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# [4 + 2] Cycloaddition of $\alpha$ -bromotrifluoromethylhydrazone with alkenes: synthesis of trifluoromethyltetrahydropyridazines†

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A catalyst-free [4 + 2] cyclization process between trifluoromethyl-containing 1,2-diazabuta-1,3-diene and simple olefins was developed by *in situ* generation. Under mild conditions, trifluoromethyl-containing 1,4,5,6-tetrahydropyridazine compounds were obtained, in high yields (up to 96% yields).

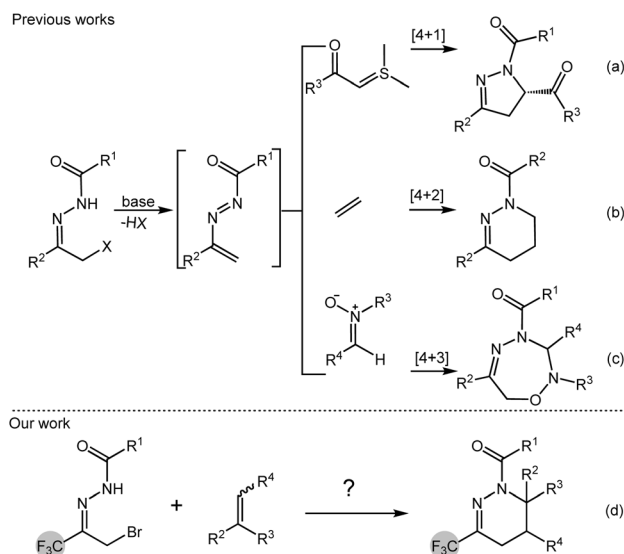
1,4,5,6-Tetrahydropyridazines<sup>1</sup> are important six-membered nitrogen heterocycles that are widely found in numerous natural products. They also serve as structural subunits in various bioactive molecules and drugs, such as the antihypertensive hydralazine, dihydralazine, and endralazine, as well as the antidepressant drug piperazine.<sup>2</sup>

In addition, the introduction of trifluoromethyl groups (CF<sub>3</sub>) into drug molecules can significantly improve the physical and chemical properties, metabolic stability, and drug activity of drug molecules.<sup>3</sup> Therefore, CF<sub>3</sub> plays an important role in medicine, pesticides, and materials. So far, the direct introduction of trifluoromethylation using trifluoromethylation reagents has been well developed.<sup>4</sup> The synthesis of trifluoromethylated organic molecules using trifluoromethylation building blocks is equally attractive and important as another important approach.<sup>5</sup>

At the same time, by consulting the literature, it was found that  $\alpha$ -bromoacylhydrazone can generate 1,2-diazabuta-1,3-diene *in situ* under the action of alkali, and can undergo [4 + 1]<sup>6</sup> cycloaddition, [4 + 2]<sup>7</sup> cycloaddition and [4 + 3]<sup>8</sup> cycloaddition with dienophiles to prepare biologically active nitrogen heterocyclic compounds. Therefore, in recent years,  $\alpha$ -bromoacylhydrazone has been widely used in organic synthesis as a diene precursor. For example, in 2012, Bolm's group reported the asymmetric [4 + 1] cycloaddition of 1,2-diazabuta-1,3-diene *in situ* generated by  $\alpha$ -haloacylhydrazone with a sulfur ylide, catalyzed by copper trifluoromethanesulfonate and Tol-BINAP,

a series of dihydropyrazole compounds were obtained in up to 97% yield and 94% enantioselectivity (Scheme 1a).<sup>9</sup> In 2015, Luo's group performed the [4 + 2] cycloaddition of  $\alpha$ -haloacylhydrazone to 1,2-diazabuta-1,3-diene with simple olefins, especially ethylene, and obtained 1,4,5,6-tetrahydropyridazine compounds in up to 99% yield (Scheme 1b).<sup>10</sup> In 2016, Zhao's group obtained 1,2,4,5-oxatriazepines from the [4 + 3] cycloaddition of  $\alpha$ -halogenated acylhydrazones with nitrones in the presence of sodium carbonate (Scheme 1c).<sup>11</sup>

Based on the above research, a catalyst-free [4 + 2] cyclization process between trifluoromethyl-containing 1,2-diazabuta-1,3-diene and simple olefins was developed by *in situ* generation. Under mild conditions, trifluoromethyl-containing 1,4,5,6-tetrahydropyridazine compounds were obtained (Scheme 1d).



Scheme 1 Selected examples of  $\alpha$ -bromoacylhydrazones participated cycloaddition reactions.

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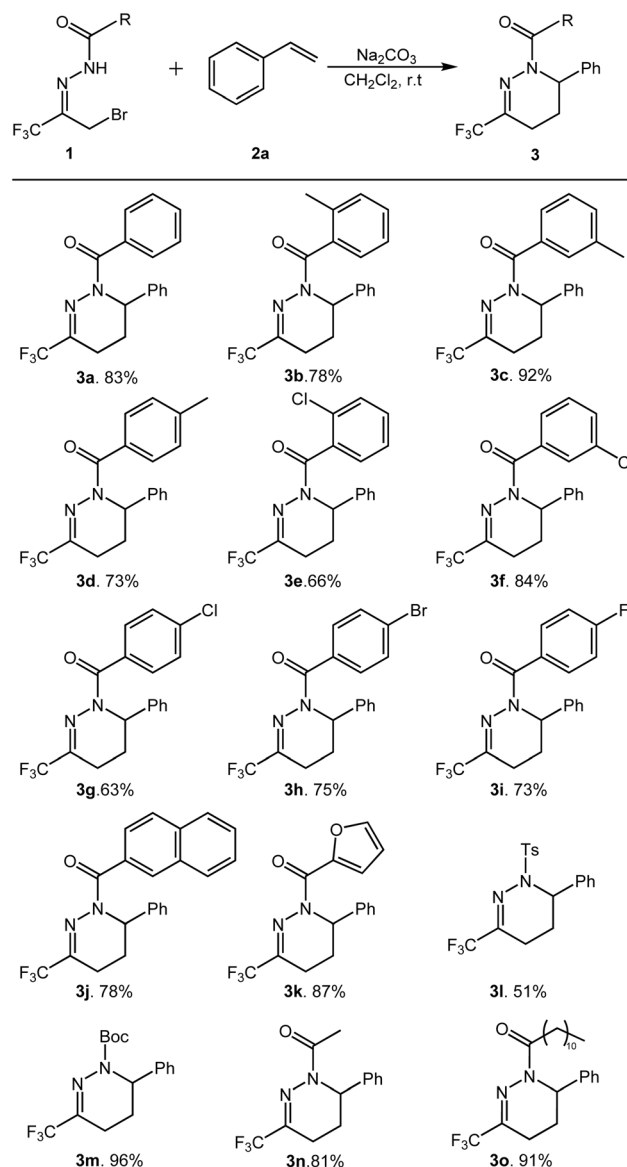
† Electronic supplementary information (ESI) available: Experimental procedures, analytical data for products, and NMR spectra of products. See DOI: <https://doi.org/10.1039/d5ra03000e>



Initially,  $\alpha$ -bromotrifluoromethyl acylhydrazone **1a** (1.0 equiv.), styrene **2a** (3.0 equiv.) and  $K_2CO_3$  (2.0 equiv.) were reacted in dichloromethane at room temperature to give the target compound **3a** in 64% yield (Table 1, entry 1). To further improve the yield of the target product, the reaction conditions were optimized in terms of solvents, bases, and material ratios, and representative results are summarized in Table 1. When we studied the effect of different bases on the reaction, such as  $CS_2CO_3$ , compound **3a** was obtained in 25% yield (Table 1, entry 2). When the base is  $Na_2CO_3$ , compound **3a** was obtained in 83% yield (Table 1, entry 3). At the same time, we also investigated the effect of organic base  $Et_3N$  on the reaction, and obtained compound **3a** in 16% yield (Table 1, entry 4). Therefore, we use  $Na_2CO_3$  as the optimal alkali. Subsequently, we optimized the material ratio of the reaction (Table 1, entry 5–8). The results showed that the appropriate molar ratio of **1a/2a/Na<sub>2</sub>CO<sub>3</sub>** was 1/3/2 (Table 1, entry 3). Finally, we optimized the effects of different solvents on the reaction. We explored the effects of THF,  $CH_3CN$ , and MeOH on the reaction (Table 1, entry 9–11). The results show that the optimal solvent is  $CH_2Cl_2$ .

Under the optimized conditions, the substrate suitability of this transformation reaction was further investigated. The results are shown in Scheme 2.

Firstly, the reaction adaptability of substrate **1** was studied, and the effect of  $R^1$  substituent on substrate activity was investigated. Various substituted  $\alpha$ -bromotrifluoromethyl acylhydrazones can efficiently generate the target products in moderate to good yields (Scheme 2, **3a–3o**). The results indicate that the reaction proceeds efficiently when the  $R^1$  group is either aromatic or aliphatic, affording the corresponding products in good yields. Notably, for aromatic  $R^1$  groups, the electronic characteristics of substituents on the phenyl ring exhibit minimal influence on product yield, whereas the positional



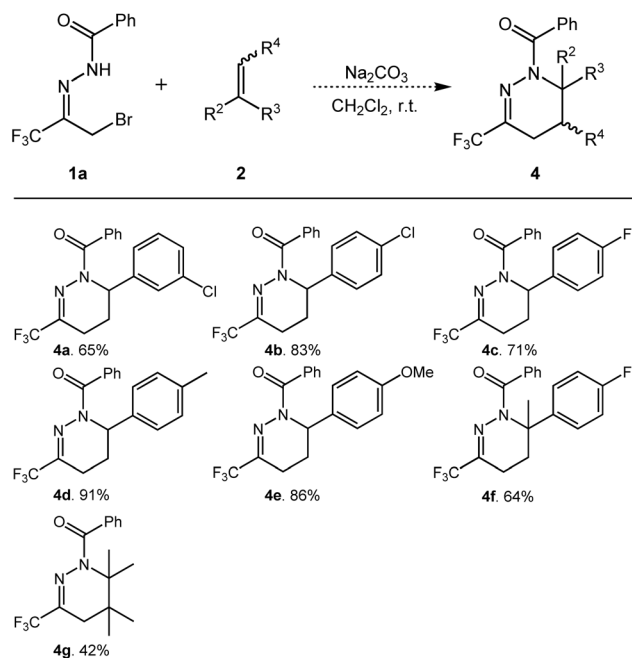
**Scheme 2** Substrate scope of hydrazones<sup>a,b</sup>. <sup>a</sup>All reactions were carried out by using 0.2 mmol of **1**, 3 eq. of **2a** and 2 eq. of  $Na_2CO_3$  in 3 mL of  $CH_2Cl_2$ . <sup>b</sup>Isolated yields.

**Table 1** Optimization of additive and temperature<sup>a</sup>

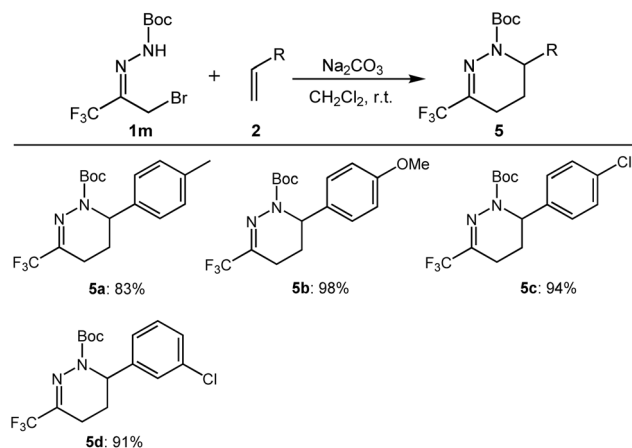
Entry	Molar ratio of <b>1a/2a/base</b>	Base	Solvent	Yield <sup>b</sup> (%)
1	1 : 3 : 2	$K_2CO_3$	$CH_2Cl_2$	64
2	1 : 3 : 2	$CS_2CO_3$	$CH_2Cl_2$	25
3	1 : 3 : 2	$Na_2CO_3$	$CH_2Cl_2$	83
4	1 : 3 : 2	$Et_3N$	$CH_2Cl_2$	16
5	1 : 2 : 2	$Na_2CO_3$	$CH_2Cl_2$	66
6	1 : 1.5 : 2	$Na_2CO_3$	$CH_2Cl_2$	50
7	1 : 2 : 2.5	$Na_2CO_3$	$CH_2Cl_2$	52
8	1 : 2 : 1.5	$Na_2CO_3$	$CH_2Cl_2$	66
9	1 : 2 : 2	$Na_2CO_3$	THF	19
10	1 : 2 : 2	$Na_2CO_3$	$CH_3CN$	28
11	1 : 2 : 2	$Na_2CO_3$	MeOH	N. R.

<sup>a</sup> All reactions were carried out by using 0.2 mmol of **1a**, 3 eq. of **2a** and 2 eq. of base in 3 mL of solvent. <sup>b</sup> Isolated yields.

isomerism of substituents on the phenyl ring demonstrates a pronounced effect on yield. For example, when  $R^1$  was the *o*-/ *m*-/ *p*-methylphenyl (**3b–3d**), the *m*-methylphenyl product (**3c**), was obtained with the highest yield. When  $R^1$  is *o*-/ *m*-/ *p*-chlorophenyl, *m*-chlorophenyl gives the target product in the highest yield (**3e–3g**). When  $R^1$  is *p*-bromophenyl and *p*-fluorophenyl, the target product was obtained in 75% and 73% yields, respectively (**3h–3i**). When  $R^1$  is a fused ring or a heterocyclic ring, such as 2-naphthyl and 2-furan groups, the corresponding products can also be successfully generated (**3j–3k**). When the  $R^1$  group was Ts (**3l**) and Boc (**3m**), the yields obtained were 51 and 96%, respectively. In addition, when  $R^1$  is aliphatic ethyl and lauryl, the target products can also be obtained in good to excellent yields (**3n–3o**).



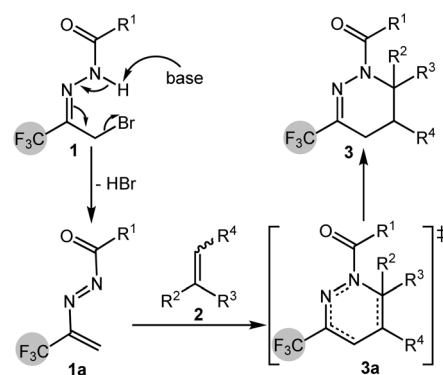
**Scheme 3** Substrate scope for simple alkenes<sup>a,b</sup>. <sup>a</sup>All reactions were carried out by using 0.2 mmol of **1a**, 3 eq. of **2** and 2 eq. of  $\text{Na}_2\text{CO}_3$  in 3 mL of  $\text{CH}_2\text{Cl}_2$ . <sup>b</sup>Isolated yields.



**Scheme 4** Substrate scope for hydrazone **1m** with substituted styrenes<sup>a,b</sup>. <sup>a</sup>All reactions were carried out by using 0.2 mmol of **1m**, 3 eq. of **2** and 2 eq. of  $\text{Na}_2\text{CO}_3$  in 3 mL of  $\text{CH}_2\text{Cl}_2$ . <sup>b</sup>Isolated yields.

To further expand the substrate scope, other simple olefins were tested next. As seen from Scheme 3, styrenes bearing either electron-donating or -withdrawing moieties can both be used equally well for this reaction, with slightly higher yields for the former (**4a–4f**). The yield of 2,3-dimethyl-2-butene was 42% (**4g**).

With  $\alpha$ -bromo trifluoromethyl *N*-Boc acylhydrazone compounds, we also examined different olefins, and the results are shown in Scheme 4. Olefins bearing either electron-donating (**5a–5b**) or electron-withdrawing groups (**5c–5d**) could be applied to give good yields.



**Scheme 5** Proposed reaction mechanism.

A plausible reaction mechanism was proposed based on a review of literature and reaction outcomes, as illustrated in Scheme 5. In the presence of a base,  $\alpha$ -bromotrifluoromethyl acylhydrazone **1** undergoes dehydrohalogenation to eliminate one equivalent of  $\text{HBr}$ , generating the 1,2-diazabuta-1,3-diene intermediate **1a**. This intermediate then participates in a Diels–Alder reaction with substituted olefin **2**, forming the cyclic transition state **3a**. The transition state subsequently evolves into the final product molecule **3**, wherein the cleavage of preexisting bonds and the formation of new bonds occur in a concerted manner during a single mechanistic step.

## Conclusions

In summary, we reported here in a mild and catalyst-free [4 + 2] cycloaddition between *in situ* generated trifluoromethyl 1,2-diazabuta-1,3-diene with simple olefins. This protocol provides facile and atom economic access to trifluoromethyltetrahydropyridazine with moderate to excellent yields.

## Data availability

The authors confirm that the data supporting the findings of this study are available within the article and its ESI.†

## Author contributions

Yanhui Zhao: investigation, data curation, and methodology. Hemin Rong: investigation and data curation. Khurshed Bozorov: investigation and data curation. Buer Song: writing – original draft. Wei Liu: supervision and writing – review & editing. Xueqing Zhang: writing – review & editing, supervision, funding acquisition, and conceptualization.

## Conflicts of interest

There are no conflicts to declare.



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## References

- (a) S. Xu, R. Chen, Z. Qin, G. Wu and Z. He, *Org. Lett.*, 2012, **14**, 996–999; (b) R. Na, C. Jing, Q. Xu, H. Jiang, X. Wu, J. Shi, J. Zhong, M. Wang, D. Benitez, E. Tkatchouk, W. A. Goddard, H. Guo and O. Kwon, *J. Am. Chem. Soc.*, 2011, **133**, 13337–13348; (c) L. Shen, L. Sun and S. Ye, *J. Am. Chem. Soc.*, 2011, **133**, 15894–15897; (d) Q. Zhang, L. Yang and X. Tong, *J. Am. Chem. Soc.*, 2010, **132**, 2550–2551; (e) A. J. Oelke, D. J. France, T. Hofmann, G. Wuitschik and S. V. Ley, *Angew. Chem.*, 2010, **122**, 6275–6278; *Angew. Chem., Int. Ed.*, 2010, **49**, 6139–6142.
- C. G. Wermuth, G. Schlewer, J. J. Bourguignon, G. Maghioros, M.-J. Bouchet, C. Moire, J.-P. Kan, P. Worms and K. Biziere, *J. Med. Chem.*, 1989, **32**, 528–537.
- (a) K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881–1886; (b) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa and H. Liu, *Chem. Rev.*, 2016, **116**, 422–518; (c) W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359–4369.
- (a) C. Zhang, *Org. Biomol. Chem.*, 2014, **12**, 6580–6589; (b) L. Chu and F.-L. Qing, *Acc. Chem. Res.*, 2014, **47**, 1513–1522; (c) X. Liu, C. Xu, M. Wang and Q. Liu, *Chem. Rev.*, 2015, **115**, 683–730; (d) J. Charpentier, N. Früh and A. Togni, *Chem. Rev.*, 2015, **115**, 650–682.
- (a) J. H. Sim, J. H. Park, P. Maity and C. E. Song, *Org. Lett.*, 2019, **21**, 6715–6719; (b) Z. Chen, N. Ren, X. Ma, J. Nie, F.-G. Zhang and J.-A. Ma, *ACS Catal.*, 2019, **9**, 4600–4608; (c) L. Trulli, F. Sciubba and S. Fioravanti, *Tetrahedron*, 2018, **74**, 572–577; (d) L. Trulli, V. Raglione and S. Fioravanti, *Eur. J. Org. Chem.*, 2018, 3743–3749; (e) W. N. Mszar, M. S. Mikus, S. Torker, F. Haeffner and A. H. Hoveyda, *Angew. Chem., Int. Ed.*, 2017, **56**, 8736–8741; (f) M. Miyagawa, M. Yoshida, Y. Kiyota and T. Akiyama, *Chem.–Eur. J.*, 2019, **25**, 5677–5681.
- (a) O. A. Attanasi, L. De Crescentini, G. Favi, F. Mantellini, S. Mantenuto and S. Nicolini, *J. Org. Chem.*, 2014, **79**, 8331–8338; (b) O. A. Attanasi, P. Filippone, B. Guidi, T. Hippe, F. Mantellini and L. F. Tietze, *Tetrahedron Lett.*, 1999, **40**, 9277–9280.
- (a) A. M. Shelke and G. Suryavanshi, *Org. Lett.*, 2016, **18**, 3968–3971; (b) R. Huang, X. Chang, J. Li and C. J. Wang, *J. Am. Chem. Soc.*, 2016, **138**, 3998–4001; (c) S. M. M. Lopes, M. S. C. Henriques, J. A. Paixao and T. M. V. D. P. E. Melo, *Eur. J. Org. Chem.*, 2015, 6146–6151; (d) J. Li, R. Huang, Y. K. Xing, G. Qiu, H. Y. Tao and C. J. Wang, *J. Am. Chem. Soc.*, 2015, **137**, 10124–10127; (e) M. C. Tong, X. Chen, J. Li, R. Huang, H. Tao and C. J. Wang, *Angew. Chem., Int. Ed. Engl.*, 2014, **53**, 4680–4684.
- (a) W. Yang, C. Yuan, Y. Liu, B. Mao, Z. Sun and H. Guo, *J. Org. Chem.*, 2016, **81**, 7597–7603; (b) C. Guo, B. Sahoo, C. G. Daniliuc and F. Glorius, *J. Am. Chem. Soc.*, 2014, **136**, 17402–17405.
- J.-R. Chen, W.-R. Dong, M. Candy, F.-F. Pan, M. Jörres and C. Bolm, *J. Am. Chem. Soc.*, 2012, **134**, 6924–6927.
- X. Zhong, J. Lv and S. Luo, *Org. Lett.*, 2015, **17**, 1561–1564.
- H.-W. Zhao, H.-L. Pang, T. Tian, B. Li, X.-Q. Chen, X.-Q. Song, W. Meng, Z. Yang, Y.-Y. Liu and Y.-D. Zhao, *Adv. Synth. Catal.*, 2016, **358**, 1826–1832.

