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Interception of Amide Ylides with Sulfonamides: Synthesis of (*E*)-*N*-Sulfonyl Amidines Catalyzed by $Zn(OTf)_2$

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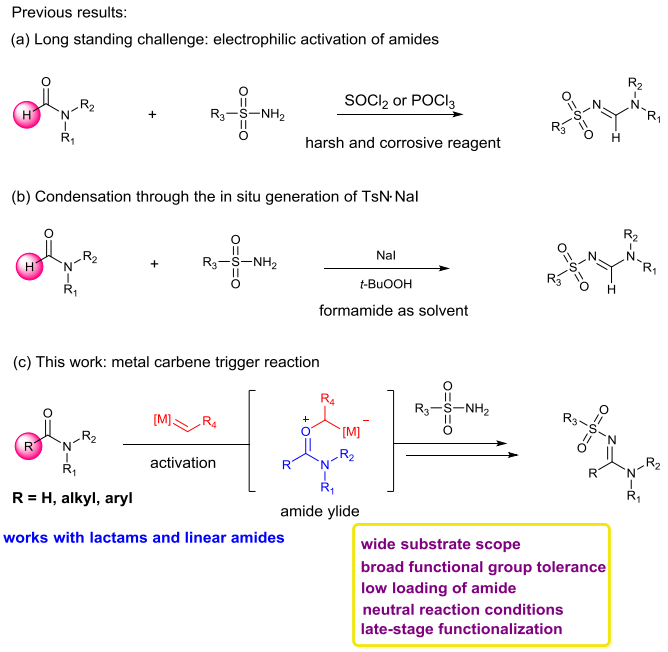
Through the interception of amide ylides with sulfonamides, we herein report the first general example of intermolecular condensation reaction between sulfonamides and amides. Beyond formamides, this approach was successfully applied to a variety of lactams and linear amides, giving rise to a broad array of (*E*)-*N*-sulfonyl amidines.

Amidine-based compounds are ubiquitous in nature and play critical roles in pharmaceutical and agrochemical industries.[1] Amidine often serves as a key scaffold in drug discovery, a useful building block for heterocyclic construction, and a common coordinating ligand of transition metals.[2] Unfortunately, conventional synthetic approaches that produce amidines from substrates such as thioamides,[3a] isonitriles[3b] and aldoximes[3c] often have inadequate reaction efficiency and rely on precursors that themselves are not readily available and thus need to be prepared beforehand. The development of new, efficient and sustainable methods for the generation of amidine-containing molecules has always been a focus of synthetic chemistry.[4] Recently, several excellent strategies have been reported, including one that involves Cu-catalyzed three-component coupling via a ketenimine intermediate[5] and another that features oxidative dehydrogenation of tertiary amines coupled with a tandem reaction with sulfonyl azides.[6] In theory, the condensation of amides and amines represents the most direct and atom-economical method to synthesize amidines.

Condensation of reactive carbonyl compounds, including aldehydes, ketones and esters, with various nucleophiles is one of the most critical tools in synthetic chemistry for building molecular complexity from simple and readily available substrates.[7] In contrast, amides are generally considered unsuitable for these transformations due to their poor electrophilicity. In fact, current research on amide condensation reactions has largely been limited to those with activated methylene moieties to construct C=C double bonds,[8] whereas condensation with other nucleophiles has found far less success. One example of the latter case is the condensation reaction between formamides and sulfonamides,[9] whose synthetic utility is impaired by its requirement of hazardous reagents and harsh conditions (Scheme 1a).



Scheme 1 Condensation of sulfonamides and amides.

Recently, we described the NaI-catalyzed direct condensation of sulfonamides and formamides based on the in situ generation of TsN•NaI.[10] Although this approach was a significant improvement over earlier methods of *N*-sulfonyl formamidine synthesis, it required the use of formamide as solvent to ensure satisfactory yields. Another well-known obstacle lies in the accomplishment of intermolecular condensation between sulfonamides and common amides,

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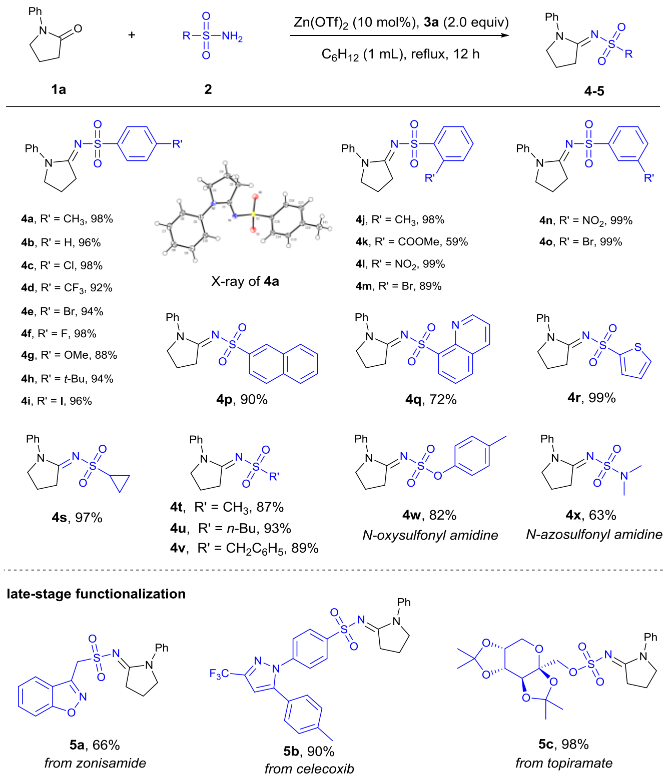
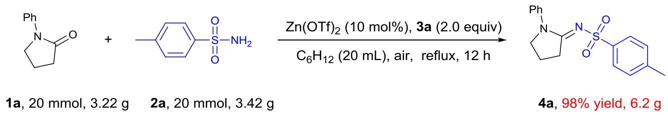
though successful intramolecular reactions have been reported.[11]. To simultaneously address both challenges, we drew inspiration from the well-established methodology, in which an amide is first activated by a transition-metal carbene[12] to generate a reactive ylide intermediate, which then underwent classical [3+2] cycloadditions with alkynes or alkenes for synthesizing heterocyclic compounds.[13] We reason that the interception of amide ylides with sulfonamides would generate the desired amidine products in a mechanistically distinct manner (Scheme 1c). This methodology is compatible with a wide range of lactams and linear amides carrying diverse functional groups, thereby creating infusive opportunities for the late-stage functionalization of drug molecules.

Given the abundance of lactam-based natural products, we began our study by exploring the condensation between 1-phenyl-2-pyrrolidinone **1a** and *p*-toluenesulfonamide **2a** using commercially available EDA (ethyl diazoacetate) **3a** as additive. The key to success is finding a suitable transition-metal catalyst that favors the formation of the desired amidine product **4a**, over the competing N–H insertion of **2a** into **3a**.[14] Gratifyingly, we detected a trace amount of the desired product **4a** when $Cu(OAc)_2$ was used as catalyst (Table S1, entry 1, see ESI). As expected, increasing the EDA loading enhanced the reaction efficiency (Table S1, entries 2-3). Encouraged by the result, we then optimized the reaction by screening a panel of different transition-metal catalysts with varying degrees of success (Table S1, entries 4-8). In particular, we discovered that **4a** was generated in nearly quantitatively yield under the catalysis of $Zn(OTf)_2$ (Table S1, entry 9). The choice of solvent was also found to have a critical impact (Table S1, entries 10-15). As expected, the condensation was largely abolished in the absence of either $Zn(OTf)_2$ or EDA **3a** (Table S1, entries 16 and 17). Screening of different diazo reagents (Table S1, entries 18-22) revealed that ethyl phenyldiazoacetate **3d** and trimethylsilyldiazomethane **3f** had considerably poorer catalytic performance than **3a** (Table S1, entries 20 and 22), whereas dimethyl 2-diazomalonate **3e** bearing two electron-withdrawing substituents failed completely (Table S1, entry 21). Notably, the reaction was not sensitive to moisture or oxygen, and therefore can be set up under atmospheric conditions.

We next explored the substrate scope of our reaction by screening different sulfonamides (Scheme 2). A variety of synthetically useful functionalities with diverse electronic properties, such as halides (**4c**, **4e**, **4f**, **4i**, **4m** and **4o**), ester (**4k**) and nitryl (**4l** and **4n**), were well tolerated and intactly preserved, opening up the possibility for further derivatization. Furthermore, the position of the substituent on the phenyl ring showed no apparent negative effect on the reaction efficiency (**4a**–**4o**). Heteroaryl sulfonamides, such as those bearing a quinolone or a thiophene moiety, were shown to be suitable substrates and furnished medicinally important heterocyclic amidines (**4q**–**4r**) in satisfactory yields. For alkyl and benzyl sulfonamides, the corresponding *N*-sulfonyl amidines were still obtained in remarkable yields (**4s**–**4v**). Challengingly, oxy-sulfamide and azo-sulfamide could also be installed to generate the desired products in good yields (**4w**, **4x**, and **5c**). Several sulfonamide-containing therapeutic compounds, including zonisamide, celecoxib and topiramate, were found to be amenable to condensation with 1-phenyl-2-pyrrolidinone **1a** to produce the target amidines in good yields (**5a-5c**), which highlighted the utility of our method for generating novel and potentially bioactive drug derivatives. The exact (*E*)-configuration of the lactam amidine product was unequivocally confirmed by single-crystal X-ray analysis of **4a** (For details, see ESI). To demonstrate the scalability and operational simplicity of the condensation method, we successfully synthesized 6.2 g of *N*-sulfonyl amidine **4a** in almost quantitative yield from 3.22 g of **1a** and 3.42 g of **2a** in just 20 mL of C_6H_{12} (Scheme 3).



Scheme 2 Variation of the sulfonamide. Conditions: **1a** (0.2 mmol), **2** (0.2 mmol), **3a** (0.4 mmol), $Zn(OTf)_2$ (10 mol%) in C_6H_{12} was stirred under reflux for 12 h under air.



Scheme 3 Gram-scale reaction.

We also tested various lactam substrates (Scheme 4) and found an electronically diverse set of substituents, including the strongly electron-withdrawing cyano (**6f**) and nitryl groups (**6m**), to be well tolerated on the N-phenyl ring. Polysubstituted aryl lactams were shown to be compatible with the condensation reaction (**6p**–**6r**). The phenyl group in **1a** could also be replaced with naphthyl (**6s**), thiophene (**6t**, **6u**), or even an alkyl moiety such as alkyl (**7f**–**7h**), cyclohexyl (**7i**) or benzyl (**7j**), without significant decline in reaction efficiency. On the other hand, our method could accommodate other cyclic amides, including a proline derivative (**7a**), strained *β*-lactams (**7c**-**7e**) and spiro-amide compound (**7b**).

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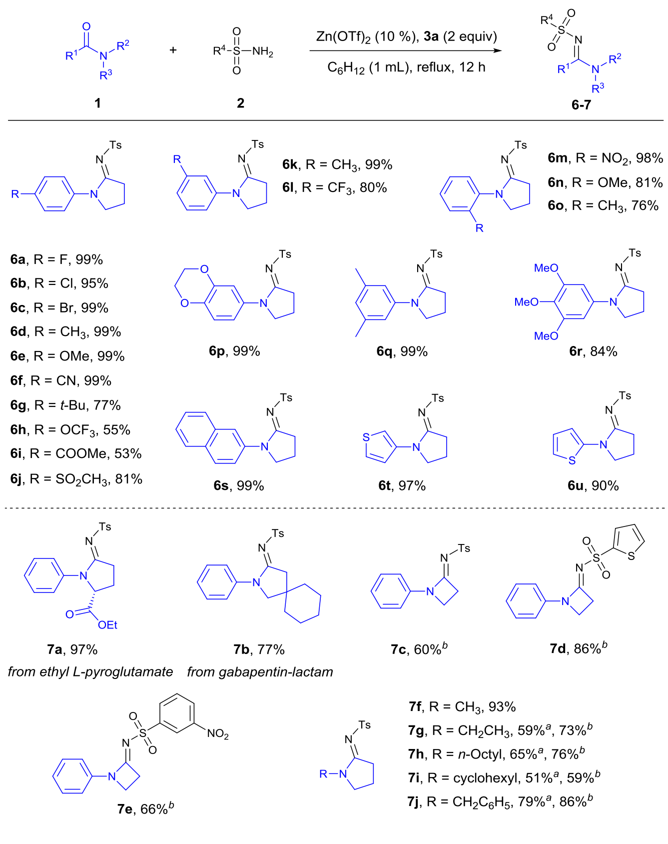
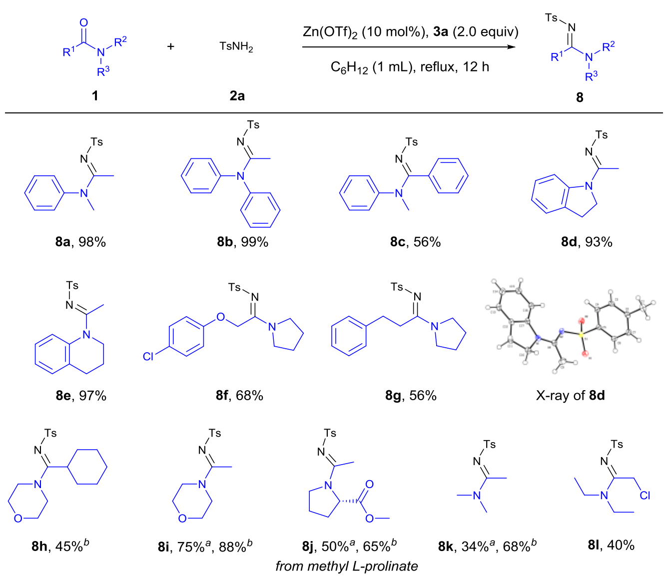


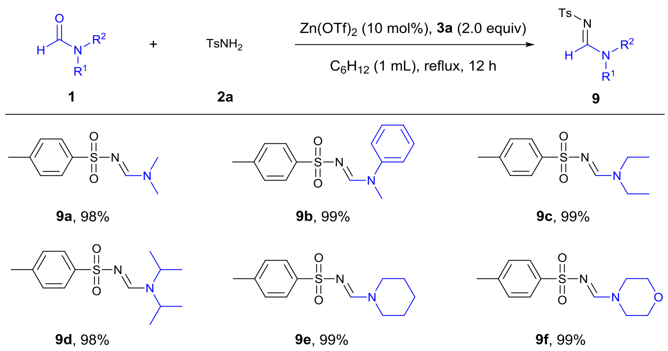
Scheme 4 Variation of the lactam. [a]Conditions: **1** (0.2 mmol), **2** (0.2 mmol), **3a** (0.4 mmol), $Zn(OTf)_2$ (10 mol%) in C_6H_{12} was stirred at reflux for 12 h under air. [b]**3a** (0.6 mmol), $Zn(OTf)_2$ (30 mol%).



Scheme 5 Variation of the linear amide. [a]Conditions: **1** (0.2 mmol), **2a** (0.2 mmol), **3a** (0.4 mmol), $Zn(OTf)_2$ (10 mol%) in C_6H_{12} was stirred at reflux for 12 h under air. [b]**3a** (0.6 mmol), $Zn(OTf)_2$ (30 mol%).

We next demonstrated that the scope of our protocol could be extended to include linear amides as substrates, which have shown to be prevalent in a series of marketed drugs.[15] Remarkably, sterically demanding amides (**8b**, **8c**, and **8h**), which were generally incompatible with several previously described condensation reactions,[9,10,16] readily reacted with **2a** and furnished the corresponding amidine products in moderate to high yields. Condensation of amide containing proline structure with **2a** resulted in the formation of **8j** with the preservation of the stereo configuration at the chiral center. The exact (*E*)-configuration of the linear amidine product was confirmed by single crystal X-ray analysis of **8d** (For details, see ESI). Unfortunately, both primary and secondary amides were poor substrates for this transformation under the optimized reaction conditions.

Finally, despite not being the main focus of the current study, we showed that formamide derivatives could also serve as suitable substrates (Scheme 6). It was especially noteworthy that the nitrogen atom in the formamide could be functionalized with two a bulky isopropyl groups (**9d**) or be part of a heterocycle (**9e**–**9f**).



Scheme 6 Variation of the formamide. Conditions: **1** (0.2 mmol), **2a** (0.2 mmol), **3a** (0.4 mmol), $Zn(OTf)_2$ (10 mol%) in C_6H_{12} was stirred at reflux for 12 h under air.

To probe the mechanism of the zinc-catalyzed condensation reaction, 4-*tert*-butylstyrene, which was proven to be an efficient carbene trap, was added to the model reaction of **1a** and **2a**. The cyclopropanation product **10** was detected by GC-MS, confirming the involvement of a carbene intermediate (Scheme S1a). On the other hand, the reaction of **1a** with compound **11**, which could be seen as derived from the N–H insertion of $TsNH_2$ into EDA, produced no amidine produce **4a** and therefore provided counterevidence against the alternative N–H insertion/condensation pathway (Scheme S1b). Substitution of H_2O for $TsNH_2$ led to the formation of compound **12** based on HRMS detection (Scheme S1c). Moreover, when H_2O^{18} was used, [^{18}O]-**1a** was observed by HRMS (Scheme S1d). Taken together, these experiment data indicated that an amide ylide intermediate was generated in situ and subsequently trapped with a nucleophile. ^{1}H NMR study of the model reaction suggested that EDA was converted to 2,2'-oxydiacetate **14** (Figure S1). This was further corroborated by the observation that ethyl glycolate **13** could undergo O–H insertion into **3a** to generate **14** in the presence of $Zn(OTf)_2$.

Based on the abovementioned investigations and recently published studies, a tentative reaction mechanism was described in Scheme 7. The catalytic cycle begins with formation of an electrophilic carbenoid species **A** from the Zn-promoted decomposition of EDA.[17] Subsequently, the amide substrate performs a nucleophilic attack on **A** and leads to the generation of an ylide intermediate **B**, which is in equilibrium

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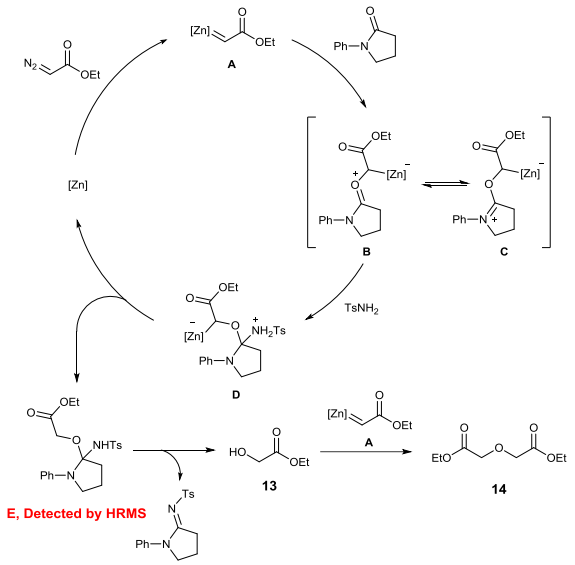
with imine **C**.[13,18] Trapping of **B** or **C** with sulfonamide furnishes intermediate **D**, which then decomposes into **E** and the Zn catalyst.[19] Finally, **E** undergoes elimination to afford the desired amidine product and ethyl glycolate **13**, the latter of which is immediately trapped by **A** and results in the generation of 2,2'-oxydiacetate **14** through O–H insertion.[13a] The detection of **E** by HRMS (For details, see see ESI) provided the most convincing evidence in support of our proposed mechanism.



Scheme 7 Proposed mechanism.

In conclusion, we herein reported the first intermolecular condensation reaction of common amides and sulfamides, leading to a broad array of (*E*)-*N*-sulfonyl amidines in good yields and with excellent stereoselectivity. The wide substrate scope, exceptional functional group tolerance, operational simplicity and neutral reaction conditions would make this mechanistically novel method particularly well suited for preparing various amidine compounds. Future efforts will focus on the discovery of condensation reaction of amides and other nucleophiles, which triggered by the amide ylides.

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Notes and references

1 (a) J. V. Greenhill and P. Lue, *Prog. Med. Chem*., **1993**, *30*, 203; (b) D. Schade, J. Kotthaus, L. Riebling, J. Kotthaus, H. Müller-Fielitz, W. Raasch, O. Koch, N. Seidel, M. Schmidtke and B. Clement, *J. Med. Chem*., **2014**, *57*, 759; (c) M.-J. Wang, X.-B. Zhao, D. Wu, Y.-Q. Liu, Y. Zhang, X. Nan, H. Liu, H.-T. Yu, G.-F. Hu and L.-T. Yan, *J. Agric. Food Chem*., **2014**, *62*, 5429.

2 (a) S.-Y. Chang, S. J. Bae, M. Y. Lee, S.-H. Baek, S. Chang and S. H. Kim, *Bioorg. Med. Chem. Lett*., **2011**, *21*, 727; (b) Y.-F. Wang, H. Chen and S. Chiba, *J. Am. Chem. Soc*., **2012**, *134*, 3679; (c) W. Cho, H. Cho, C. S. Lee, B. Y. Lee, B. Moon and J. Kang, *Organometallics* **2014**, *33*, 1617.

3 (a) M. Aswad, J. Chiba, T. Tomohiro and Y. Hatanaka, *Chem. Commun*., **2013**, *49*, 10242; (b) Z. Zhang, B. Huang, G. Qiao, L. Zhu, F. Xiao, F. Chen, B. Fu and Z. Zhang, *Angew. Chem. Int. Ed*., **2017**, *56*, 4320; (c) J. Cesar, K. Nadrah and M. S. Dolenc, *Tetrahedron Lett*., **2004**, *45*, 7445.

4 Selected examples: (a) J. Kim and S. S. Stahl, *J. Org. Chem*. **2015**, *80*, 2448; (b) A. Mulati and A. Wusiman, *Heterocycles* **2015**, *91*, 2163.

5 Selected examples: (a) I. Bae, H. Han and S. Chang, *J. Am. Chem. Soc*., **2005**, *127*, 2038; (b) J. Kim, Y. Lee, J. Lee, Y. Do and S. Chang, *J. Org. Chem*., **2008**, *73*, 9454 and references cited therein; (c) I.-H. Lee, H. Kim and T.-L. Choi, *J. Am. Chem. Soc*., **2013**, *135*, 3760; (d) M.-H. Shen, K. Xu, C.-H. Sun and H.-D. Xu, *Org. Lett*., **2015**, *17*, 5598.

6 (a) X. Xu, X. Li, L. Ma, N. Ye and B. Weng, *J. Am. Chem. Soc*., **2008**, *130*, 14048; (b) S. Wang, Z. Wang and X. Zheng, *Chem. Commun*., **2009**, *45*, 7372; (c) X. Xu, D. Cheng, L. Ma, C. Lu, Q. Zhang, N. Yao and X. Li, *Org. Lett*., **2010**, *12*, 897; (d) L. Zhang, J.-H. Su, S. Wang, C. Wan, Z. Zha, J. Du and Z. Wang, *Chem. Commun*., **2011**, *47*, 5488.

7 (a) M. B. Smith and J. March, *March's advanced organic chemistry*: *reactions, mechanisms, and structure*, 5th ed.; John Wiley & Sons: New York, **2007**; p 279; (b) T. Murase, Y. Nishijima and M. Fujita, *J. Am. Chem.Soc*., **2012**, *134*, 162; (c) J. M. Álvarez-Calero, Z. D. Jorge and G. M. Massanet, *Org. Lett*., **2016**, *18*, 6344; (d) S. Das, N. Majumdar, C. K. De, D. S. Kundu, A. Döhring, A. Garczynski anf B. List, *J. Am. Chem. Soc*., **2017**, *139*, 1357.

8 (a) D. L. Priebbenow and C. Bolm, *RSC Adv*., **2013**, *3*, 10318; (b) P.-Q. Huang, W. Ou, K.-J. Xiao and A.-E. Wang, *Chem. Commun*., **2014**, *50*, 8761; (c) P.-Q. Huang, W. Ou and J.-L. Ye, *Org. Chem. Front*., **2015**, *2*, 1094; (d) P.-Q. Huang and W. Ou, *Eur. J. Org. Chem*., **2017**, 582.

9 (a) G. R. Pettit and R. E. Kadunce, *J. Org. Chem*., **1962**, *27*, 4566; (b) M. Gazvoda, M. Kočevar and S. Polanc, *Eur. J. Org. Chem*., **2013**, 5381; (c) J. Vastl, R. Kartika, K. Park, A. E. Cho and D. A. Spiegel, *Chem. Sci*., **2016**, *7*, 3317.

10 S. Chen, Y. Xu and X. Wan, *Org. Lett*., **2011**, *13*, 6152.

11 (a) Y. S. Shvetsov, V. D. Cherepinskii-Malov, A. N. Shirshov, V. S. Rezink and V. G. Andrianov, *Izv. Akad. Nauk. SSSR, Ser. Khim*., **1980**, 2356; (b) V. S. Fedenko, Z. F. Solomko and V. I. Avramenko, *Khim. Geterotsikl. Soedin*., **1984**, 907. (c) B. Pirotte, P. D. Tullio, P. Neven, D. Dewalque, J. Delarge, D.-H. Caignard and P. Renard, *Bull. Soc. Chim. Belg*., **1997**, *106*, 781; (d) WO. Pat., 118845 A1, **2013**; (e) P. Kundu, A. Mondal and C. Chowdhury, *J. Org. Chem*., **2016**, *81*, 6596 and references cited therein.

12 Selected reviews on carbene chemistry, see: (a) H. M. L. Davies and D. Morton, *Chem. Soc. Rev.,* **2011**, *40*, 1857; (b) L. Liu and J. Zhang, *Chem. Soc. Rev*., **2016**, *45*, 506 and references cited therein.

13 (a) A. Padwa, *Chem. Soc. Rev*., **2009**, *38*, 3072; (b) D. B. England and A. Padwa, *Org. Lett*., **2007**, *9*, 3249; (c) S. A. Bonderoff, A and Padwa, *J. Org. Chem*., **2017**, *82*, 642.

14 Q.-H. Deng, H.-W. Xu, A. W.-H. Yuen, Z.-J. Xu and C.-M. Che, *Org. Lett*., **2008**, *10*, 1529.

15 (a) C. L. Allen and J. M. J. Williams, *Chem. Soc. Rev*., **2011**, *40*, 3405; (b) Marketed drugs: Lipitor, Glivec, Januvia etc.

16 (a) N. Chandna, N. Chandak, P. Kumar, J. K. Kapoor and P. K. Sharma, *Green Chem*., **2013**, *15*, 2294; (b) S. Y. Chow and L. R. Odell, *J. Org. Chem*., **2017**, *82*, 2515.

17 S. Mata, L. A. López and R. Vicente, *Angew. Chem. Int. Ed*., **2017**, *56*, 7930 and references cited therein.

18 (a) D. L. Priebbenow and C. Bolm, *RSC Adv*., **2013**, *3*, 10318; (b) S. Goudrdranche, C. Besnard, L. Egger and J. Lacour, *Angew. Chem. Int. Ed*., **2016**, *55*, 13775.

19 Trapping ylide with nucleophilic reagents: (a) S. N. Karad and R.-S. Liu, *Angew. Chem. Int. Ed*., **2014**, *53*, 5444; (b) J. Chen, Y. Shao, L. Ma, M. Ma and X. Wan, *Org. Biomol. Chem*., **2016**, *14*, 10723.

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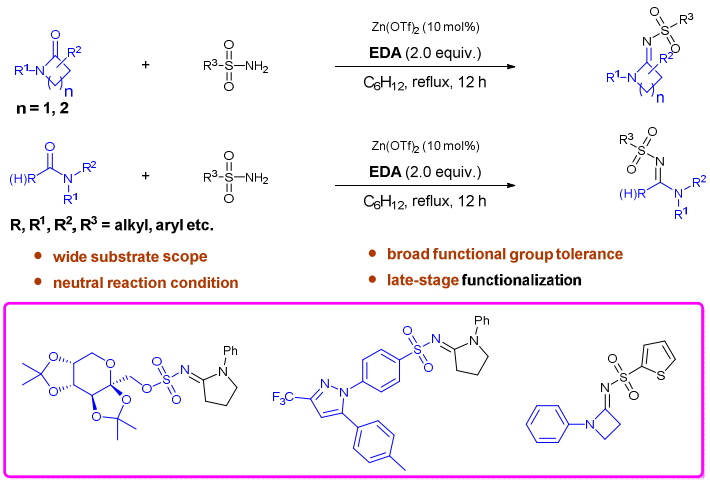

Through the interception of amide ylides with sulfonamides, we herein report an intermolecular condensation reaction between sulfonamides and common amides.