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Synthesis of Thioureas, Thioamides and Aza-Heterocycles via DMSO-Promoted Oxidative Condensation of Sulfur, Malonic Acids and Amines

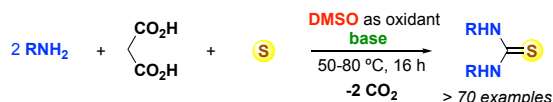
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Supporting Information Placeholder



ABSTRACT: Malonic acid and derivatives have been well known to undergo monodecarboxylation under relatively mild conditions and have been exclusively used as C₂ synthon. We report herein their new application as C₁ synthon via double decarboxylation promoted by sulfur and DMSO. In the presence of amines as nucleophiles, a wide range of thioureas and thioamides as well as *N*-heterocycles were obtained in good to excellent yields under mild heating conditions.

Decarboxylation of carboxylic acids has emerged as a powerful strategy for the synthesis of various of natural and unnatural molecules.^{1,2} Among them, the malonic acid **1a**³ as well as its 2-monosubstituted derivatives have been known to undergo monodecarboxylation⁴ and used as C₂ synthon for the synthesis of acetic and cinnamic acid derivatives.⁵ On the other hand, the didecarboxylation has been generally known with non-enolizable malonic acid derivatives, *i.e.* 2,2-disubstituted malonic acids.⁶

Over the last few years, we have been exploring new reactivities of sulfur S₈ for different organic transformations, especially for the formation of C=S bonds in thioureas⁷ and thioamides.^{8,9} *Inter alia*, we reported sulfur promoted decarboxylation of phenylacetic⁸ and maleic/fumaric acids⁹ for the synthesis of diverse organo-sulfur and/or organo-nitrogen compounds.

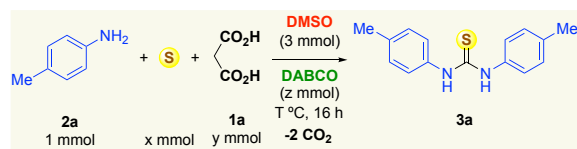
In continuation of our previous development, herein we report an approach for the synthesis of thioureas,¹⁰ thioamides¹¹ and aza-heterocycles¹² using S₈/DMSO combination to promote oxidative sulfurative didecarboxylation of malonic acids in the presence of amines as nucleophiles.

For this purpose, we optimized the reaction conditions for the synthesis of thiourea **3a** from malonic acid **1a** as C₁ source, *p*-toluidine **2a** and sulfur. As previously observed, we employed DMSO (3 mmol, 0.2 mL) as oxidizing agent thank to its specific activating effect on sulfur (Table 1). At 100 °C, the expected thiourea **3a** was formed in a moderate yield of 66% along with

some unidentified products (entry 1). We noticed also that a small amount of starting amine **2a** remained unchanged. This could be explained by spontaneous thermal decarboxylation of malonic acid into acetic acid before the reaction with **2a**. Consequently, to limit this unwanted decomposition, the temperature was lowered to 80 °C (entry 2). Gratifyingly, this modification resulted in a markedly better yield. Further trials at lower temperatures slowed down (60 °C, entry 3) or even stopped (at 40 °C, entry 4) the reaction to **3a**. Further investigation focusing on lowering the quantity of DABCO (entries 5 and 6) and sulfur (entry 7) led to lower yields. We reasoned that at lower temperature, malonic acid **1a** would be more stable and thus could be used in lower quantity. Logically, both DABCO and sulfur amounts could be diminished. This hypothesis was validated by significant improvement of yields when temperature and the amounts of sulfur, malonic acid and DABCO were decreased (entries 8-11). Under the optimized conditions, if the amount of DMSO was halved (entry 12) or the temperature was dropped to 40 °C (entry 13), the formation of thiourea was deeply compromised (entry 12). On the other hand, replacement of DMSO by a dipolar aprotic and non-oxidizing solvent such as *N*-methylpyrrolidin-2-one led to low yield of **3a**, suggesting that DMSO was required as an oxidant. The yield in the absence of DMSO could be improved by adding more sulfur (2 equiv) (entries 15-16), indicating that sulfur could act as both reactant and oxidant in this case. On the other hand, acetonitrile failed to

promote the didecarboxylation even in the presence of a stoichiometric amount of sulfur (entry 17). For comparison purpose, while an inorganic base such as K_2CO_3 (entry 18) or a weaker organic base such as pyridine (entry 19) was not effective for this reaction, a tertiary aliphatic amine such as DIPEA displayed good reactivity (entry 20).

Table 1. Screening of the Reaction Conditions



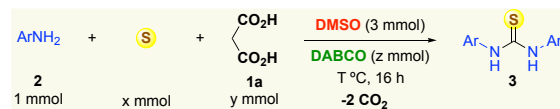
Entry ^a	x	y	z	Temp (°C)	Yield (%) ^b
1	1.5	1	0.5	100	66
2	1.5	1	0.5	80	86
3	1.5	1	0.5	60	65
4	1.5	1	0.5	40	<5 ^c
5	1.5	1	0.2	80	42
6	1.5	1	0.1	80	25
7	0.75	1	0.5	80	63
8	0.75	1	0.5	60	85
9	0.75	0.6	0.3	60	87
10	0.6	0.6	0.3	60	89
11	0.6	0.6	0.3	50	92
12 ^d	0.6	0.6	0.3	50	20 ^c
13	0.6	0.6	0.3	40	22 ^c
14 ^e	0.6	0.6	0.3	50	33 ^c
15 ^e	2	0.6	0.3	50	77
16 ^f	2	0.6	0.3	50	60
17 ^g	2	0.6	0.3	50	0 ^c
18	0.6	0.6	0.3 ^h	50	15
19	0.6	0.6	0.3 ⁱ	50	11
20	0.6	0.6	0.3 ^j	50	75

^a Reaction conditions: *p*-toluidine **2a** (1 mmol, 107 mg), sulfur (x mmol, 32 mg·mmol⁻¹), malonic acid **1a** (y mmol), DABCO (z mmol) in DMSO (3 mmol, 0.2 mL) at T °C for 16 h. ^b Yield of **3a** after column chromatography. ^c Yield determined by ¹H NMR of the crude reaction mixture. ^d DMSO (1.5 equiv) was used. ^e *N*-methylpyrrolidin-2-one (0.2 mL) was used in place of DMSO. ^f *N,N*-dimethylformamide (0.2 mL) was used in place of DMSO. ^g Acetonitrile (0.2 mL) was used in place of DMSO. ^h K_2CO_3 was used as a base. ⁱ Pyridine was used as a base. ^j DIPEA was used as a base.

With this set of optimized conditions in hand (Table 1, entry 11), we investigated the scope of amines with slight modification when necessary (Table 2). Anilines bearing electron neutral (**2b-2g**) or electron donating groups (**2h-2m**) in different position of the aromatic ring displayed high reactivity, leading to the expected thioureas in good to excellent yields (**3b-3m**). The reaction conditions could be successfully applied to 2,5-di-*tert*-butylaniline **2g** bearing a sterically demanding *o*-*tert*-butyl group as well as to 4-aminophenol **2m** having an unprotected phenol group.

Halogen containing substrates with all four halogens (F, Cl, Br and I) **2n-2t** provided the corresponding thioureas **3n-3t** in moderate to high yields. The efficiency depends not only on the nature of halogen atoms but also on their position. In general, *para*-haloanilines gave better yields than *meta* or *ortho* analogues.

Table 2. Reactions of Anilines with Malonic Acid 1a^a



2	Ar	x	y	z	T (°C)	3 , Yield (%) ^b
2b	Ph	0.6	0.6	0.3	60	3b , 67, (70) ^d
2c	<i>m</i> -MeC ₆ H ₄	0.6	0.6	0.3	60	3c , 79
2d	<i>p</i> -BuC ₆ H ₄	0.6	0.6	0.3	50	3d , 66
2e	2,5-Me ₂ C ₆ H ₃	0.6	0.6	0.3	60	3e , 78
2f	2-MeC ₆ H ₄	1	1	0.5	60	3f , 86
2g	2,5- <i>t</i> -Bu ₂ C ₆ H ₃	1.5	1	0.5	80	3g , 84
2h	2-MeOC ₆ H ₄	0.6	0.6	0.3	60	3h , 87
2i	3-MeOC ₆ H ₄	1.5	1	0.5	60	3i , 57
2j	4-MeOC ₆ H ₄	1.5	1	0.5	50	3j , 68
2k	3,4-(MeO) ₂ C ₆ H ₃	1.5	0.6	0.3	50	3k , 89
2l	2,5-(MeO) ₂ C ₆ H ₃	1	1	0.5	60	3l , 63
2m	4-HOC ₆ H ₄	1	1	0.5	60	3m , 90
2n	4-ClC ₆ H ₄	1.5	1	0.5	60	3n , 82
2o	4-BrC ₆ H ₄	1.5	0.6	0.3	80	3o , 74
2p	4-IC ₆ H ₄	1.5	1	0.5	80	3p , 79
2q	3-BrC ₆ H ₄	0.6	0.6	0.3	60	3q , 74
2r	3-ClC ₆ H ₄	0.6	0.6	0.3	60	3r , 27
2s	2-FC ₆ H ₄	0.6	0.6	0.3	60	3s , 63
2t	2-ClC ₆ H ₄	0.6	0.6	0.3	60	3t , 46
2u	3-MeO ₂ CC ₆ H ₄	0.6	0.6	0.3	60	3u , 45
2v	3-F ₃ CC ₆ H ₄	1.5	1	0.5	60	3v , 71
2w	1-Naphthyl	1	1	0.5	60	3w , 82
2x	2-Naphthyl	1	0.6	0.3	50	3x , 86
2y	3-Pyridyl	1	1	0.5	50	3y , 74
2z	4-Pyridyl	1	0.75	1 ^c	40	3z , 31

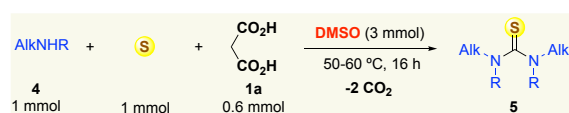
^a Reaction conditions: aniline **2** (1 mmol), sulfur (x mmol, 32 mg·mmol⁻¹), malonic acid **1a** (y mmol), DABCO (z mmol) in DMSO (3 mmol, 0.2 mL) at T °C for 16 h. ^b Yield of **3a** after column chromatography. ^c *N*-methylpiperidine (1 mmol) was used instead of DABCO. ^d Yield of 2.5 mmol scale reaction.

Next, we started exploring challenging anilines appended with electron withdrawing groups such as 3-MeO₂C (**2u**) and 3-CF₃ (**2v**). Although their reactivity is lower than toluidines, and anisidines, we could obtain the desired thioureas in good yields by appropriately increasing the reaction temperature as well as the amounts of both malonic acid and DABCO to compensate the loss of malonic acid due to the precocious thermal decarboxylation of malonic acid (*vide infra*). The naphthylamines (**2w-2x**) and 3-aminopyridine (**2y**) were also excellent substrates. On the contrary, 4-aminopyridine (**2z**) was less reactive than anilines. Its reaction at 40 °C using excess liquid base *N*-

methylpiperidine afforded thiourea **3z** in a low yield (31%). On the other hand, at higher temperature (50-80 °C), the formation of **3z** is limited by spontaneous decarboxylation of malonic acid without sulfuration, which could probably be catalyzed by **2z**.

After a successful demonstration of the aromatic amines, we continued investigating aliphatic amine partners. A series of aliphatic substrates with different chain lengths and substituent motifs (**4a-4n**) were transformed smoothly into the corresponding thioureas (**5a-5n**) in moderate to good yields (Table 3). We were delighted to note that since aliphatic amines were sufficiently basic, DABCO additive could be excluded. Functional groups such as morpholino, allyl (**4m**, **4n**) were well tolerated. It should be emphasized that due to low steric requirement, pyrrolidine **4o** displayed similar reactivity compared to that of aliphatic primary amines, while the reactions of more bulky secondary amines (i.e. dibutylamine, morpholine) led to the thioformamides (*vide infra*, end of Scheme 3).

Table 3. Reactions of Alkylamine with Malonic Acid 1a^a



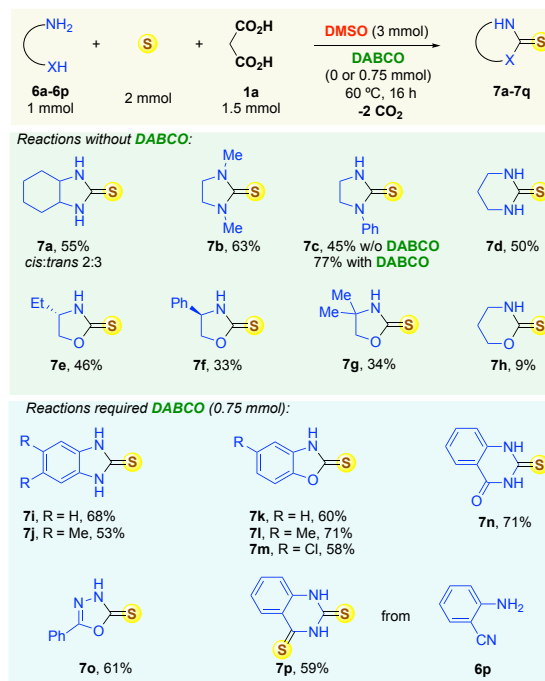
4	AlkNHR	T (°C)	5 , Yield (%) ^b
4a	<i>n</i> -BuNH ₂	60	5a , 65
4b	<i>n</i> -PentNH ₂	60	5b , 64
4c	<i>n</i> -HexNH ₂	60	5c , 68
4d	<i>n</i> -PrNH ₂	50	5d , 48
4e	PhCH ₂ NH ₂	50	5e , 51
4f	PhCH ₂ CH ₂ CH ₂ CH ₂ NH ₂	60	5f , 55
4g	PhCH ₂ CH ₂ CH ₂ NH ₂	60	5g , 52
4h	<i>rac</i> -2-EthylhexylNH ₂	60	5h , 61
4i	IsopentylNH ₂	60	5i , 63
4j	CyclohexylNH ₂	60	5j , 65
4k	CyclopentylNH ₂	60	5k , 51
4l	MeOCH ₂ CH ₂ NH ₂	60	5l , 42
4m	2-Morpholinoethylamine	60	5m , 53
4n	AllylNH ₂	50	5n , 50
4o	Pyrrolidine	50	5o , 45

^a Reaction conditions: amine **2** (1 mmol), sulfur (1 mmol, 32 mg), malonic acid **1a** (0.6 mmol) in DMSO (3 mmol, 0.2 mL) at 50-60 °C for 16 h. ^b Yield of **5** after column chromatography.

The robustness of our reaction was further investigated by applying to the synthesis of a series of aza heterocycle thioureas **7** from amines **6** bearing a wide range of cyclizable group of various natures (Scheme 1). Aliphatic 1,2- and 1,3- diamines **6a-6d** reacted smoothly to provide cyclic thioureas **7a-7d** in good yields, even with secondary amines and/or aromatic (**6b** and **6c**). In case of **7c**, using DABCO allowed the reaction to occur in a cleaner way. The reaction of 1,2-aminoalcohols **6e-6g** proceeded cleanly to give **7e-7g** although the amino group is linked with a highly hindered secondary or tertiary carbon. It is noteworthy that some of these oxazolidin-2-thiones were previously known to serve as chiral auxiliaries¹³ for asymmetric synthesis and their syntheses required more complex conditions.¹⁴ Using 1,3-aminopropanol, the yield of thiocarbamate **7h**

dropped markedly, possibly due to low propensity to cyclize to form 6-membered ring.

Scheme 1. Reactions of Amines 6 with Malonic Acid 1a



The presence of an alkyl (**1b-1d**) or aryl (**1e**) group did not prevent the didecarboxylation. The subsequent cascade of sulfuration and amination led to thioamides **8a-8n**.

Our conditions were also applicable to aromatic amines **6i-6n** bearing an *ortho*-cyclizable group such as amino (**6i-6j**), hydroxy (**6k-6m**) or even weakly nucleophilic carboxamide (**6n**) to afford 2-mercapto- benzimidazole (**7i-7j**), benzoxazoles (**7k-7m**), and quinazolinone **7n**. Benzhydrazide **6o** could also undergo annulation to 1,3,4-oxadiazole **7o**. It was noteworthy that the reaction with 2-aminobenzonitrile **6p** with 2 equiv of sulfur could deliver dithione **7p** in high yield and readily isolated by trituration with methanol and filtration. In this domino transformation, H₂S generated from interaction of S₈ and malonic acid was fully absorbed by the adjacent cyano group of **6p**. We emphasized that in cases of substrates without an aliphatic amine group (**6i-6p**), DABCO was required to ensure a good reactivity.

Finally, to complete this study, we investigated the reactions of some selected alkyl malonic acids **1b-1e** (Scheme 2).

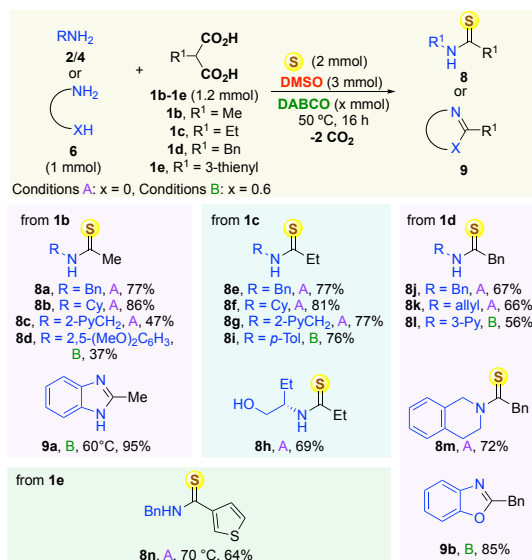
As expected, due to low reaction temperatures (50-70 °C) and mild reactions conditions, our thioamide formation tolerated a wide range of functional groups such as 2-pyridylmethyl (**8c,8g**), methoxy-rich aryl (**8d**), free alcohol (**8h**) and allyl (**8k**).

The method was shown to be suitable for aliphatic, aromatic and heteroaromatic amines although DABCO was required for aromatic ones. Interestingly, a secondary aliphatic amine such as 1,2,3,4-tetrahydroisoquinoline was found to be a competent substrate, leading to thioamide **8m**.

Additionally, cyclic products such as **9a** and **9b** could be readily accessible from bifunctional amines *o*-phenylenediamine and *o*-aminophenol. We noticed however that malonic acid **1e** bearing a 3-thienyl group is less reactive than other alkyl-substituted ones (**1b-1d**). Indeed, high temperature (70 °C)

was needed for its reaction with benzylamine to happen in a good yield.

Scheme 2. Reaction with Substituted Malonic Acids 1b-1e



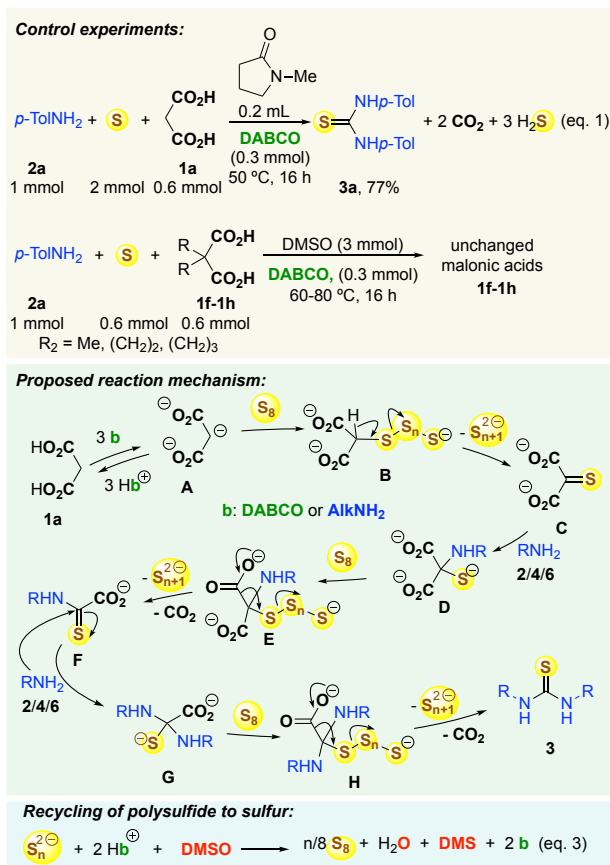
To probe the reaction pathways, some control experiments were performed (Scheme 3). First, as mentioned previously in Table 1, entry 15, high yield could be obtained even in the absence of DMSO as long as sulfur was used in at least stoichiometric amount, i.e. ≥ 2 equiv in *N*-methylpyrrolidin-2-one (eq. 1). This result suggested that sulfur acted as both sulfur source and oxidant, being reduced to hydrogen sulfide, which could be recycled into S_8 by the oxidation with DMSO.

Second, disubstituted malonic acids **1f-1h** remained unchanged under the typical conditions even at higher temperatures (60–80 °C, eq. 2), indicating that C-H deprotonation in malonic acid is an essential step for sulfur and amine incorporation.

Based on these observations, we tentatively proposed a plausible reaction mechanism to explain the formation of different types of the products. Since the reactions happened with aliphatic amines without DABCO or with aromatic amine with DABCO, it was very likely that the active form of malonic acid is the trideprotonated species **A**. The first sulfuration of **A** could occur via nucleophilic ring opening of S_8 to give 3-thionemalonnate **C** via polysulfide **B**. Strongly activated by two carboxylate groups, **C** underwent nucleophilic addition of amine **2/4/6** to yield *gem*-aminosulfide **D**, which reacted next with sulfur S_8 followed by decarboxylative fragmentation to give thioamide **F** via polysulfide **E**. At this stage, the outcome of the reaction depends on the feasibility of the nucleophilic attack of another amine molecule. In case of primary amine **2/4/6**, such a process occurs without any difficulty, giving rise to **G**, which was next polysulfurated with elemental sulfur to form polysulfide **H**, which underwent a cascade of depolysulfurative fragmentation to afford **3**.

Along with the activation of sulfur-amine complex, DMSO acted as a terminal oxidant, oxidizing polysulfide to sulfur as indicated in eq. 3.

Scheme 3. Survey of the Reaction Mechanism



In conclusion, the trio sulfur/DMSO/amine was found to promote an unprecedented didecarboxylation of malonic acid. A wide range of thioureas could be synthesized via multicomponent reactions under mild conditions. This unique reactivity could be further extended to mono-*C*-substituted malonic acids as a new way for synthesizing thioamides. We believe that this method could be very useful for the synthesis of thioureas and thioamides under redox conditions. Once again, elemental sulfur was demonstrated to be unique as a polyvalent yet affordable reagent that awakens new reactivities of common organic functional groups.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information Statement

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterizations of compounds **3**, **5** and **7-10** and copies of their NMR spectra (PDF).

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