Liu, M. S. Bryant, J. Chen, S. Lee, B. Yaremko, Z. Li, J. Dell, P. Lipari, M. Malkowski, N. Prioli, R. R. Rossman, W. A. Korfmacher, A. A. Nomeir, C. C. Lin, A. K. Mallams, R. J. Doll, J. J. Catino, V. M. Girijavallabhan, P. Kirschmeier and W. R. Bishop, *Cancer Chemother. Pharmacol.*, 1998, **43**, 50; (b) J.-H. Chern, K.-S. Shia, T.-A. Hsu, C.-L. Tai, C.-C. Lee, Y.-C. Lee, C.-S. Chang, S.-N. Tseng and S.-R. Shih, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 2519; (c) V. Summa, A. Petrocchi, V. G. Matassa, C. Gardelli, E. Muraglia, M. Rowley, O. G. Paz, R. Laufer, E. Monteagudo and P. Pace, *J. Med. Chem.*, 2006, **49**, 6646; (d) H. Anagnostopulos, R. R. Bartlett, U. Elben and P. Stoll, *Eur. J. Med. Chem.*, 1989, **24**, 227; (e) T. J. Ritchie, S. J. F. Macdonald, R. J. Young and S. D. Pickett, *Drug Discovery Today*, 2011, **16**, 164.
- Some selected examples: (a) T. Niwa, H. Yorimitsu and K. Oshima, *Org. Lett.*, 2008, **10**, 4689; (b) T. Niwa, T. Suehiro, H. Yorimitsu and K. Oshima, *Tetrahedron*, 2009, **65**, 5125; (c) G. I. McGrew, J. Temaismithi, P. J. Carroll and P. J. Walsh, *Angew. Chem., Int. Ed.*, 2010, **49**, 5541; (d) G. I. McGrew, C. Stanciu, J. Zhang, P. J. Carroll, S. D. Dreher and P. J. Walsh, *Angew. Chem., Int. Ed.*, 2012, **51**, 11510; (e) M. Li, S. Berritt and P. J. Walsh, *Org. Lett.*, 2014, **16**, 4312; (f) B.-S. Kim, J. Jimenez, F. Gao and P. J. Walsh, *Org. Lett.*, 2015, **17**, 5788; (g) J. A. FernandezSalas, E. Marelli and S. P. Nolan, *Chem. Sci.*, 2015, **6**, 4973; (h) M. Li, B. Yücel, J. Adrio, A. Bellomo and P. J. Walsh, *Chem. Sci.*, 2014, **5**, 2383.
- (a) B. Lipp, A. M. Nauth and T. Opatz, *J. Org. Chem.*, 2016, **81**, 6875; (b) A. M. Nauth, A. Lipp, B. Lipp and T. Opatz, *Eur. J. Org. Chem.*, 2017, 2099; (c) B. Lipp, A. Lipp, H. Detert and T. Opatz, *Org. Lett.*, 2017, **19**, 2054.
- (a) M. Andrew, K. P. Christopher and D. W. C. MacMillan, *Science*, 2011, **334**, 1114; (b) Z. Zuo and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2014, **136**, 5257; (c) J. D. Cuthbertson and D. W. C. MacMillan, *Nature*, 2015, **519**, 74.
- (a) J. A. Vega, J. M. Alonso, G. Mendez, M. Ciordia, F. Delgado and A. A. Trabanco, *Org. Lett.*, 2017, **19**, 938; (b) C. Yan, L. Li, Y. Liu and Q. Wang, *Org. Lett.*, 2016, **18**, 4686.
- T. Hoshikawa and M. Inoue, *Chem. Sci.*, 2013, **4**, 3118.
- Some selected examples: (a) S. S. Hanson, N. A. Richard and C. A. Dyker, *Chem. – Eur. J.*, 2015, **21**, 8052; (b) S. S. Hanson, E. Doni, K. T. Traboulsee, G. Coulthard, J. A. Murphy and C. A. Dyker, *Angew. Chem., Int. Ed.*, 2015, **54**, 11236; (c) E. Doni, S. O'Sullivan and J. A. Murphy, *Angew. Chem., Int. Ed.*, 2013, **52**, 2239; (d) E. Doni, B. Mondal, S. O'Sullivan, T. Tuttle and J. A. Murphy, *J. Am. Chem. Soc.*, 2013, **135**, 10934; (e) E. Cahard, F. Schoenebeck, J. Garnier, S. P. Y. Cutulic, S. Zhou and J. A. Murphy, *Angew. Chem., Int. Ed.*, 2012, **51**, 3673.
- H. S. Farwaha, G. Bucher and J. A. Murphy, *Org. Biomol. Chem.*, 2013, **11**, 8073.
- (a) *Electron Transfer in Chemistry*, ed. V. Balzani, Wiley-VCH, Weinheim, 2001; (b) *Electron Transfer Reactions in Organic Synthesis*, ed. P. Vanelle, Research Signpost, Trivandrum, 2002; (c) R. A. Rossi, A. B. Pierini and A. B. Peñeñory, *Chem. Rev.*, 2003, **103**, 71; (d) A. Houmam, *Chem. Rev.*, 2008, **108**, 2180.
- (a) M. Rueping, P. Nikolaienko, Y. Lebedev and A. Adams, *Green Chem.*, 2017, **19**, 2571; (b) Y. Su, Y. Li, R. Ganguly and R. Kinjo, *Chem. Sci.*, 2017, **8**, 7419; (c) F. Cumine, S. Zhou, T. Tuttle and J. A. Murphy, *Org. Biomol. Chem.*, 2017, **15**, 3324; (d) Y. Liu, J. Xu, J. Zhang, X. Xu and Z. Jin, *Org. Lett.*, 2017, **19**, 5709; (e) D. Munz, J. Chu, M. Melaimi and G. Bertrand, *Angew. Chem., Int. Ed.*, 2016, **55**, 12886; (f) J. Broggi, M. Rollet, J. L. Clément, G. Canard, T. Terme, D. Gigmes and P. Vanelle, *Angew. Chem., Int. Ed.*, 2016, **55**, 5994; (g) J. P. Barham, G. Coulthard, K. J. Emery, E. Doni, F. Cumine, G. Nocera, M. P. John, L. E. A. Berlouis, T. McGuire, T. Tuttle and J. A. Murphy, *J. Am. Chem. Soc.*, 2016, **138**, 7402; (h) R. Rayala, A. Giuglio-Tonolo, J. Broggi, T. Terme, P. Vanelle, P. Theard, M. Médebielle and S. F. Wnuk, *Tetrahedron*, 2016, **72**, 1969.
- (a) M. Li, O. Gutierrez, S. Berritt, A. Pascual-Escudero, A. Yeşilçimen, X. Yang, J. Adrio, G. Huang, E. Nakamaru-Ogiso, M. C. Kozłowski and P. J. Walsh, *Nat. Chem.*, 2017, **9**, 997; (b) M. Li, S. Berritt, L. Matuszewski, G. Deng, A. Pascual-Escudero, G. B. Panetti, M. Poznik, X. Yang, J. J. Chruma and P. J. Walsh, *J. Am. Chem. Soc.*, 2017, **139**(45), 16327.
- N. G. R. Hearn, R. Clérac, M. Jennings and K. E. Preuss, *Dalton Trans.*, 2009, 3193.
- (a) H. Fisher, *J. Am. Chem. Soc.*, 1986, **108**, 3925; (b) H. Fisher, *Chem. Rev.*, 2001, **101**, 3581; (c) A. Studer, *Chem. – Eur. J.*, 2001, **7**, 1159; (d) K.-S. Focsaneanu and J. Scaiano, *Helv. Chim. Acta*, 2006, **89**, 2473.