Green Chemistry

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Green Chem.*, 2021, **23**, 767

Received 12th November 2020,
Accepted 4th January 2021

DOI: 10.1039/d0gc03832f

rsc.li/greenchem

Solvent-driven C(sp^3)–H thiocarbonylation of benzylamine derivatives under catalyst-free conditions†

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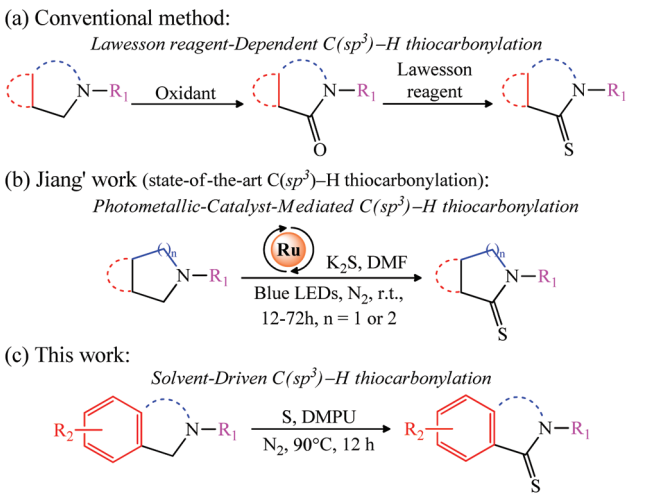
Due to the particularity of the thiocarbonyl group (C═S bond), only limited C(sp^3)–H thiocarbonylation methods, especially efficient and convenient methods, have been developed for the synthesis of thioamides. Inspired by the "solvent-specificity-based" design strategy, we discovered a simple, practical and environmentally friendly C(sp^3)–H thiocarbonylation of benzylamine substrates for facile thioamide synthesis under catalyst-free conditions. A diverse array of benzylamine derivatives were tolerated by this catalyst-free thiocarbonylation. Furthermore, the (QM) computations and well-designed experiments on the reaction mechanism revealed that this thiocarbonylation depends on the specific solvent that initially drives this reaction through the intermolecular hydrogen atom transfer (HAT). And the following single electron transfer (SET) induces the electron-catalyzed C–S bond formation and intramolecular HAT realizing the final establishment of the C═S bond.

One class of non-negligible sulfur-containing groups is the thiocarbonyl motif (C═S bond) of thioamides, which is attracting increased research attention on account of its excellent chemical functions in organic chemistry and distinctive biological activities in medicinal chemistry.[1] For chemical functions, the potential in the formation of the C–C bond and C═C bond, such as the synthesis of jerantinine compound, has recently been shown convincingly.[2] For biological activities, the distinct positive effect has been shown continuously in many preclinical and clinical drugs, such as the clinically applied antineoplastic drug mercaptopurine and hypnotic drug quazepam, as well as the potential DNA gyrase inhibitor hydroxymethyl thiolactam cyclothialidine.[3] Thus, the development of an efficient and convenient thioamide synthesis method is of great methodological and pharmaceutical interest.[4] In the past three decades, various thioamide synthesis systems have been investigated, such as sulfur–phosphorus-type,[5] Friedel–Crafts-type,[6] Willgerodt–Kindler-type[7] and three-component-type[8] thioamide synthesis. Although very successful, all these methods started from carboxylic acids, nitriles, isothiocyanates, aryl aldehydes or aryl ketones, and avoided direct C(sp^3)–H thiocarbonylation. So, limited C(sp^3)–H thiocarbonylation methods have been developed so far. One conventional C(sp^3)–H thiocarbonylation method is the Lawesson reagent-dependent thiocarbonylation of amine derivatives[9] in which the amine was first oxidized to amide and the Lawesson reagent or its analogues subsequently transformed the amide to thioamide (Scheme 1a). However, because it scarcely avoids



Scheme 1 (a) Conventional Lawesson reagent-dependent C(sp^3)–H thiocarbonylation of amine derivatives. (b) State-of-the-art photometallic-catalyst-mediated C(sp^3)–H thiocarbonylation of N-heterocyclic skeleton. (c) Proposed solvent-driven C(sp^3)–H thiocarbonylation of benzylamine derivatives under catalyst-free conditions.

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†Electronic supplementary information (ESI) available: Experimental procedures, computational methods, Fig. S1 and S2, characterization data, references, NMR spectra, molecular coordinates and free energies. See DOI: 10.1039/d0gc03832f

the high temperature and produces by-products that are difficult to separate, as well as requires the non-economical oxidants and Lawesson reagent, this method is accompanied by the disadvantage of low environmental friendliness.[9b] Thus, it is highly desirable to develop an efficient and economical C(sp^3)–H thiocarbonylation method for thioamide synthesis.[10]

The trisulfur radical anion ($S_3^{\bullet-}$) has been studied for half a century and can be very easily obtained from the inorganic sulfide or elemental sulfur in DMF solvent at room temperature (Fig. 1a).[11] In recent years, some applications of $S_3^{\bullet-}$ species for C–S bond formation have been reported, such as the sulfur insertion reactions, providing a brand new perspective to explore the C(sp^3)–H thiocarbonylation method for thioamide synthesis.[12] And indeed, through continuous studies of $S_3^{\bullet-}$ species, in 2019 Jiang's group found that the iminium ion (B state) readily interacted with the $S_3^{\bullet-}$ species to form the thioamide under environmentally friendly conditions (Fig. 1b).[10e] Based on this result, they reported the photometallic-catalyst-mediated C(sp^3)–H thiocarbonylation of the N-heterocyclic skeleton (Scheme 1b) in which the photometallic catalyst of $Ru(bpy)_3Cl_2{\cdot}6H_2O$ was introduced to transform the N-heterocycle to the α-aminoalkyl radical (A state), which subsequently could undergo single electron transfer (SET) affording the necessary iminium ion (B state) to couple with the $S_3^{\bullet-}$ species (Fig. 1c), and thus realized the thioamide synthesis *via* C(sp^3)–H thiocarbonylation.[10e] Considering that the metal catalyst is usually costly and non-environmentally friendly, a more efficient transformation method from amine to iminium ion without a metal catalyst is highly desirable. In 2016, Ji's group found that in addition to converting the inorganic sulfide/sulfur into the $S_3^{\bullet-}$ species (Fig. 1a), DMF solvent has another specificity that the produced DMF radical anion ($DMF^{\bullet-}$) during the formation of $S_3^{\bullet-}$ species has the ability to undergo the hydrogen atom transfer (HAT) in the sulfur insertion reaction.[13] Herein, guided by the above two specificities of the DMF solvent and our previous studies of the amine substrate,[14] we developed a "solvent-specificity-based" design strategy for solvent-driven C(sp^3)–H thiocarbonylation under catalyst-free conditions (Scheme 1c). In this strategy, we hypothesized that the DMF solvent could firstly react with the inorganic sulfide to produce the $DMF^{\bullet-}$ species and $S_3^{\bullet-}$ species (Fig. 1a), and then through HAT and SET the $DMF^{\bullet-}$ species could transform the amine substrate to the necessary iminium ion (Fig. 1d), which subsequently could couple with the $S_3^{\bullet-}$ species to finally form the thioamide (Fig. 1b). Since all steps have been available under environmentally friendly conditions except for the transformation step between the amine substrate and iminium ion, our research focus in this work was whether or how the $DMF^{\bullet-}$ species could transform the amine substrate to the iminium ion without a metal catalyst under environmentally friendly conditions.

To examine the feasibility of our hypothesis, an amine substrate of 2-phenyl-1,2,3,4-tetrahydroisoquinoline (**1a**) was selected to react with the inorganic sulfide (K_2S) in the specific DMF solvent under very mild conditions (nitrogen atmosphere, room temperature and 12 h reaction time). Unfortunately, even after the introduction of light (425 nm LED or sunlight), the expected C(sp^3)–H thiocarbonylation reaction did not occur (entries 1–3 in Table 1). This indicated that unless some necessary conditions were adopted, the $DMF^{\bullet-}$ species seemed difficult to replace the $Ru(bpy)_3Cl_2{\cdot}6H_2O$ catalyst to transform **1a** to the expected iminium ion (B state). Our QM calculation[15] of HAT between the $DMF^{\bullet-}$ species and **1a** found that through a 30.93 kcal mol^{-1} energy barrier in kinetics and a −5.72 kcal mol^{-1} feasible energy in thermodynamics (Fig. 1e), the $DMF^{\bullet-}$ species could transform **1a** to the α-aminoalkyl radical (A state), which could be further transformed to the iminium ion (B state) *via*

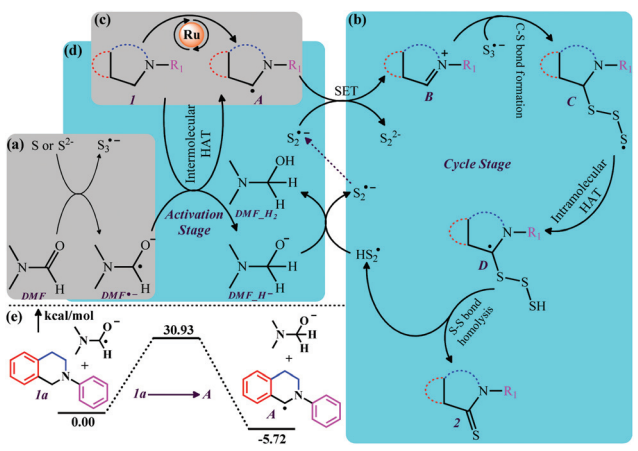
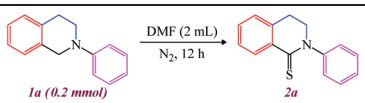


Fig. 1 (a)–(e) Proposed "solvent-specificity-based" design strategy for the solvent-driven C(sp^3)–H thiocarbonylation.

Table 1 Reaction optimization[a] for our C(sp^3)–H thiocarbonylation of **1a**



Entry	Sulfur reagent (equiv.)	Temp.	Yield[b]
1	K_2S (2.0)	r.t.	—
2	K_2S (2.0)	425 nm LED	—
3	K_2S (2.0)	Sunlight	—
4	K_2S (2.0)	50 °C	47%
5	S (1.0)	50 °C	32%
6	S (2.0)	50 °C	58%
7	S (3.0)	50 °C	56%
8	S (2.0)	80 °C	71%
9	S (2.0)	90 °C	75%
10	S (2.0)	120 °C	70%
11[c]	S (2.0), O_2	90 °C	—
12[d]	S (2.0), BHT	90 °C	20%
13[e]	S (2.0), DPPH	90 °C	15%

[a] Reactions were conducted with **1a** (0.2 mmol), DMF (2 mL), 12 h, under a nitrogen atmosphere. [b] Isolated yield. [c] Reaction was carried out under an oxygen atmosphere. [d] BHT (0.2 mmol) was added. [e] DPPH (0.2 mmol) was added.

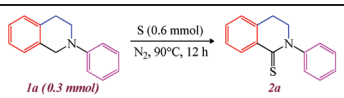
SET. We considered that the higher energy barrier of HAT limited the reaction ability of the $DMF^{\bullet-}$ species, and thus, a 50 °C heating step was added (entry 4 in Table 1). Fortunately, a 47% yield of the anticipated product 2-phenyl-3,4-dihydroisoquinoline-1(2*H*)-thione (**2a**) was obtained. Based on this successful case, the type and equivalent of sulfur reagent, as well as reaction temperature, oxygen atmosphere and reaction time for our C(sp^3)–H thiocarbonylation were optimized (entries 4–11 in Table 1). After optimization, the following reaction conditions were employed: 2.0 equivalents of elemental sulfur, 90 °C, nitrogen atmosphere and 12 h reaction time. Overall, our proposed C(sp^3)–H thiocarbonylation reaction could not only produce excellent yield (75%), but also is simple, practical, environmentally friendly and noteworthy in that it does not require any catalysts. Meanwhile, we also investigated the influence of radical scavengers (BHT and DPPH) on our C(sp^3)–H thiocarbonylation (entries 12 and 13 in Table 1). It was revealed that our reaction could be inhibited by radical scavengers, implicating some radical intermediates formed during thiocarbonylation.

Some control experiments were carried out for the verification of the solvent dependence (solvent specificity) proposed in our hypothesis. As shown in Table 2, taking **1a** as an example, once the DMF solvent was changed to the solvent that cannot react with the elemental sulfur to form the solvent radical anion to drive the thiocarbonylation, no yields (dioxane, CH_3OH, NMP, EtOAc, THF, DCM, HMPA and CH_2ClCH_2Cl) or only unmeasurable trace yields (toluene and DMSO) of the expected thiocarbonylation product (**2a**) were detected, suggesting that our thiocarbonylation cannot occur in the absence of solvent actuation under the optimized reaction conditions. Intriguingly, if DMF was replaced by acetone or CH_3CN which can be similar to DMF as solvent to react with the elemental sulfur to form the solvent radical anion (acetone$^{\bullet-}$ species and $CH_3CN^{\bullet-}$ species) to drive the thiocarbonylation, our thiocarbonylation could still be effectively maintained but with a lower yield of thiocarbonylation product (17% and 31% for acetone and CH_3CN, respectively). This indicated that as long as the solvent replacing the DMF solvent has similar specificities with the DMF solvent, our thiocarbonylation can occur. More interestingly, our thiocarbonylation reaction also showed that the yield of thiocarbonylation product (**2a**) in DMF-like solvents, such as DMA and DMPU, was almost comparable to that in DMF solvent (72%, 76% and 70% for DMA, DMPU and DMF, respectively), indicating that our thiocarbonylation was specific to DMF-like solvents. Meanwhile, compared to previously reported C(sp^3)–H thiocarbonylations,[9,10e] which usually need the toxic DMF solvent or non-environmentally friendly Lawesson reagent, our thiocarbonylation to some extent not only included solvent (DMA), but also adapted to more environmentally friendly solvent (DMPU), although in the classification of green solvents[16] the toxicity of DMA is as dangerous as that of DMF and the greener DMPU remains problematic in scaling up of applications. To sum up, we can see it indeed was the specific DMF-like solvents (DMF, DMPU and DMA) that drove the C(sp^3)–H thiocarbonylation under catalyst-free conditions.

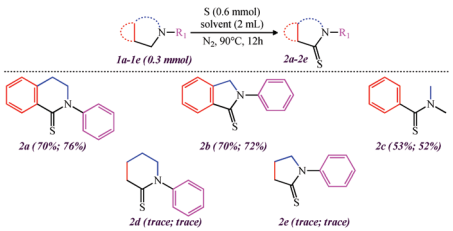
With the optimal reaction conditions in hand, we then further explored our C(sp^3)–H thiocarbonylation with different types of amine substrates (Scheme 2). For cyclic benzylamines, besides the above-mentioned tetrahydroisoquinoline (**1a**), isoindoline (**1b**) also exhibited good reactivity, furnishing the thiocarbonylation product (**2b**) in 70% and 72% yields in DMF and DMPU solvents, respectively. The non-cyclic benzylamines were also considered. For example *N*,*N*-dimethyl-1-phenylmethanamine (**1c**) produced the thiocarbonylation product (**2c**) in a relatively low but acceptable yield (53% in DMF and 52% in DMPU). For naphthenic amines of piperidine (**1d**) and pyrrolidine (**1e**), the yields of thiocarbonylation products (**2d**–**2e**) in DMF and DMPU solvents further decreased to trace amounts. Obviously, the higher the conjugation of the amine substrate, the more it is tolerated by our C(sp^3)–H thiocarbonylation.

We next turned our attention to the substituents in the benzene rings of **1a** to expand the scope of the best tolerated cyclic benzylamine substrate (Scheme 3). For example, electron-donating group substitution of 2-methyl (**1aa**), 3-methyl (**1ab**), 4-methyl (**1ac**), 3,5-dimethyl (**1ad**) and 4-methoxyl (**1ae**)

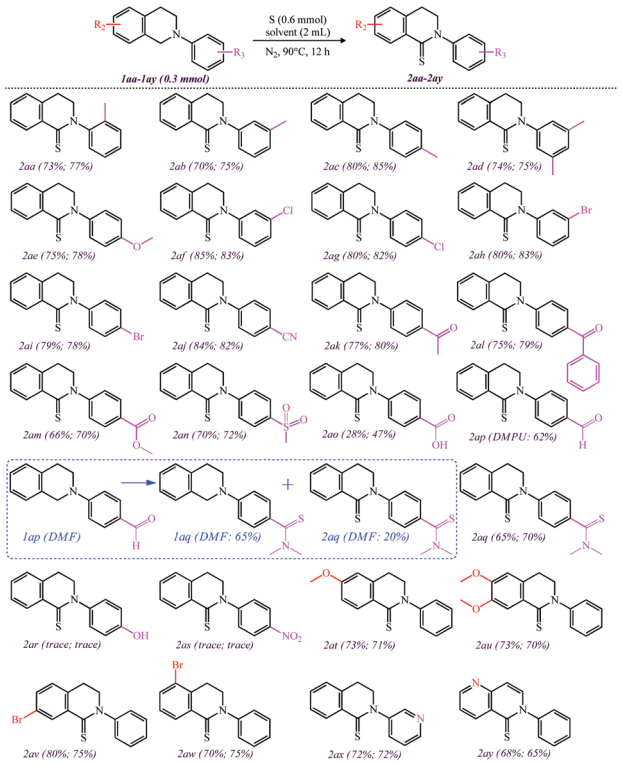
Table 2 Solvent dependence (solvent specificity) of our C(sp^3)–H thiocarbonylation. Isolated yield



Entry	Solvent (2 mL)	Yield
1	DMF	70%
2	Dioxane	—
3	CH_3OH	—
4	NMP	—
5	EtOAc	—
6	THF	—
7	DCM	—
8	HMPA	—
9	CH_2ClCH_2Cl	—
10	Toluene	Trace
11	DMSO	Trace
12	Acetone	17%
13	CH_3CN	31%
14	DMA	72%
15	DMPU	76%



Scheme 2 C(sp^3)–H thiocarbonylation of different types of amine substrates (**1a–1e**). Only benzylamine derivatives (**1a–1c**) were tolerated by our thiocarbonylation. Data: (DMF; DMPU). Isolated yield.

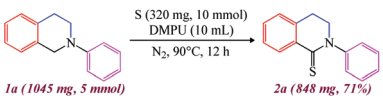


Scheme 3 Substrate scope with respect to the benzylamine derivatives (**1aa–1ay**). Both electron-donating and electron-withdrawing groups were tolerated by our C(sp^3)–H thiocarbonylation. Data: (DMF; DMPU). Isolated yield.

in an *N*-substituted benzene ring, as well as electron-withdrawing group substitution of 3-chlorine (**1af**), 4-chlorine (**1ag**), 3-bromine (**1ah**), 4-bromine (**1ai**), 4-nitrile (**1aj**), 4-acetyl (**1ak**), 4-benzoyl (**1al**), 4-methoxycarbonyl (**1am**) and 4-methylsulfonyl (**1an**) in an *N*-substituted benzene ring, in DMPU solvent they all afforded the thiocarbonylation products (**2aa–2an**) in comparable yields of 70%–85%. And in DMF solvent their yields of thiocarbonylation products (**2aa–2an**) were almost equal to those in DMPU solvent. The electron-withdrawing group substitution of 4-carboxyl (**1ao**) in an *N*-substituted benzene ring was also tolerated by our thiocarbonylation but only with 28% and 47% yields of the thiocarbonylation product (**2ao**) in DMF and DMPU solvents, respectively. The electron-withdrawing group substitution of 4-formyl (**1ap**) in an *N*-substituted benzene ring could directly afford the expected C(sp^3)–H thiocarbonylation product (**2ap**) in an acceptable yield of 62% in DMPU solvent. Surprisingly, in DMF solvent the **1ap** was not converted to the desired **2ap**, but to another two products, *N*,*N*-dimethylthioamide (**1aq**, 65% yield) and its thiocarbonylation product (**2aq**, 20% yield). We guess that in DMF solvent the **1ap** was first converted to **1aq**, and then converted to the C(sp^3)–H thiocarbonylation product (**2aq**) of **1aq**. Further verification confirmed our guess and found that the **1aq** indeed could afford its thiocarbonylation product (**2aq**) in yields of 65% and 70% in DMF and DMPU solvents, respectively. Unfortunately, the electron-donating group substitution of 4-hydroxyl (**1ar**) and electron-withdrawing group substitution of 4-nitro (**1as**) only afforded unmeasurable trace yields of thiocarbonylation products (**2ar–2as**), and most of them were not reacted. In fact, this non-reactivity of hydroxyl and nitro groups has been reported for many radical reactions.[17] We considered that the hydroxyl and nitro groups may play a role in scavenging free radicals, thereby inhibiting the occurrence of our thiocarbonylation. The electron-donating group substitution of methoxyl (**1at–1au**) and electron-withdrawing group substitution of bromine (**1av–1aw**) in the benzene ring of tetrahydroisoquinoline in DMPU solvent also afforded the thiocarbonylation products (**2at–2aw**) in comparable yields of 71%, 70%, 75% and 75%, respectively. And similar degree of yields were also obtained in DMF solvent. Thus, so to speak, most electron-donating and electron-withdrawing groups maintained, even improved, the yield of our thiocarbonylation. In addition, we also considered the heterocyclic substitution of the cyclic benzylamine substrate. Similar to *N*-substituted pyridine (**1ax**) and 1,6-naphthyridine (**1ay**), they also provided their thiocarbonylation products (**2ax–2ay**) in good yields of 72% and 65% in DMPU solvent, respectively (corresponding to 72% and 68% in DMF solvent). Overall, although our thiocarbonylation reaction is affected by the type of amine substrate, it is hardly restricted by various substituents for the appropriate type of amine substrate.

The gram scale reaction was also employed to test the utility of our C(sp^3)–H thiocarbonylation. As shown in Scheme 4, when substrate **1a** was expanded to 5 mmol, a 71% yield of desired thiocarbonylation product (**2a**) was isolated, which was almost as good as the 76% yield of the small sample experiment. This indicated the potential applications of our C(sp^3)–H thiocarbonylation reaction.

Considering the above experimental results, the first key question is why the DMF-like solvents could drive our C(sp^3)–H thiocarbonylation under catalyst-free conditions. Based on the reaction mechanism proposed in Fig. 1, we calculated the whole reaction free energy profiles[15] for the different types of amine substrates in Scheme 2 (**1a–1e**) in DMPU solvent. As shown in Fig. 2, we can see that under the condition that elemental sulfur and DMPU solvent have reacted to form the $DMPU^{\bullet-}$ species and $S_3^{\bullet-}$ species, the $DMPU^{\bullet-}$ species could react with the substrate (1 state) through the intermolecular HAT with a high energy barrier (28.63, 30.88, 31.88, 39.89 and 41.09 kcal mol^{-1} for **1a–1e**, respectively) to generate the α-aminoalkyl radical (A state) and $DMPU\_H^-$ species. Then,



Scheme 4 5 mmol (1045 mg) scale reaction of our C(sp^3)–H thiocarbonylation for substrate **1a**. After the reaction, DMPU was recycled through vacuum distillation at 145 °C in 60 mbar, and the crude product was purified with flash chromatography.

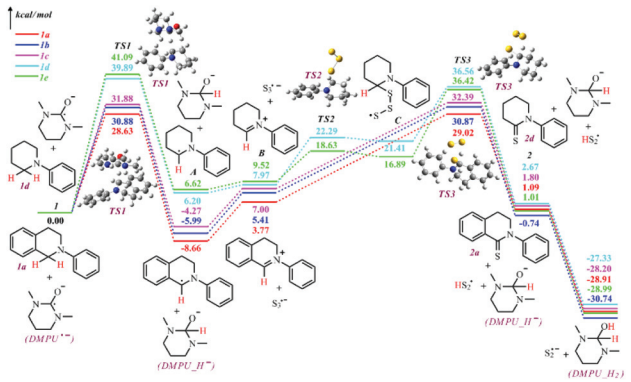


Fig. 2 Reaction profiles of **1a–1e** in DMPU solvent based on the reaction mechanism in Fig. 1 (mechanistic studies 1).

the obtained α-aminoalkyl radical (A state) would be willing to undergo a low endothermic energy (12.43, 11.40, 11.27, 1.77 and 2.90 kcal mol^{-1} for **1a–1e**, respectively) to facilely realize the SET and form the expected iminium ion (B state). Finally, through the C–S bond formation reaction and following S–S bond homolysis reaction (induced by the intramolecular HAT) also with a high total reaction barrier (25.25, 25.46, 25.39, 28.59 and 26.90 kcal mol^{-1} for **1a–1e**, respectively), previously generated $S_3^{\bullet-}$ species could interact with the iminium ion (B state) to establish the C=S bond and form the final thiocarbonylation product (2 state) and $HS_2^{\bullet}$ species whose proton could further be transferred to the previously generated DMPU_H^- species, producing the DMPU_H_2 species and $S_2^{\bullet-}$ species with the release of much energy and leading free energy lower than the initial reactant (−28.91, −30.74, −28.20, −27.33 and −28.99 kcal mol^{-1} for **1a–1e**, respectively). Clearly, the driving property of DMPU solvent was mainly reflected in three aspects: (1) DMPU solvent and elemental sulfur reacted to form the DMPU$^{\bullet-}$ species and $S_3^{\bullet-}$ species; (2) under heating condition, DMPU$^{\bullet-}$ species and $S_3^{\bullet-}$ species overcame the high energy barrier in kinetics to activate the double C(sp^3)–H bonds through the intermolecular HAT and intramolecular HAT, respectively; and (3) formed DMPU_H^- species during intermolecular HAT accepted the proton of final produced $HS_2^{\bullet}$ species to push the whole thiocarbonylation reaction to be exothermic. The above driving property was also reflected in the DMF solvent based on the free energy profile calculations for substrates **1a–1e** in DMF solvent (Fig. S1†). Thus, due to the kinetic feasibility that can be achieved by heating and the thermodynamic feasibility, the DMF-like solvents could drive the C(sp^3)–H thiocarbonylation through simple heating under catalyst-free conditions.

The next key question is why our C(sp^3)–H thiocarbonylation was specific to the benzylamine substrates (**1a–1c**) and DMF-like solvents. By further analysis on the final step of our thiocarbonylation (the reaction between DMF_H^- species and $HS_2^{\bullet}$ species in Fig. 1) we can deduce two processes: (1) the formed $S_2^{\bullet-}$ species to some extent could prefer to act as an oxidant to participate in the SET of α-aminoalkyl radical (A state) to form the iminium ion (B state), accomplishing the cycle from the α-aminoalkyl radical (A state) to the thiocarbonylation product (2 state); (2) the simultaneously formed DMF_H_2 species to some extent could improve the intermolecular HAT between the substrate (1 state) and DMF$^{\bullet-}$ species by promoting the right shift of reaction equilibrium, which could lead more α-aminoalkyl radical (A state) to join in the above cycle reaction and more DMF_H^- species to react with the $HS_2^{\bullet}$ species produced by the above cycle reaction to generate the $S_2^{\bullet-}$ species and DMF_H_2 species again to continue to repeat the above two processes. Thus, our thiocarbonylation process could partition into two stages (Fig. 1): one was the activation stage in which the DMF$^{\bullet-}$ species activated the substrate through intermolecular HAT (from 1 state to A state), and the other was the cycle stage driven by the DMF_H^- species (from A state to 2 state). Obviously, the higher the thermodynamic feasibility of the activation stage, the easier the occurrence of the subsequent cycle stage, and correspondingly, the more completely our thiocarbonylation will be carried out. As shown in Fig. 2, from benzylamines (**1a–1c**) to naphthenic amines (**1d–1e**), the thermodynamic energy of the activation stage in DMPU solvent gradually changed from exothermic to endothermic (−8.66, −5.99, −4.27, 6.20 and 6.62 kcal mol^{-1} for **1a–1e**, respectively), accompanied by a gradual decrease in yield of the thiocarbonylation product. A similar tendency was also found in DMF solvent (−5.72, −2.14, 1.74, 8.06 and 8.49 kcal mol^{-1} for **1a–1e**, respectively) as shown in Fig. S1.† Thus we considered that it was the thermodynamic property of the activation stage that determined the specificity of our thiocarbonylation to the benzylamine substrates (**1a–1c**). A similar explanation could also explain why our thiocarbonylation was specific to the DMF-like solvents (DMPU, DMF and DMA), as shown in Fig. 3. In addition, our calculation[15] also found that the stability of the C state in the cycle stage may also have an influence on our thiocarbonylation (Fig. 4 and Fig. S2†). We considered that a stable C state may cause some side reactions to quench our thiocarbonylation. This was confirmed by **1d** and **1e** since they have both

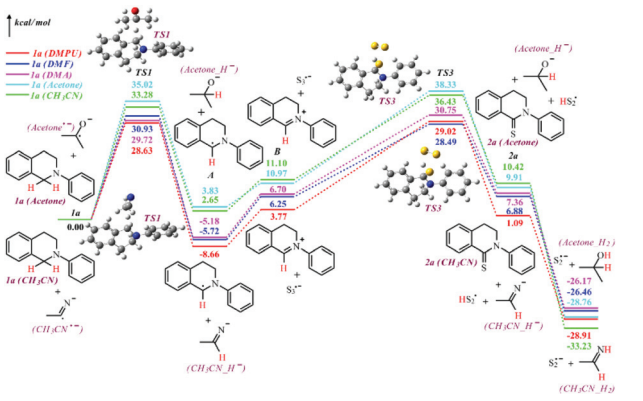


Fig. 3 Reaction profiles of **1a** in different solvents (DMPU, DMF, DMA, acetone and CH_3CN) based on the reaction mechanism in Fig. 1 (mechanistic studies 2).

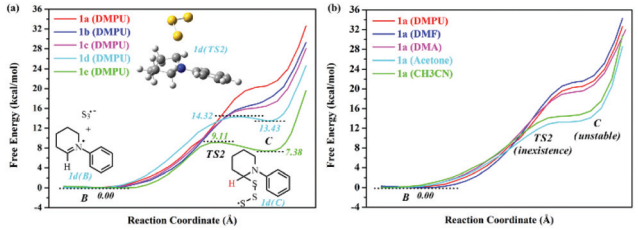


Fig. 4 Influence of the C state on our C(sp^3)–H thiocarbonylation (mechanistic studies 3).

the computational stable C state and some experimental by-products.

Conclusions

In summary, based on the "solvent-specificity-based" design strategy, we have developed a solvent-driven C(sp^3)–H thiocarbonylation of benzylamine derivatives, which proceeded efficiently for thioamide synthesis under catalyst-free, operationally simple and environmentally friendly conditions. A wide variety of substituents on the benzylamine substrates were tolerated by our thiocarbonylation with excellent yields. Our methodology is worth noting in that it cleverly utilized the specificities of solvent instead of the property of the previously reported metal catalyst to drive the C(sp^3)–H thiocarbonylation and got a good result. Given this, further studies on the application of solvent specificities are ongoing in our laboratories. In addition, our thiocarbonylation may play a role in the site-directed thiocarbonylation since it focuses on the benzylamine substrate and is almost unaffected by the substituents on the benzylamine substrate, such as achieving the site-directed thiocarbonylation of some compounds containing multiple thiocarbonylation sites.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the National Science Foundation of China (81803436 and 21702236) And Guangzhou Science Technology and Innovation Commission Technology Research Projects (201805010005). We thank the National Supercomputing Center in Guangzhou for providing the computational resources. We also thank Prof. Ruibo Wu at SYSU for his help in mechanism analysis.

Notes and references

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