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COMMUNICATION

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Elemental Sulfur/DMSO-Promoted Multicomponent One-pot Synthesis of Malonic Acid Derivatives from Maleic Anhydride and Amines

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Abstract. Malonic acid derivatives could be conveniently prepared with high degree of functional flexibility via redox condensation reactions between anhydride maleic, amines, elemental sulfur and DMSO as oxidant. This multicomponent decarboxylative transformation consists in a cascade of ring opening, decarboxylative oxidative thioamidation at temperature as low as 50 °C.

Keywords: sulfur; decarboxylation; DMSO; oxidative condensation; multicomponent reactions

Organic chemists have long strived to develop new multicomponent reactions to construct complex and high added value molecules from many simple starting materials. This strategy with high atom-, step-, and redox economy is designed to reduce waste, time and work compared to classical approaches involving only sequence of separated simple transformations.[1] For this purpose, we have been developing in recent years the use of elemental sulfur as a versatile tool to promote such transformations using only simple, inexpensive and readily available starting materials. We report here a straightforward synthesis of malonic acid derivatives with high degree of functional flexibility (amide, thioamide, ester, ketone, 2-azaheterocycle). This multicomponent reaction was based on decarboxylative cascade redox condensation between cheap, bench-stable, user-friendly and commercially available starting materials such as anhydride maleic, amines, elemental sulfur and DMSO as oxidant. Such products have a wide range of applications such as bioactive scaffolds for development of new drug, and starting materials for the synthesis of complex and polyfunctional molecules (Figure 1).[2] Access to such malonic derivatives required in general multistep sequences with narrow range of functional group distinction for the two carbonyl moieties (Scheme 1).[3]

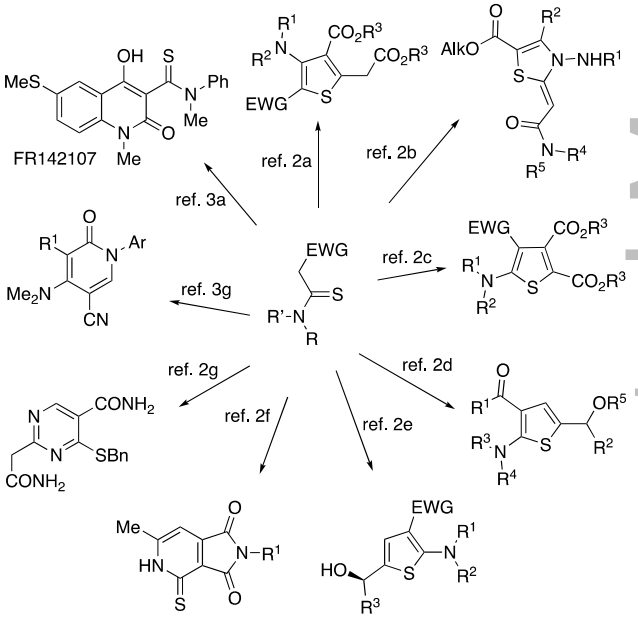

Figure 1. Selective synthetic applications of a monothioamide malonic acid derivatives

In spite of the simple appearance of sulfur, this element exhibits a wide range of reactivities that could be exploited in both redox and non-redox transformations by appropriately changing external activator, substrates and reaction conditions.[4]

At the outset of our study, upon dissolution with vigorous vortex shaking of benzylamine **A1** (2 equiv) and anhydride maleic (1 equiv, 1 mmol) in DMSO (4.5 equiv) at rt followed by addition of elemental sulfur (1.25 equiv, 32 mg.mol^{-1}) and then heating at 50 °C for

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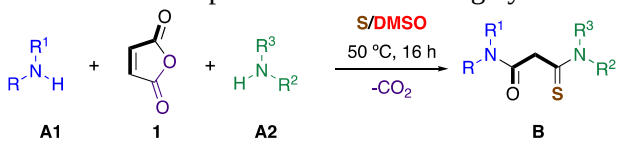
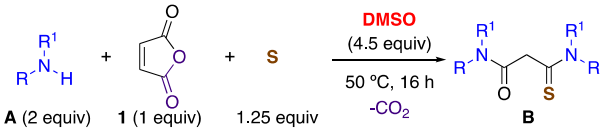
16 h, we observed the formation of amide-thioamide **B1** in excellent yield (Table 1, entry 1). The yields dropped when the reaction was performed at higher or lower temperature (entries 2 and 3). We proceeded to explore the reactivities of other primary aliphatic amines, namely **A2**-**A10** at the optimal temperature 50 °C. These reacted in similar manner, leading to various amide-thioamide products **B2**-**B10** in high yields.



Scheme 1. Four-component access to malonic acid derivatives **B**

It should be emphasized that although benzylamines **A2**-**A3** (entries 4-5) and **A7**-**A9** (entries 9-11) were known to undergo sulfurative dimerization when heating with sulfur, such a reaction was found to occur only to a lesser extent, suggesting that the decarboxylative oxidative thioamidation took place much more rapidly and efficiently than other side reactions.[5] Moreover, the formation of carboxylate salt between amine **A** and anhydride maleic **1** (see Scheme 4, **1**→**ii**) could limit the direct sulfuration of amine **A** by sulfur.

Table 1. Reaction with alkylamines A with anhydride maleic, sulfur and DMSO



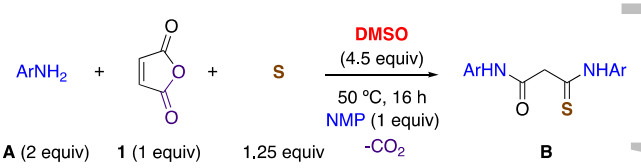
entry	**A**	R-NH-R[1]	**B**, yield (%)
1	**A1**	$BnNH_2$	**B1**, 76
2[a]	**A1**	$BnNH_2$	**B1**, 71
3[b]	**A1**	$BnNH_2$	**B1**, 67
4	**A2**	3-$MeOC_6H_4CH_2NH_2$	**B2**, 78
5	**A3**	4-$ClC_6H_4CH_2NH_2$	**B3**, 72
6	**A4**	$PhCH_2CH_2NH_2$	**B4**, 75
7	**A5**	cyclopentylamine	**B5**, 69
8	**A6**	cyclohexylamine	**B6**, 73
9	**A7**	(*S*)-Ph(Me)$CHNH_2$	**B7**, 77
10	**A8**	(±)-2-Naphthyl(Me)$CHNH_2$	**B8**, 71
11	**A9**	(±)-Ph(Et)$CHNH_2$	**B9**, 75
12	**A10**	$PhNHCH_2CH_2NH_2$	**B10**, 65
13	**A11**	pyrrolidine	**B11**, 71
14	**A12**	piperidine	**B12**, 72
15	**A13**	morpholine	**B13**, 70
16	**A14**	1,2,3,4-tetrahydroisoquinoline	**B14**, 72

[a] Reaction performed at 60 °C. [b] Reaction performed at 40 °C

The same procedure could be applied successfully to a range of primary aliphatic amines with increasing steric hindrance on the branched alpha carbon atom (**A5**-**A9**, entries 7-11). When enantiomerically pure amine **A7** was used, the amide-thioamide product **B7** was obtained as a single product with only one set of NMR signals (entry 9). On the other hand, when **A8** and **A9** were used as racemic mixture, two couple of diastereomers (*S,S* & *R,R*) *vs* (*R,S* & *S,R*) were formed in practically equimolar amounts with readily distinguishable ^{1}H NMR signals (entries 10-11). When another aromatic/aliphatic secondary amine function was present in the amine substrate as in **A10**, the reaction proceeded without any event (entry 12). Cyclic secondary amines **A11**-**A14** were found to be competent substrates, providing tertiary amide-thioamides **B11**-**B14** in excellent yields (entries 13-16). As in previous cases with benzylic amines, no undesirable oxidation of the benzylic position of amine **A14** was observed. The product **M14** was obtained in high yield as a mixture of four possible rotamers (by ^{1}H NMR).

Next, we studied the scope of the reaction for aromatic amine (Table 2). Because of the low basicity of aniline **A15**, which resulted in an inefficient activation of elemental sulfur, it was not surprising that the similar transformation failed in the absence of additive. On the other hand, addition of a stoichiometric amount of *N*-methylpiperidine (NMP), which was found to be a good sulfur activator,[6] overcame this drawback and led cleanly to the desired product **B15** (entry 1). Extension of these conditions to other anilines **A16**-**A21** provided the expected products **B16**-**B21**. In general, anilines with electron-donating groups such as OMe, OH (**A17** and **A22**) gave better yields.

Table 2. Reaction of aniline A with anhydride maleic, sulfur and DMSO



entry[a]	**A**	$ArNH_2$	**M**, yield (%)
1	**A15**	$PhNH_2$	**B15**, 71
2	**A16**	2-$MeC_6H_4NH_2$	**B16**, 32
3	**A17**	4-$MeOC_6H_4NH_2$	**B17**, 75
4	**A18**	3-$MeOC_6H_4NH_2$	**B18**, 68
5	**A19**	3-$ClC_6H_4NH_2$	**B19**, 63
6	**A20**	4-$BrC_6H_4NH_2$	**B20**, 62
7	**A21**	4-$IC_6H_4NH_2$	**B21**, 65
8	**A22**	4-$HOC_6H_4NH_2$	**B22**, 71

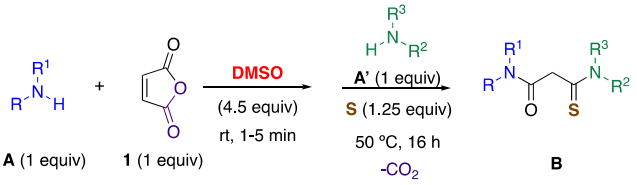
The reaction conditions tolerated free hydroxy (**A22**) and halogen (Cl, Br, I in **A19**-**A21**) substituents. The reactions *o*-substituted aniline **A16** gave less efficient formation of amide-thioamide product **B16**.

At this stage, we wanted to explore the flexibility in installing two amine moieties to the malonic skeleton. It should be noted that while the first step of ring opening of maleic anhydride occurred spontaneously and rapidly with a stoichiometric amount of aliphatic and aromatic amines (< 5 min at rt for completion), the second step of decarboxylative thioamidation required an effective activation of sulfur by an aliphatic amine and longer reaction time.

Based on this analysis, we could introduce two different amine moieties into the final malonic acid derived amide-thioamide at the expected positions by simply changing the order of addition of these amines.

When the secondly added amine is aliphatic, the decarboxylative thioamidation proceeded spontaneously at 50 °C. In cases of anilines, the presence of (NMP) was necessary to achieved the expected transformation. Such strategy resulted in a reasonable yield of product **B23** from benzylamine **A1** and its 3-methoxy derivative **A2** (Table 3, entry 1). By simple changing the order of addition **A2** then **A1**, isomeric product **B24** was obtained in the same manner. Similar reaction with alkylamine(1)/alkylamine(2) (entries 3-4) or aniline/ alkylamine (entries 5-15) or aniline(1)/aniline(2) (entries 16-17) or alkylamine/aniline (entry 18) furnished a wide range of products with high functional group tolerance (halogens, ester, nitro, heterocycle, tertiary amine) and high structural diversity.

Table 3. Reaction of two different amines with anhydride maleic, sulfur and DMSO

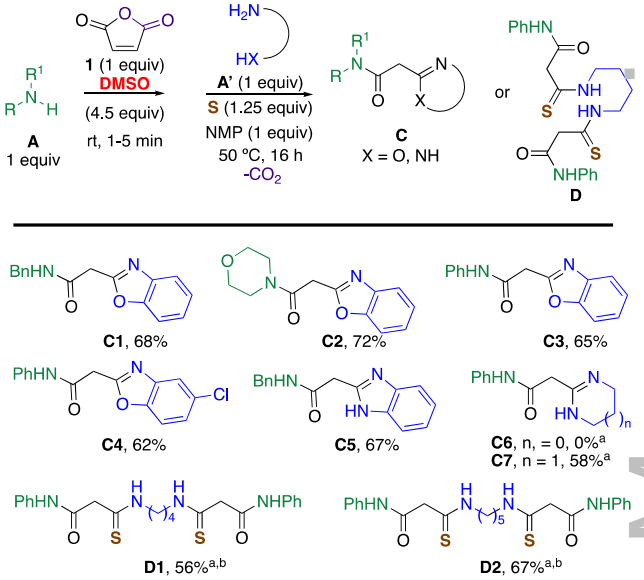


entry[a]	R/R^1 - R^2/R^3	**M**, yield (%)
1	H/Bn - H/3-MeOC$_6$H$_4$CH$_2$	**B23**, 65
2	H/*m*-MeOC$_6$H$_4$CH$_2$ - H/Bn	**B24**, 67
3	H/*p*-ClC$_6$H$_4$CH$_2$ - H/PhNH(CH$_2$)$_2$	**B25**, 63
4	*n*-Bu/*n*-Bu - H/Bn	**B26**, 64
5	H/*o*-MeOC$_6$H$_4$ - H/Bn	**B27**, 68
6	Me/Ph - H/Bn	**B28**, 71
7	H/2-FC$_6$H$_4$ - H/Bn	**B29**, 68
8	H/1-Naphthyl - H/Bn	**B30**, 62
9	H/*m*-MeO$_2$CC$_6$H$_4$ - H/Bn	**B31**, 61
10	H/*m*-O$_2$NC$_6$H$_4$ - H/Bn	**B32**, 62
11	H/3-Pyridyl - H/Bn	**B33**, 65
12	H/Ph - H/CH$_2$CH$_2$Ph	**B34**, 70
13	H/*p*-IC$_6$H$_4$ - H/ CH$_2$CH$_2$Ph	**B35**, 65
14	H/Ph - piperidino	**B36**, 69
15	H/Ph - morpholino	**B37**, 73
16[a]	H/4-BrC$_6$H$_4$ - H/Ph	**B38**, 63
17[a]	H/Ph - H/4-BrC$_6$H$_4$	**B39**, 59
18[a]	H/Me$_2$NCH$_2$CH$_2$CH$_2$ - H/Ph	**B40**, 56

[a] NMP (99 mg, 1 mmol) as added if **A'** is an aromatic aniline.

When the secondly added amine **A'** was an aniline bearing an *o*-cyclizable group such as OH or NH$_2$, i.e. *o*-aminophenols or *o*-phenylenediamine, the final malonamide derivatives **C1-C6** obtained did not contain any thioamide moiety but a corresponding benzazole ring in generally good yields (Scheme 2). The formation of such heterocyclic compounds is remarkable in view of low temperature of the whole process of decarboxylation and heterofunctionalization. [6d]

Since these nitrogen nucleophiles are weakly basic, the presence of NMP was necessary. We emphasized that although these heterocyclic products did not contain sulfur, their formation required stoichiometric amount of sulfur. Indeed, using only 0.5 equiv sulfur resulted in very low yield of the benzazole products. When aliphatic diamines were used as the secondly added amines, depending on the distance between two amino function, we could obtain the corresponding cyclic amidine **C7** or bis-thioamides **D1-D2**. In case of ethylenediamine, due to its strong interaction with sulfur, the reaction resulted in a complexed mixture in which we could detect the presence of the expected amidine **C6**.



[a] Without NMP. [b] Diamine (0.5 equiv) was used.

Scheme 2. Reaction of cyclizable amines

The structures of amide-thioamide malonic derivatives **B4** and **B30** were confirmed unambiguously by X-ray diffraction study as presented in Figure 2.

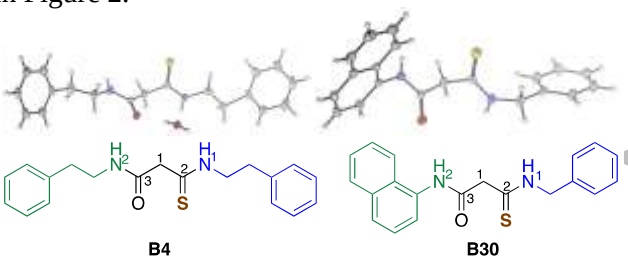


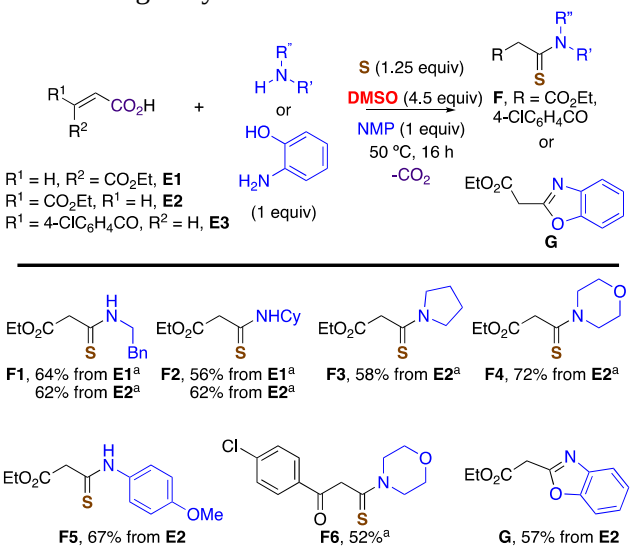
Figure 2. X-ray structures of **B4** and **B30**

In both structures, the carbonyl and the thiocarbonyl group are in a gauche conformation. The bonds N1–C2 and N2–C3 (averaged 1.315(2) Å, 1.320(2) Å resp.) are still remarkably short, while the attached C=O (1.242(2) Å, 1.226(2) Å resp.) and the C=S (1.677(2)

Å, 1.667(2) Å) bonds are slightly elongated. Bond lengths and angles around the central methylene carbon atom C1 are as expected (C–C averaged 1.512(2) Å, 1.516(2) Å resp.; C–C–C 111.3(2)°, 109.5(2)° resp.).

Finally, we extended our strategy to acrylic acids **E1**-**E3** bearing an electron-withdrawing group on the β position (Scheme 3). Similar reactivity of decarboxylative thioamidation of the acrylic acid moiety was observed with monoethyl ester of either maleic acid **E1** as well as its *E* isomer fumaric acid **E2** in the reaction with 2-phenethylamine and cyclohexylamine.

Other cyclic aliphatic secondary amines (pyrrolidine, morpholine) and aromatic amines (*p*-anisidine and *o*-aminophenol) reacted with acid **E2** in the similar manner. Although a Willgerodt reaction of morpholine with the benzoyl moiety of acid **E3** could be potentially problematic, the expected product was obtained in good yield.

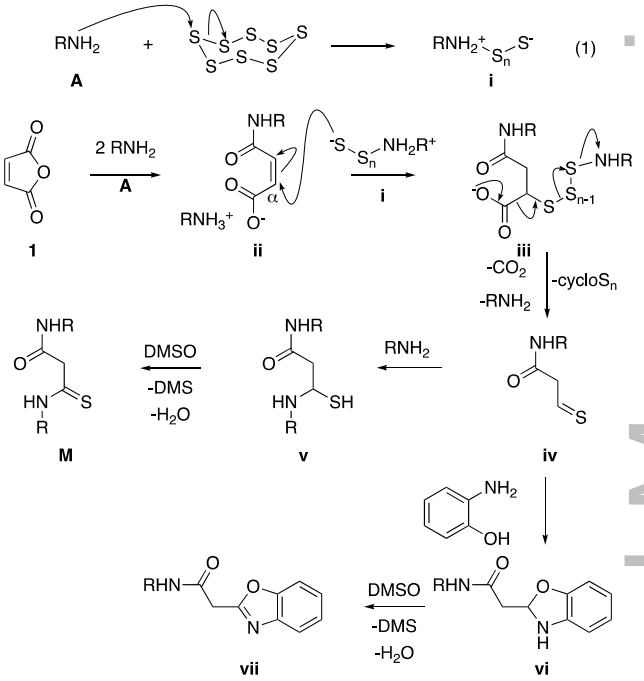


[a] Reaction performed without NMP.

Scheme 3. Reaction of β-substituted acrylic acids

Although the detailed mechanism is not fully elucidated for the moment, based on the obtained product structures as well as previous observations, we suggest a possible reaction pathway (Scheme 4). The interaction of aliphatic amine **A** with cyclooctasulfur could provide highly nucleophilic polysulfide **I** according to equation (1). In the presence of amine **A**, anhydride maleic **1** is readily transformed into ammonium carboxylate **ii** via ring opening. Although the C=C bond of acrylate **ii** is substituted by two electron withdrawing groups, its α position is more electrophilic since the carboxamide group is more electrophilic than the anionic carboxylate group.

Consequently, addition of sulfur-amine complex **i** to maleate **ii** would provide regioselectively to give succinate **iii**. Subsequent decarboxylative and desulfurative deamination of **iii** would lead to thioaldehyde **iv**. Addition of amine, followed by an DMSO-assisted oxidation of adduct **v** would yield the final thioamide **B**. In case of 1,2-bis-nucleophiles such as *o*-aminophenols, the reaction of such nucleophiles with thioaldehyde **iv** would give benzoxazoline **vi**, readily oxidized to give the final benzoxazole **vii**. It should be noted that a similar decarboxylative thioamidation of cinnamic acids with either aliphatic amines,[7] small *N*,*N*-dialkylformamide[8] or *o*-aminophenols[9] was described at higher temperatures (80, 100 and 130 °C, respectively) with excess use of elemental sulfur as both sulfur source and oxidant. The scope of such reaction is thus not applicable to amine nucleophiles that can react with sulfur such as benzylic ones. Favored by the presence of both carbonyl groups, decarboxylative thioamidation in our case could occur at much lower temperature and undoubtedly compatible with a wide range of amines.



Scheme 4. Proposed Mechanism

In summary, we have reported a multicomponent access to malonic acid derivatives starting with maleic anhydride, elemental sulfur and amines in the presence of DMSO as oxidant under mild conditions.[10] The method is characterized by its simplicity and a high level of structural diversification by simply varying the amines as well as the order of amine addition. The transformation is highlighted by a decarboxylation at temperature as low as 50 °C.[11] The generality of this method was further demonstrated with other acrylate derivatives β-substituted by an electron withdrawing group such as ester and ketone. Further exploration of this decarboxylative heterofunctionalization of carboxylic acids is underway in our laboratory and the related results will be reported in due course.

Experimental Section

Reaction with only one amine (Tables 1 and 2)

Amine A (2 mmol) and DMSO (0.3 mL, 4.5 equiv) was added to a 7-mL test tube containing solid anhydride maleic. The resulting mixture was shaken vigorously with a vortex mixer (0.5-1 min) to give a viscous pale yellow to brown solution (in cases of some anilines, the dissolution of anhydride maleic result in a slurry). Sulfur (40 mg, 1.25 mmol), *N*-methylpiperidine (99 mg, 1 mmol) (used for aniline derivatives) and a magnetic stir bar were added. The tube was closed with a septum, purged with Ar. An Ar balloon was put on the top of the septum and the tube was stirred at 50 °C for 16 h. The reaction mixture was purified by column chromatography on silica gel (eluent CH_2Cl_2:EtOAc 1:0 to 20:1 or CH_2Cl_2:MeOH:NH_3).

Reaction with two amines (Table 3 and Schemes 2-3)

Amine **A** (1 mmol) and DMSO (0.3 mL, 4.5 equiv) was added to a 7-mL test tube containing solid anhydride maleic. The resulting mixture was shaken vigorously with a vortex mixer (5 min) to give a viscous pale yellow to brown solution (in cases of some anilines, the dissolution of anhydride maleic result in a slurry). Amine **A'** (1 mmol), sulfur (40 mg, 1.25 mmol), *N*-methylpiperidine (99 mg, 1 mmol) (used if **A'** is an aniline) and a magnetic stir bar were added. The next step was performed as in the previous cases.

CCDC-1885231 and CCDC-1885232 (compounds **B4** and **B30** respectively) contain contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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