Multicomponent Reaction

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Multicomponent Reactions with Cyclic Tertiary Amines Enabled by Facile C–N Bond Cleavage

Qiming Zhu, Qinghe Yuan, Mingwei Chen, Mengping Guo, and Hanmin Huang**

Abstract: *A novel and catalyst-free multicomponent reaction with cyclic tertiary amines, electron-deficient aryl halides or heteroaromatic halides, and Na_2S enabled by facile C–N bond cleavage of the cyclic tertiary amines was developed. This direct and operationally simple method can be applied with a wide range of functional groups and provides an efficient and rapid approach to potentially drug-like products containing amine, azaarene, thioether, or phenol ether functionalities in good to excellent yields. The utility of this method was demonstrated by the rapid synthesis of the analgesic ruzadolane.*

Multicomponent reactions (MCRs) have proved to be one of the most powerful strategies for assembling complicated structures from simple staring materials in a one-pot manner and have been widely used for the synthesis of organic materials, natural products, and bioactive molecules.[1,2] Crucial to the successful development of these reactions is the identification of an active species or a process that can trigger subsequent multiple bond formations with several reactants. In principle, C–N bond cleavage could simultaneously produce two active reactive species (carbon and nitrogen nucleophiles),[3,4] which might be utilized to trigger a multicomponent reaction under appropriate reaction conditions. However, the realization of such a reaction remains a challenge owing to the formidable challenge of activating simple C–N bonds. Herein, we report that cyclic tertiary amines can act as a key component for initiating a multicomponent reaction enabled by facile C–N bond cleavage, in which a valuable sulfur atom is efficiently incorporated with simple and inexpensive Na_2S as the sulfur source. Such a reaction would be particularly valuable for the synthesis of piperazine- and sulfur-containing molecules, which represent ubiquitous motifs that are widely found in natural products and medicinal compounds (Figure 1).[5]

The alkylation of primary and secondary amines with alkyl halides is a traditional C–N formation reaction that offers an effective pathway for the synthesis of complex amines with simple amines as the nitrogen source. In contrast, when simple aryl halides are utilized instead of alkyl halides, the same type reaction is difficult realize owing to the lower electrophilicity of aryl halides. An attractive and complementary approach to address this problem is the use of more nucleophilic tertiary amines as coupling partners to react with electron-deficient aromatic halides through nucleophilic substitution and subsequent C–N bond cleavage.[6] However, the fast configuration inversion at the nitrogen center of simple tertiary amines significantly reduces exposure of the nitrogen lone pair to electrophiles, and thus reduces their reactivity. In contrast, cyclic tertiary amines show higher nucleophilicity since the corresponding configuration inversion is restricted,[7] and they could thus be utilized as an amine source for a catalyst-free amination reaction with aromatic halides. In this context, the nucleophilic displacement reaction between nitrochlorobenzenes and 1,4-diazabicyclo-(2.2.2)octane (DABCO) has been developed, in which the active quaternary ammonium salt is formed as the key intermediate and the corresponding C–N bond, which is activated by the attached electron-withdrawing group, can then be cleaved through nucleophilic attack by another molecular of DABCO.[8] Inspired by these results, we reasoned that intermediate **A** could be accessed through nucleophilic displacement between electron-deficient aromatic halide **1** and DABCO (**2**; Scheme 1). It would be expected that the active quaternary ammonium salt **A** might be intercepted by the more nucleophilic Ar^2S^- generated in situ from the reaction of aromatic halide **3** and Na_2S to give the C–N-difunctionalization product **4**. As a result, a new

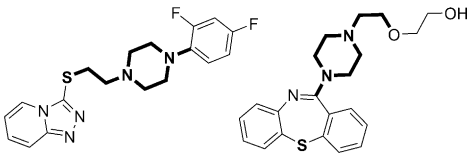
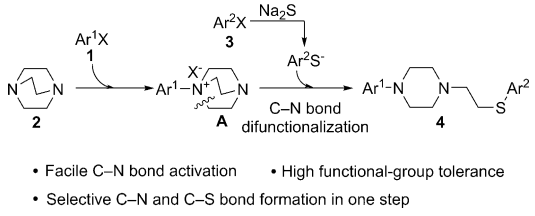


Figure 1. Examples of piperazine- and sulfur-containing bioactive molecules.



Scheme 1. A new multicomponent reaction via C–N bond cleavage.

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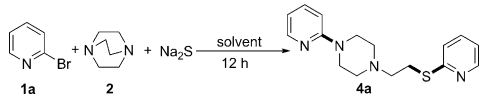
multicomponent reaction involving C–N bond cleavage as well as C–S and C–N bond formation would be established. One of the potential problems facing the development of this multicomponent reaction is the competitive nucleophilic reaction of intermediate **A** with the cyclic tertiary amine **2** instead of the proposed reaction with Ar^2S^-. We hypothesized that these rates could be controlled by tuning the electronic nature of the aromatic halides and reaction conditions.

To validate our hypothesis, we started the investigation by exploring the reaction of 2-bromopyridine (**1a**) with DABCO (**2**) and Na_2S in the absence of catalyst. To our delight, the desired product (**4a**) was successfully obtained in 80% yield of isolated product when the reaction was conducted at 120°C with DMF as the solvent (Table 1). Inspired by this promising result, we sought to improve the efficiency of the multicomponent reaction through solvent screening, and we observed that an aprotic polar solvent is beneficial for the desired reaction. Other nonpolar solvent and protic solvents were unsuitable (Table 1, entries 3–8). The best yield was obtained with DMSO as the solvent, and the diaryl thioether was not observed at all under these reaction conditions (Table 1, entry 2). Subsequently, the effect of temperature was also investigated. When the temperature was reduced to 80°C, the yield of **4a** decreased to 66% (Table 1, entry 10). However, when the temperature was increased to 140°C, **4a** was obtained in 82% yield, which indicates that further increasing the reaction temperature does not improve the efficiency.

Table 1: Optimization of the reaction conditions.[a]



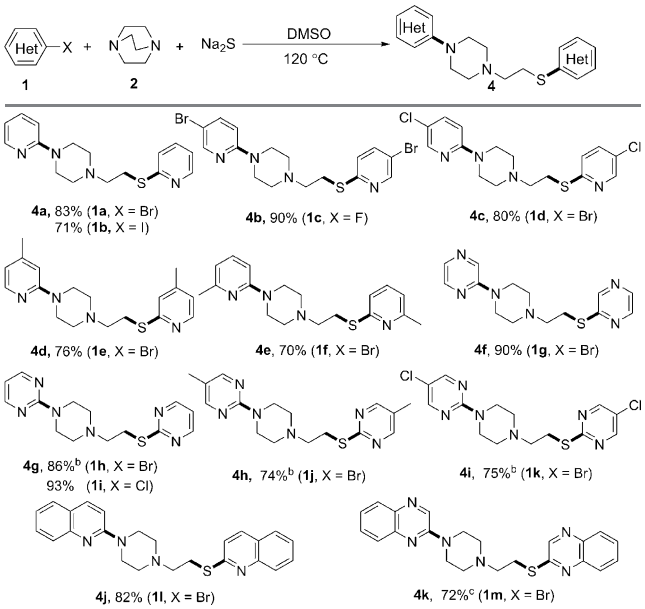
1a 2 4a

Entry	Solvent	*T* [°C]	Yield **4a** [%][b]
1	DMF	120	80
2	DMSO	120	83
3	dioxane	120	18
4	THF	120	23
5	CH_3CN	120	15
6	CH_3OH	120	17
7	CH_2Cl_2	120	<5%
8	toluene	120	16
9	DMSO	100	80
10	DMSO	80	66
11	DMSO	140	82

[a] Reaction condition: **1** (1 mmol), **2** (2 mmol), Na_2S (0.5 mmol) and solvent (2 mL) for 12 h. [b] Yield of isolated product. DMF = *N*,*N*-dimethylformamide, THF = tetrahydrofuran.

With the optimized conditions in hand, the substrate scope of this three-component reaction was studied. As shown in Table 2, a range of azaarene halides were tolerated to give the desired products **4a**–**4k** in good to excellent yields. Product **4a** was obtained in good yield with either 2-bromopyridine and 2-iodopyridine as the electrophile. This result indicates that the leaving group does not exert a strong effect on the reactivity, which is further demonstrated by the reactivity of **1c**, which has fluorine as a leaving group. Several

Table 2: Substrate scope of the three-component reaction.[a]

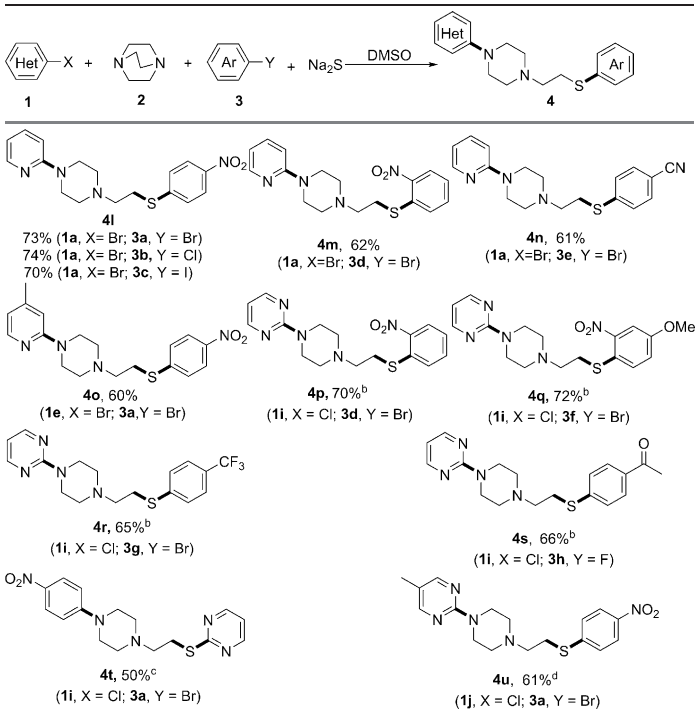


[a] Reaction conditions: **1** (1 mmol), **2** (2 mmol), Na_2S (0.5) and DMSO (2 mL), under N_2 at 120°C for 12 h; yield of isolated product. [b] Room temperature. [c] 80°C.

electron-withdrawing or -donating substituents were tolerated at the different positions of the pyridine ring, providing ample opportunity for further elaboration of the products. Aside from pyridine halides, 2-bromopyrazine was also compatible with this process and afforded the desired adduct **4f** in 90% yield. Furthermore, the pyrimidine-containing halides showed higher reactivity, and the corresponding reactions could be conducted at room temperature to provide the desired products in good yields (**4g**–**4i**). In addition, 2-bromoquinoline and 2-bromoquinoxaline gave the corresponding products in 82% and 72% yields, respectively. It is worth pointing out that no diaryl thioethers were observed in these three-component reactions. The good chemoselectivity may stem from the higher reactivity of intermediate **A** compared to azaarene halides. In the former, the strong electron-withdrawing ability of the azaarene contained in intermediate **A** could weaken the C–N bond and thus facilitate the nucleophilic attack by ArS^-.

Encouraged by the above results, we decided to further explore a four-component reaction for the synthesis of more complex azaarene-containing aminoalkyl thioethers (Table 3). 2-bromopyridine (**1a**), DABCO (**2**), Na_2S, and 1-bromo-4-nitrobenzene (**3a**) were successfully subjected to the C–N-difunctionalization method to give the desired product **4l** in 73% yield. The structure of product **4l** was confirmed by single-crystal X-ray diffraction analysis.[9] Further experiments demonstrated that the leaving group on the phenyl ring of nitrobenzene does not influence the reactivity. With these results in hand, the substrate scope of this reaction was investigated with 2-bromopyridine as a coupling partner. For the electron-deficient aryl halides **3**, typical strongly electron-withdrawing groups, such as $-NO_2$ and -CN, were tolerated to

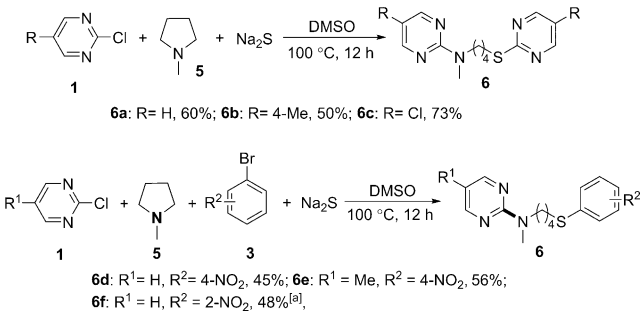
Table 3: Substrate scope of the four-component reaction.[a]



[a] Reaction conditions: **1** (0.5 mmol), **2** (2 mmol), **3** (0.5 mmol), Na_2S (0.5 mmol) and DMSO (2 mL) under N_2 at 120 °C for 12 h, isolated yield. [b] **3** (0.5 mmol), Na_2S (0.5 mmol) and DMSO (1 mL) were stirred under N_2 at room temperature for 2 h; then **1** (0.5 mmol), **2** (2 mmol) and DMSO (1 mL) added and stirred at room temperature for 2 h. [c] **1i** (0.5 mmol), Na_2S (0.5 mmol) and DMSO (1 mL) stirred under N_2 at room temperature for 2 h; **3a** (0.5 mmol), **2** (2 mmol) and DMSO (1 mL) added and stirred 140 °C for 12 h. [d] 80 °C.

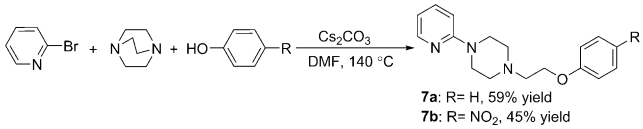
give the corresponding products **4m**–**4o** in good yields (60–62%). However, the one-pot four-component reaction of aryl halides **3** with 2-chloro-pyrimidine (**1i**), DABCO (**2**) and Na_2S did not proceed, and only the three-component product **4g** was observed. In this case, 2-chloropyrimidine is a more reactive electrophile than 4-halonitrobenzene (**3**), so the sulfide anion reacts selectively with the pyrimidine to tgive **4g**. This issue can be avoided by following a two-step sequential procedure, in which Na_2S and 4-halonitrobenzene are pre-mixed prior to the addition of chloropyrimidine (**1**) and DABCO (**2**), which gives the desired 4-component product **4** in good yield. With this two-step sequential process, a wide range of four-component reactions could be successfully carried out using 2-chloropyrimidine and various electron-deficient aryl halides as electrophiles to generate the corresponding adducts **4p**–**4s** in good yields. Some typical electron-withdrawing substituents, such as nitro, trifluoromethyl, and acetyl groups, were shown to be compatible with the reaction. One advantage of this two-step sequential reaction process is that the structure of the product can be easily tuned by changing the reactant-addition sequence (**4t**). Notably, reducing the electrophilicity of the pyrimidine moiety by introducing a methyl group in the *para* position of the pyrimidine ring enabled the four-component reaction to be conducted in a one-pot manner at a relatively low temperature (**4u**), which further demonstrates that finely tuning the electrophilicity of the two aromatic halides is crucial for the multicomponent reaction.

To further demonstrate the general applicability of our multicomponent reaction, 1-methylpyrrolidine (**5**) was utilized as the cyclic tertiary amine component for the corresponding three- and four-component reactions. As shown in Scheme 2, a series of desired products were obtained in moderate to good yields under slightly modified reaction conditions.

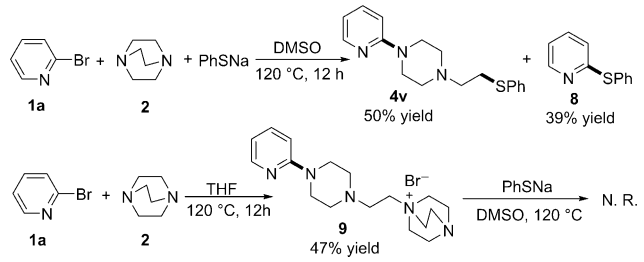


Scheme 2. Conditions for the three-component reaction: **1** (1 mmol), **5** (2 mmol), Na_2S (0.5 mmol), DMSO (2 mL) under N_2, at 100 °C or 120 °C for 12 h, isolated yield. Conditions for the four-component reaction: **1** (0.5 mmol), **5** (2 mmol), **3** (0.5 mmol), Na_2S (0.5 mmol), DMSO (2 mL), under N_2, at 100 °C or 120 °C for 12 h, isolated yield. [a] Conditions for the two-step sequential: **3** (0.5 mmol), Na_2S (0.5 mmol) and DMSO (1 mL) under N_2 at room temperature for 2 h; then **1** (0.5 mmol), **5** (2 mmol) and DMSO (1 mL) was added and stirred at 100 °C for 12 h (see the Supporting Information for details). DMSO = dimethyl sulfoxide.

Besides the aryl thiolate, phenolates can also be utilized as nucleophiles for the three-component reaction. With Cs_2CO_3 as a base, phenol and 4-nitrophenol reacted with 2-bromopyridine and DABCO smoothly to afford 1-(2-phenoxyethyl)-4-(pyridin-2-yl)piperazine (**7a**) and 1-(2-(4-nitrophenoxy)ethyl)-4-(pyridin-2-yl)piperazine (**7b**), respectively, in moderate yields. The structure of product **7b** was confirmed by single-crystal X-ray diffraction analysis.[9]



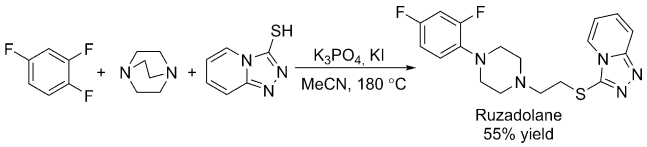
To gain insight into the mechanism of this process, several control experiments were conducted. Treatment of **1a** with DABCO (**2**) and sodium benzenethiolate (NaSPh) under the standard reaction conditions gave the desired aminoalkyl thioether **4v** in 50% yield, together with thioether **8**, thus indicating plausible intermediacy by ArS^- (Scheme 3). The quaternary ammonium salt **9** was isolated in 47% yield upon treating 2-bromopyridine with two equiv of DABCO in THF at 120 °C for 12 h [Scheme 3]. However, no reaction took place when the quaternary ammonium salt **9** was treated with



Scheme 3. Control experiments.

NaSPh under the standard reaction conditions. These results indicate that the electron-withdrawing group attached to the C–N bond of the quaternary ammonium salt is essential for facilitating C–N bond cleavage, which is the key step for the realization of these multicomponent reactions.

The usefulness of this new method was further demonstrated by the synthesis of the analgesic ruzadolane.[5c] The one-pot three-component reaction of 1,2,4-trifluorobenzene, DABCO, and [1,2,4]triazolo[4,3-a]pyridine-3-thiol was successfully realized to provide the desired drug in 55% yield under 180 °C for 72 h (Scheme 4). The reaction time could be shortened to 20 h under microwave heating to afford the desired product in 52% yield. This method thus presents an efficient and rapid approach to ruzadolane.



Scheme 4. Synthesis of ruzadolane.

In summary, we have developed a new and efficient multicomponent reaction for the construction of complex molecules from simple starting materials in the absence of catalyst and additive, in which a cyclic tertiary amine is the key component for initiating a multicomponent reaction via C–N bond cleavage. This reaction not only provides a rapid and reliable approach to potentially drug-like products containing amine, heterocycle, and thioether functionalities, but also suggests a new and efficient strategy for the difunctionalization of the inert C–N bond. Further investigations to extend the reaction scope and applications of this process in organic synthesis are currently in progress.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: catalyst-free reactions · C–N bonds · C–S bonds · multicomponent reaction · tertiary amines

[1] Reviews on multicomponent reactions: a) B. Ganem, *Acc. Chem. Res.* **2009**, *42*, 463 – 472; b) L. F. Tietze, T. Kinzel, C. C. Brazel, *Acc. Chem. Res.* **2009**, *42*, 367 – 378; c) B. B. Touré, D. G. Hall, *Chem. Rev.* **2009**, *109*, 4439 – 4486; d) N. R. Candeias, F. Montalbano, P. M. S. D. Cal, P. M. P. Gois, *Chem. Rev.* **2010**, *110*, 6169 – 6193; e) R. Scheffelaar, E. Ruijter, R. V. A. Orru, *Top. Heterocycl. Chem.* **2010**, *25*, 95 – 126; f) E. Ruijter, R. Scheffelaar, R. V. A. Orru, *Angew. Chem. Int. Ed.* **2011**, *50*, 6234 – 6246; *Angew. Chem.* **2011**, *123*, 6358 – 6371; g) D. G. Hall, T. Rybak, T. Verdelet, *Acc. Chem. Res.* **2016**, *49*, 2489 – 2500.

[2] Selected examples of multicomplonent reactions: a) I. Ugi, *Angew. Chem. Int. Ed.* **1962**, *1*, 8 – 21; *Angew. Chem.* **1962**, *74*, 9 – 22; b) L. El Kaïm, L. Grimaud, J. Oble, *Angew. Chem. Int. Ed.* **2005**, *44*, 7961 – 7964; *Angew. Chem.* **2005**, *117*, 8175 – 8178; c) G. B. Giovenzana, G. C. Tron, S. Di Paola, I. G. Menegotto, T. Pirali, *Angew. Chem. Int. Ed.* **2006**, *45*, 1099 – 1102; *Angew. Chem.* **2006**, *118*, 1117 – 1120; d) N. Elders, D. van der Born, L. J. D. Hendrickx, B. J. J. Timmer, A. Krause, E. Janssen, F. J. J. de Kanter, E. Ruijter, R. V. A. Orru, *Angew. Chem. Int. Ed.* **2009**, *48*, 5856 – 5859; *Angew. Chem.* **2009**, *121*, 5970 – 5973; e) F. Sha, X. Huang, *Angew. Chem. Int. Ed.* **2009**, *48*, 3458 – 3461; *Angew. Chem.* **2009**, *121*, 3510 – 3513; f) E. Yoshioka, S. Kohtani, H. Miyabe, *Angew. Chem. Int. Ed.* **2011**, *50*, 6638 – 6642; *Angew. Chem.* **2011**, *123*, 6768 – 6772; g) S. Maeda, S. Komagawa, M. Uchiyama, K. Morokuma, *Angew. Chem. Int. Ed.* **2011**, *50*, 644 – 649; *Angew. Chem.* **2011**, *123*, 670 – 675; h) M. Bachman, S. E. Mann, T. D. Sheppard, *Org. Biomol. Chem.* **2012**, *10*, 162 – 170; i) D. Zhang, H. Qiu, L. Jiang, F. Lv, C. Ma, W. Hu, *Angew. Chem. Int. Ed.* **2013**, *52*, 13356 – 13360; *Angew. Chem.* **2013**, *125*, 13598 – 13602; j) X. Ma, J. Jiang, S. Lv, W. Yao, Y. Yang, S. Liu, F. Xia, W. Hu, *Angew. Chem. Int. Ed.* **2014**, *53*, 13136 – 13139; *Angew. Chem.* **2014**, *126*, 13352 – 13355; k) D. Zhang, J. Zhou, F. Xia, Z. Kang, W. Hu, *Nat. Commun.* **2015**, *6*, 5801; l) H. Xue, Y. Zhao, H. Wu, Z. Wang, B. Yang, Y. Wei, Z. Wang, L. Tao, *J. Am. Chem. Soc.* **2016**, *138*, 8690 – 8693.

[3] Reviews on C–N bond activation: a) K. Ouyang, W. Hao, W.-X. Zhang, Z. Xi, *Chem. Rev.* **2015**, *115*, 12045 – 12090; b) Q. Wang, Y. Su, L. Li, H. Huang, *Chem. Soc. Rev.* **2016**, *45*, 1257 – 1272; c) G. Meng, S. Shi, M. Szostak, *Synlett* **2016**, *27*, 2530 – 2540.

[4] Selected examples of C–N bond activation: a) D. Roberto, H. Alper, *J. Am. Chem. Soc.* **1989**, *111*, 7539 – 7543; b) X. Zhao, D. Liu, H. Guo, Y. Liu, W. Zhang, *J. Am. Chem. Soc.* **2011**, *133*, 19354 – 19357; c) S. Guo, B. Qian, Y. Xie, C. Xia, H. Huang, *Org. Lett.* **2011**, *13*, 522 – 525; d) Y. Xie, J. Hu, Y. Wang, C. Xia, H. Huang, *J. Am. Chem. Soc.* **2012**, *134*, 20613 – 20616; e) P. Maity, D. M. Shacklady-McAtee, G. P. A. Yap, E. R. Sirianni, M. P. Watson, *J. Am. Chem. Soc.* **2013**, *135*, 280 – 285; f) Y. Xie, J. Hu, P. Xie, B. Qian, H. Huang, *J. Am. Chem. Soc.* **2013**, *135*, 18327 – 18330; g) J. Hu, Y. Xie, H. Huang, *Angew. Chem. Int. Ed.* **2014**, *53*, 7272 – 7276; *Angew. Chem.* **2014**, *126*, 7400 – 7404; h) H. Yu, G. Zhang, H. Huang, *Angew. Chem. Int. Ed.* **2015**, *54*, 10912 – 10916; *Angew. Chem.* **2015**, *127*, 11062 – 11066; i) M. Wang, X. Zhang, Y.-X. Zhuang, Y.-H. Xu, T.-P. Loh, *J. Am. Chem. Soc.* **2015**, *137*, 1341 – 1347; j) G. Qin, L. Li, J. Li, H. Huang, *J. Am. Chem. Soc.* **2015**, *137*, 12490 – 12493; k) Y. Liu, Y. Xie, H. Wang, H. Huang, *J. Am. Chem. Soc.* **2016**, *138*, 4314 – 4317; l) F. Hu, R. Lalancette, M.

Szostak, *Angew. Chem. Int. Ed.* **2016**, *55*, 5062 – 5066; *Angew. Chem.* **2016**, *128*, 5146 – 5150.

[5] a) K. Ishizumi, A. Kojima, F. Antoku, *Chem. Pharm. Bull.* **1991**, *39*, 2288 – 2300; b) S. Corsano, G. Strappaghetti, A. Codagnone, R. Scapicchi, G. Marucci, *Eur. J. Med. Chem.* **1992**, *27*, 545 – 549; c) S. Ballet, A. Mauborgne, S. Bourgoin, F. Caussade, A. Cloarec, M. Hamon, F. Cesselin, E. Collin, *Fundam. Clin. Pharmacol.* **1997**, *11*, 151 – 199; d) M. Modica, M. Santagati, S. Guccione, F. Russo, A. Cagnotto, M. Goegan, T. Mennini, *Eur. J. Med. Chem.* **2000**, *35*, 1065 – 1079; e) E. J. Warawa, B. M. Migler, C. J. Ohnmacht, A. L. Needles, G. C. Gatos, F. M. McLaren, C. L. Nelson, K. M. Kirkland, *J. Med. Chem.* **2001**, *44*, 372 – 389; f) C. Bharathi, K. J. Prabahar, C. S. Prasad, M. Srinivasa Rao, G. N. Trinadhachary, V. K. Handa, R. Dandala, A. Naidu, *Pharmazie* **2008**, *63*, 14 – 19.

[6] a) K. Matsumoto, S. Hashimoto, S. Otani, *J. Chem. Soc. Chem. Commun.* **1991**, 306 – 307; b) K. Yoshida, M. Taguchi, *J. Chem. Soc. Perkin Trans. 1* **1992**, 919 – 922; c) M. Lee, T. Rucil, D. Hesek, A. G. Oliver, J. F. Fisher, S. Mobashery, *J. Org. Chem.* **2015**, *80*, 7757 – 7763; d) P. Huang, B.-Y. He, H.-M. Wang, J.-M. Lu, *Synthesis* **2015**, *47*, 221 – 227.

[7] a) T. Ohwada, H. Hirao, A. Ogawa, *J. Org. Chem.* **2004**, *69*, 7486 – 7494; b) M. Salamone, G. A. DiLabio, M. Bietti, *J. Org. Chem.* **2011**, *76*, 6264 – 6270.

[8] a) S. D. Ross, M. Finkelstein, *J. Am. Chem. Soc.* **1963**, *85*, 2603 – 2607; b) S. D. Ross, J. J. Bruno, R. C. Petersen, *J. Am. Chem. Soc.* **1963**, *85*, 3999 – 4003; c) N. Maraš, S. Polanc, M. Kočevar, *Org. Biomol. Chem.* **2012**, *10*, 1300 – 1310; d) I. Yavari, M. J. Bayat, M. Ghazanfarpour-Darjani, *Tetrahedron Lett.* **2014**, *55*, 5595 – 5596.

[9] CCDC 1529696 (**4l**) and 1530808 (**7b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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Communications

Multicomponent Reaction

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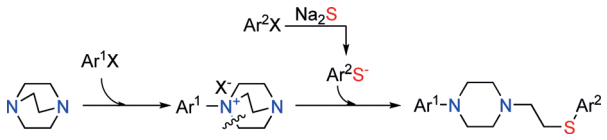
Multicomponent Reactions with Cyclic Tertiary Amines Enabled by Facile C–N Bond Cleavage



All together now: A catalyst-free multicomponent reaction with cyclic tertiary amines, electron-deficient aryl halides or heteroaromatic halides, and Na_2S enabled by facile C–N bond cleavage of the cyclic tertiary amines was developed. This direct and operationally simple method shows good functional-group tolerance and provides an efficient approach to drug-like products containing amine, azaarene, thioether, or phenol ether functionalities.

