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Selective aliphatic thiol conjugation to *α*-benzylidene succinimides: A versatile route to advanced succinimide functionalization

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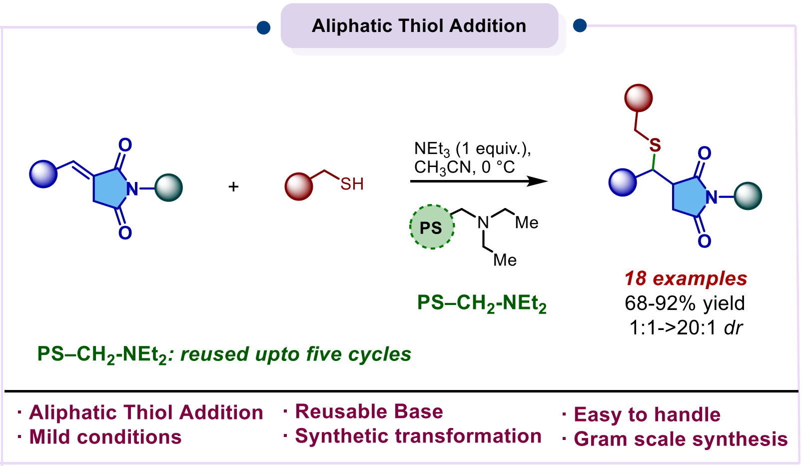
Abstract

Herein we report a mild and simple regioselective protocol for aliphatic thiol addition to *α*-benzylidene succinimide derivatives. This versatile approach enables formation of a diverse range of succinimide scaffolds containing thioether moieties with good to excellent yield and diastereoselectivity. Importantly, this protocol is amenable to gram-scale synthesis and is compatible with a polymer-supported base diethylaminomethyl-polystyrene (PS–CH_2-NEt_2). The utilized PS–CH_2-NEt_2 was then subjected to recycling process several times with the optimised condition. Finally, the thioether was transformed to its sulfoxide derivative upon oxidation.



Keywords: Thioethers, itaconimides, succinimides, diastereoselective

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Introduction

Organosulfur compounds are ubiquitous in biological systems and are of significant importance in medicinal chemistry[1-2], materials science, and catalysis because of their unique electronic, redox, and coordination properties.[3] Among sulfur-containing motifs, thioethers (C–S–C linkages) are one of the most prevalent and biologically relevant functional groups.[4-7] Thioether motifs are widely found in natural products and clinically used pharmaceuticals, where they contribute to molecular stability, lipophilicity, conformational control, and biological recognition.[8,9] For instance, biotin acts as an essential metabolic cofactor for multiple carboxylase enzymes, with its sulfur-containing heterocycle playing a key role in enzymatic activity.[10] Similarly, several clinically used drugs, such as montelukast[11] (anti-asthmatic leukotriene receptor antagonist), butoconazole[12] (antifungal agent), and arotinolol (*α/β*-adrenergic blocker), feature thioether linkages that contribute to their pharmacokinetic profiles and receptor-binding properties.[13]

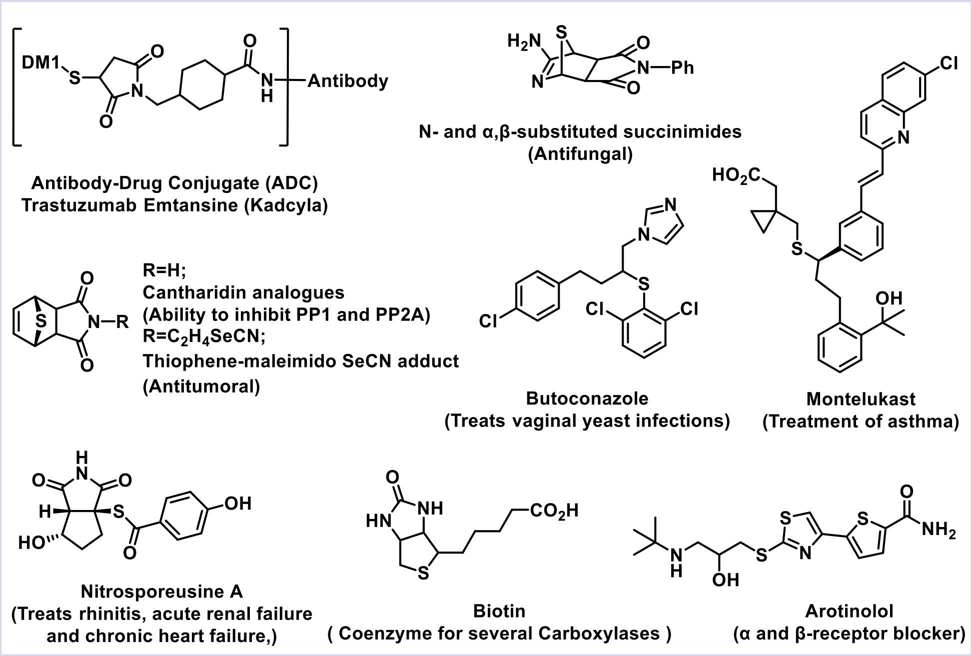
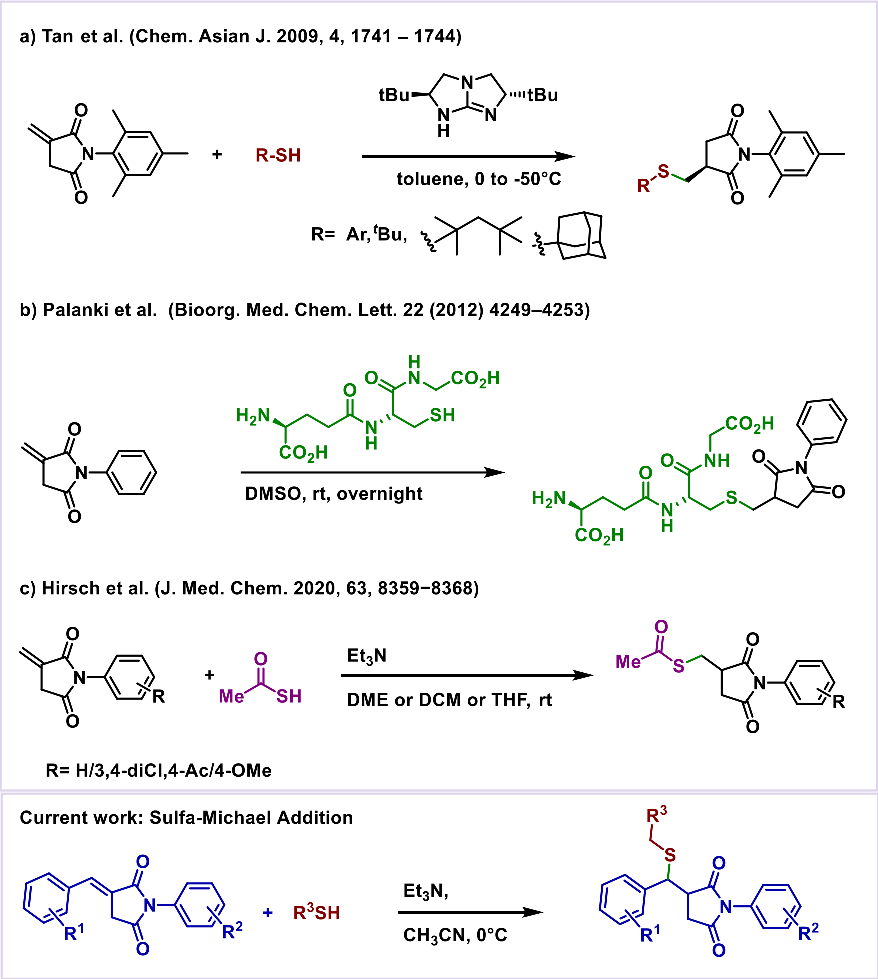


Figure 1. Selected natural products and drugs containing thioether moieties.

Beyond conventional small-molecule drugs, sulfur–imide conjugation chemistry has become an important tool in modern drug delivery systems.[14] A representative example is the antibody–drug conjugate trastuzumab emtansine (Kadcyla), where thiol–maleimide coupling enables covalent attachment of cytotoxic payloads to antibodies, emphasizing the broad synthetic and biomedical relevance of thioether-forming reactions.[15-16]

The importance of sulfur-containing succinimide frameworks is further supported by their biological activity. For instance, *N*- and *α,β*-substituted succinimides have been reported to possess antifungal properties[17-18], whereas cantharidin analogues, structurally related to imide frameworks, are well known as inhibitors of the protein phosphatases PP1 and PP2A.[19] Furthermore, thiophene–maleimido SeCN adducts display significant antitumoral activity, underscoring the therapeutic relevance of sulfur-functionalized imide frameworks.[20] Natural products such as nitrosporeusine A, which contains sulfur within a biologically active framework and has been reported for the treatment of rhinitis, acute renal failure, and chronic heart failure, further illustrate the medicinal importance of sulfur-containing heterocycles (see Figure 1).[21]

From a synthetic perspective, thiol–Michael addition to activated alkenes such as maleimides represents one of the most reliable strategies for constructing thiosuccinimide frameworks.[22] N-Aryl itaconimides are a privileged class of activated succinimides bearing both electron-deficient C=C bonds and imide carbonyl groups, thereby acting as versatile Michael acceptors.[23] Aryl substitution at the nitrogen atom further influences the electronic properties and steric environment of these systems, allowing fine control over chemo- and regioselectivity in nucleophilic addition reactions.[24] However, despite these favorable characteristics and the expanding medicinal relevance of itaconamide-based scaffolds, including recently reported HDAC inhibitors, systematic studies on aliphatic thiol addition to N-itaconimides are still largely underexplored.[25]



Scheme 1. Previous reports and current work.

Thiol–Michael addition to activated imides represents a useful strategy for constructing sulfur-containing succinimide frameworks. In 2009, Tan et al. reported a guanidine-catalyzed thiol addition to itaconimides performed in toluene at low temperatures (0 to −50 °C), which afforded thiosuccinimide derivatives with moderate stereocontrol (Scheme 1a).[26] Subsequently, Palanki and co-workers (2012) explored thiol addition to modified maleimide systems using reduced glutathione in DMSO (Scheme 1b). Their study was directed toward the development of hydrolytically stable succinimide linkers for antibody conjugation. By carefully tuning the substitution pattern on the maleimide ring, they enhanced the stability of the resulting thiosuccinimide adducts, enabling efficient attachment of pharmacophores to carrier antibodies through thiol–Michael coupling.[27] More recently, Hirsch and co-workers (2020) reported the preparation of *N*-aryl-3-mercaptosuccinamides from α-benzylidene succinimides. These compounds showed inhibitory activity against the microbial enzymes LasB and ColH (Scheme 1c), further emphasizing the biological relevance of sulfur-functionalized succinimide scaffolds.[28]

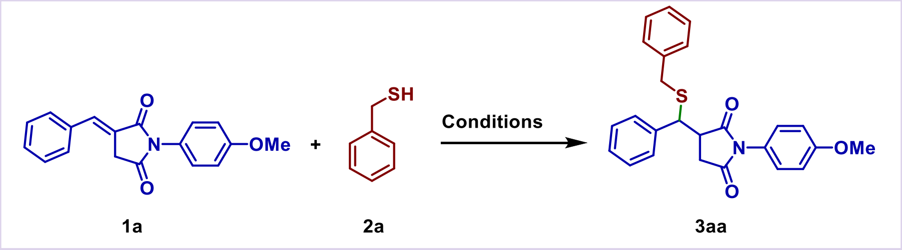
Collectively, these studies highlight the synthetic versatility and biological importance of thiol addition to activated imide systems. Nevertheless, despite these advances, a mild and general strategy for the selective conjugation of aliphatic thiols to benzylidene succinimides remains insufficiently explored. Over the years, synthetic chemists have developed numerous elegant approaches for incorporating sulfur functionalities into valuable bioactive scaffolds.[29] However, most of these efforts have predominantly focused on the addition of aromatic sulfur compounds through various methodologies. Owing to their stability and well-defined reactivity, aromatic sulfur derivatives have been widely investigated and utilized, whereas reactions involving aliphatic sulfur compounds remain relatively underexplored.[30] This is particularly notable considering their substantial potential to generate structurally diverse and functionally rich molecular architectures. The selective incorporation of sulfur into aliphatic chains offers unique opportunities for constructing novel molecules with enhanced biological activity and reactivity, thereby establishing aliphatic sulfur addition as a promising yet comparatively underexplored area in organosulfur chemistry.[31]

Therefore, the development of efficient and selective strategies for the construction of thioether-linked N-itaconamide derivatives via aliphatic sulfur addition is of considerable interest, both for advancing organosulfur chemistry and for enabling access to biologically relevant imide-based frameworks.[32]

Results and Discussion

We commenced our investigation with our model substrate *N*-aryl substituted itaconimide **1a** and benzyl mercaptan **2a** under base-free conditions (Table 1, entry 1). Unfortunately, at ambient temperature, we were unable to obtain any product even after stirring for 24 h. We then added a catalytic amount of base triethylamine (Et_3N) and stirred the reaction at 25°C for 24 hours. Surprisingly, this condition (Table 1, entry 2) afforded the desired product 3aa in 55% yield after purification. Further studies on increasing the base amount up to 2 equivalents were conducted (Table 1, entries 3-5). Increasing the base loading to 1.0 equivalent improved the yield to 76%; however, further increase in base amount to 1.5 and 2.0 equivalents led to a decline in yield to 72% and 60%, respectively (Table 1, entries 4 and 5). Thereby, indicating that 1.0 equivalent of base afforded the most efficient conversion. To further improve the yield, the reaction was screened with various organic and inorganic bases, which yielded the product **3aa** in good yield (Table 1, entries 6-13).

Table 1. Optimization of base[a]

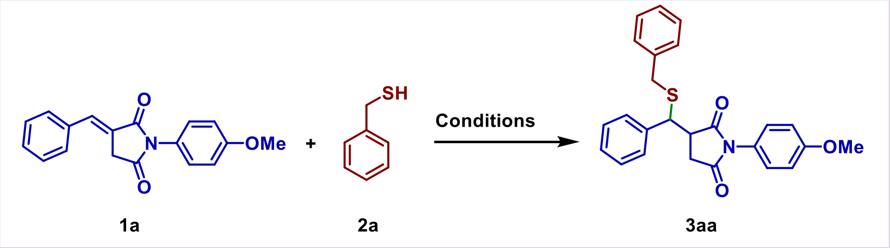


Entry	Base (equiv.)	Solvent	Time (h)	Yield[b,c] (%)
1	-	CH_3CN	24	-
2	Et_3N (0.5)	CH_3CN	24	55
3	Et_3N (1)	CH_3CN	8	76
4	Et_3N (1.5)	CH_3CN	7	72
5	Et_3N (2)	CH_3CN	6	60
6	DABCO (1)	CH_3CN	7	61
7	Piperidine (1)	CH_3CN	8	65
8	Pyridine (1)	CH_3CN	10	43
9	DBU (1)	CH_3CN	8	57
10	$NaHCO_3$ (1)	CH_3CN	10	41
11	Na_2CO_3 (1)	CH_3CN	8	51
12	K_2CO_3 (1)	CH_3CN	7	47
13	Cs_2CO_3 (1)	CH_3CN	7	45

[a]The reaction was conducted using **1a** (50 mg, 0.170 mmol), **2a** (32 mg, 0.30 µL, 0.256 mmol), solvent (3 mL) at 25 °C, unless specified; [b]Isolated yield; [c]The diastereomeric ratio (*dr*) was determined by ^{1}H NMR analysis of the crude reaction mixture (*dr* ≈ 5:1).

Comparison of various commonly used solvents was carried out, aiming to improve product formation. It was found that solvent variation had little effect on the yield of **3aa** (Table 2, entries 1-7). However, elevating the reaction temperature from room temperature (25 °C) to 40 °C and 60 °C resulted in decreased yields (Table 2, entries 8-9). Interestingly, conducting the reaction at 0 °C significantly lowered the formation of other uncharacterized side products, providing the desired product **3aa** in 87% yield (Table 2, entry 10). Finally, we decreased 1.5 equiv. of **2a** to 1.1 equiv., which produced comparable results. Thus, after screening various conditions, it was concluded that the reaction condition (Table 2, entry 11) provided the best outcome.

Table 2. Optimization of solvent and reaction temperature[a]

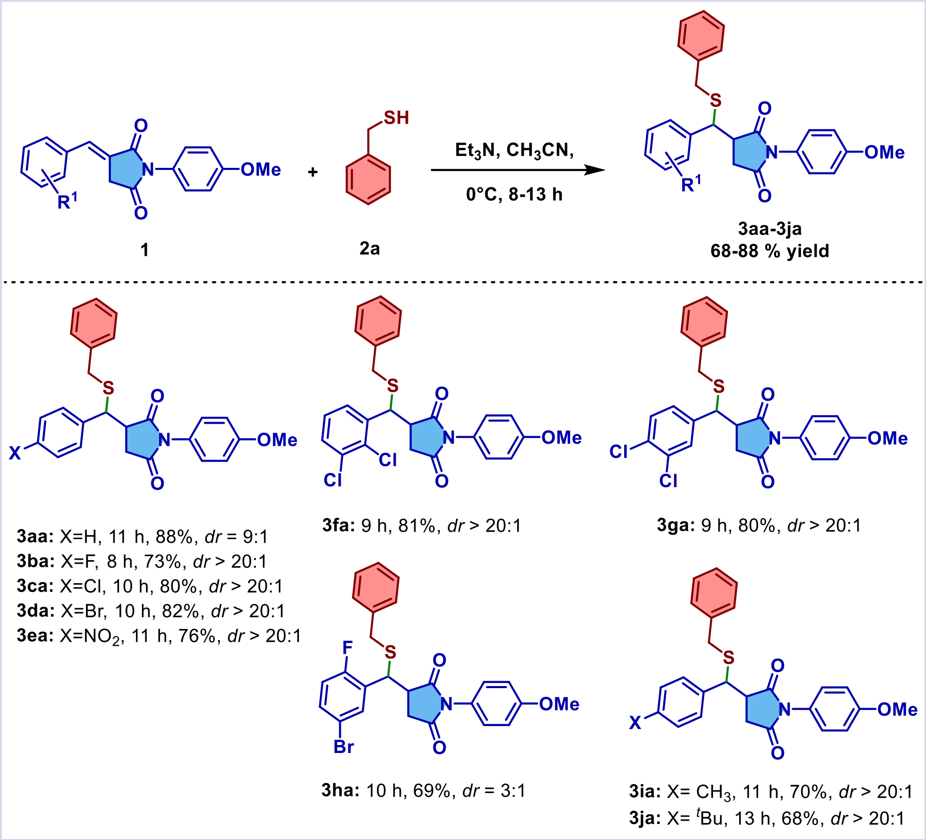


1a **2a** **3aa**

Entry	Base (equiv.)	Solvent	Temp(°C)	Time (h)	Yield[b,d] (%)
1	Et_3N (1)	DCM	25°C	8	67
2	Et_3N (1)	DCE	25°C	9	55
3	Et_3N (1)	$CHCl_3$	25°C	8	60
4	Et_3N (1)	CCl_4	25°C	10	35
5	Et_3N (1)	THF	25°C	8	58
6	Et_3N (1)	MeOH	25°C	8	61
7	Et_3N (1)	Toluene	25°C	10	42
8	Et_3N (1)	CH_3CN	40 °C	7	69
9	Et_3N (1)	CH_3CN	60 °C	7	64
10	Et_3N (1)	CH_3CN	0 °C	11	87
11[c]	Et_3N (1)	CH_3CN	0 °C	11	88

[a] The reaction was conducted using **1a** (50 mg, 0.170 mmol), **2a** (32 mg, 0.30 µL, 0.256 mmol), solvent (3 mL) unless specified. [b] Isolated yield. [c] 1.1 equiv. of **2a** is used instead of 1.5 equiv. [d] The diastereomeric ratio (*dr*) was determined by ^{1}H NMR analysis of the crude reaction mixture (*dr* ≈ 5:1).

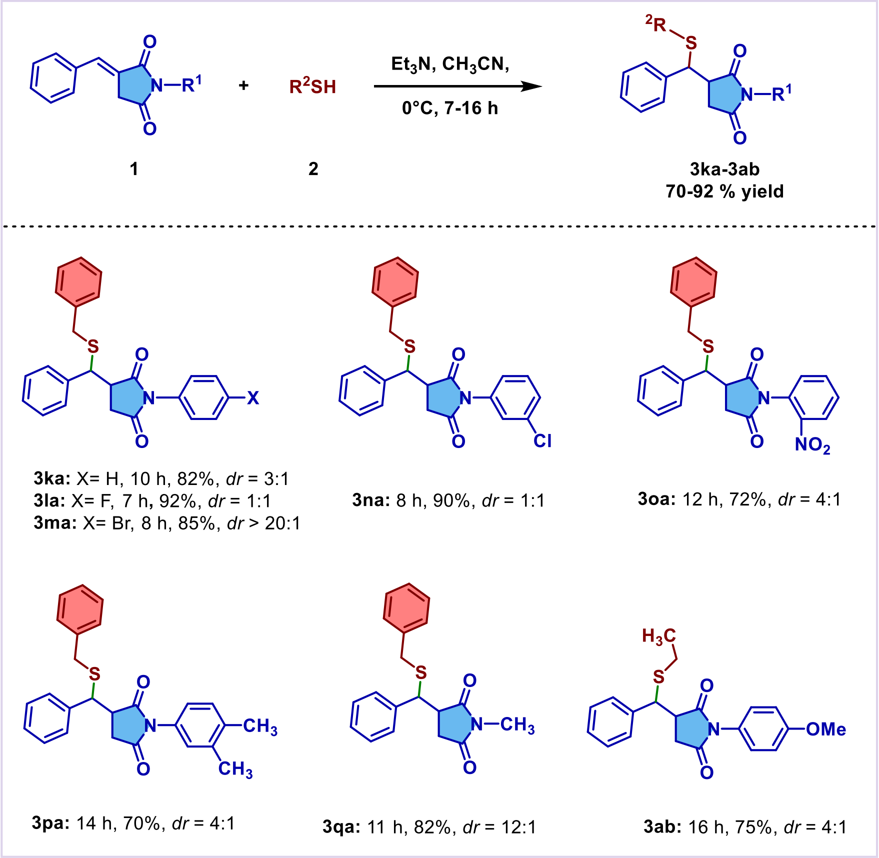
Using the optimized condition, the substrate generality of our developed methodology was evaluated. Specifically, mono-substituted *para*-halophenyl groups (F, Cl and Br), were well tolerated with our devised strategy, providing excellent yields of products (**3ba–3da**). Substrates bearing strong electron-withdrawing groups like (*p*-NO_2) also delivered the desired product (**3ea**) with good yield.



Scheme 2. Substrate scope for aryl substituted 3-benzylidene succinimides.

Succinimide derivatives with various di-halo substituted phenyl groups, like 2,3-dichloro (**1f**), 3,4-dichloro (**1g**) and electronically distinct 2-F-5-Br (**1h**) groups, all underwent the reaction efficiently, affording the corresponding *N*-aryl-substituted thiosuccinimides (**3fa–3ha**) in excellent yields (Scheme 2). Lastly, *para*-methyl (**3ia**) and *para*-*tert*-butyl (**3ja**) substituted products were also obtained in good yields under the optimized reaction conditions.

Substrates bearing electron-donating moieties, such as a *para*-methoxy group, were also evaluated; however, in these cases, no formation of products **3** occurred. This decreased reactivity is likely due to the electron-rich nature of the 3-benzylidene succinimides, which likely impairs the efficiency of the initial Michael addition step. We investigated the scope of the method by employing various thiols and substituted *N*-aryl 3-benzylidene succinimides (**3ka–3ab**). Halo-substituted phenyl derivatives at the *para*- and *meta*- positions reacted smoothly, affording products (**3ka–3na**) in excellent yields (Scheme 3).

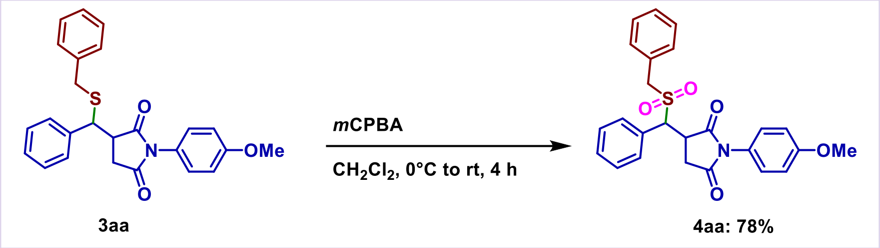


Scheme 3. Substrate scope for *N*-substituted 3-benzylidene succinimides and thiols.

In contrast, the introduction of an electron-donating dimethyl group resulted in product **3pa** being obtained in 70% yield after 14 hours. These results suggest that increasing electron density on the aromatic ring slows down the reaction, leading to longer reaction times. The *N*-methyl substituted 3-benzylidene succinimide was employed, which produced **3qa** derivative in good yield (Scheme 3).

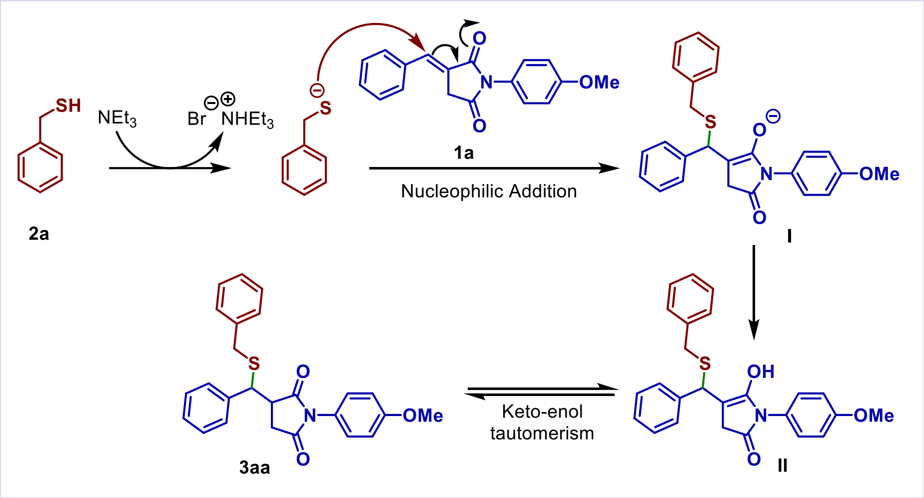
All products were formed as mixtures of diastereomers, with the diastereomeric ratios (dr) varying within the range of 3:1 to 6:1 across the substrate scope (see Experimental Section for details). In some cases, after purification by column chromatography, an almost pure single diastereomer was obtained. The dr values obtained after purification of each compound are shown in Schemes 2 and 3. Although ortho-substituted phenyl derivatives (e.g., **3fa** and **3ha**) might be expected to introduce additional steric hindrance, the results suggest that steric effects alone do not fully determine the selectivity. Electronic factors associated with the substituents and subtle conformational differences in the substrates also appear to contribute to the observed outcomes.

To extend the synthetic potential of our methodology, oxidation of product **3aa** with *m*CPBA over a 4-hour period resulted in the formation of a single sulfone product **4aa** (Scheme 4; for synthesis procedure, see Experimental Section: Procedure for the oxidation of 3aa).



Scheme 4. Product transformation.

A plausible mechanism for the thiol addition is shown in Scheme 5. Initially, triethylamine (Et_3N) deprotonates the thiol to generate the corresponding thiolate anion. The thiolate then undergoes a regioselective Michael-type 1,4-addition to the β-carbon of the activated *α*-benzylidene succinimide, forming intermediate **I**. The regioselectivity arises because the imide nitrogen lone pair is delocalized over the two carbonyl groups, reducing the electrophilicity of the carbonyl carbons and disfavoring 1,2-addition. The resulting enolate intermediate **II** is subsequently protonated and undergoes keto–enol tautomerization to furnish the final product **3aa**.



Scheme 5. Plausible mechanism.

To validate the practical utility of the method, a gram-scale reaction was executed under the optimized conditions, as shown. The model product **3aa** was isolated with a similar yield (Figure 2a). In addition to our developed protocol, a polymer-supported analogue of Et_3N, namely diethylaminomethyl-polystyrene (PS–CH_2-NEt_2), was used for the model reaction. To our delight, the reaction suitably delivers our desired product with excellent yield (Figure 2b). Further, we have reused the polymeric base, with a simple washing protocol (see Supplementary Material), for five successive cycles without loss in efficiency (Figure 2c).

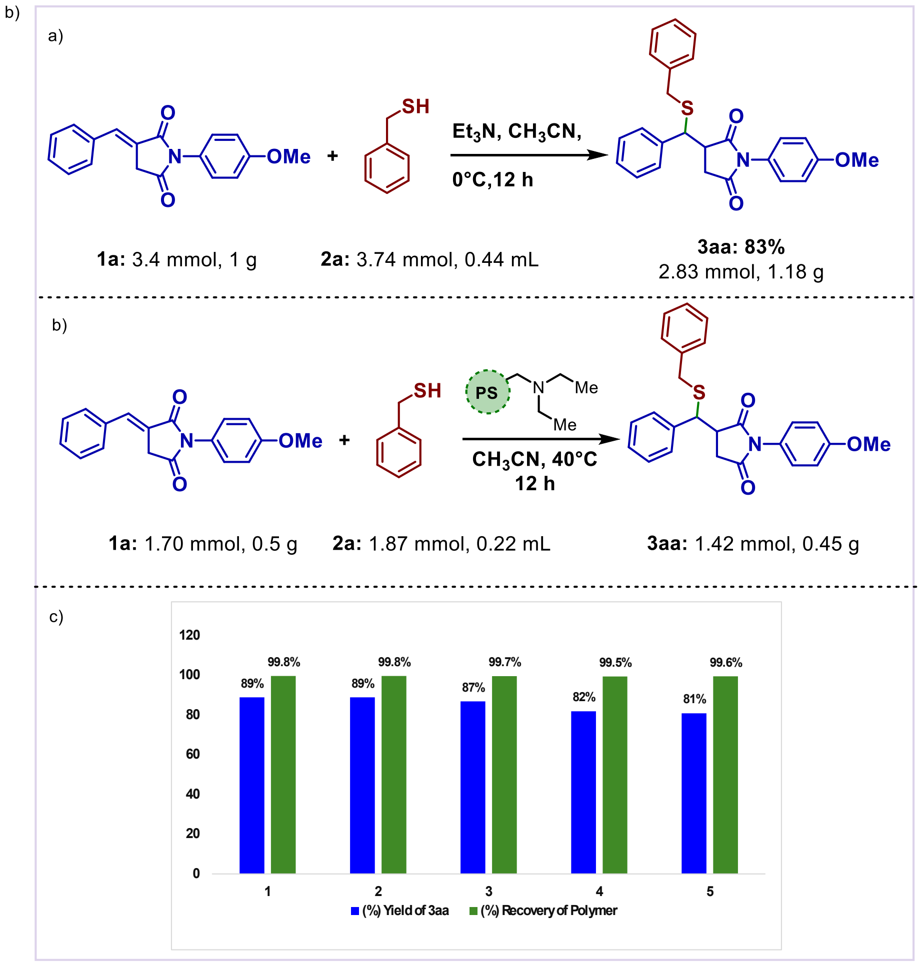


Figure 2. a) Scale up reaction. b) Solid phase reaction. c) Recycling of PS–CH$_2$-NEt$_2$.

Conclusions

We have developed a convenient aliphatic thiol addition to α-benzylidene succinimides via Michael addition reaction. The range of thioethers was synthesized in excellent yields up to 93%. The developed protocol can be carried out on gram scale to access thioethers. Furthermore, this protocol is equally efficient using PS–CH$_2$-NEt$_2$, resulting in excellent yields up to 5 cycles.

Experimental Section

General. All reactions, unless otherwise indicated, were performed in sealed vials. Nuclear magnetic resonance (NMR) spectra were recorded on a 500 MHz instrument for ^{1}H and at 125 MHz for ^{13}C. The following notation was used for signal multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Thin-layer chromatography (TLC) was conducted using silica gel GF$_{254}$ pre-coated aluminum plates, with detection achieved under UV light. Purification via flash column chromatography was carried out on silica gel. Infrared (IR) spectra were acquired using an FT-IR spectrometer, and only the key absorption frequencies (in cm^{-1}) are reported. High-resolution mass spectrometry (HRMS) was performed using electrospray ionizationtime-of-flight (ESI-TOF) techniques. The synthesis of *N*-aryl-substituted itaconimide derivatives **1a** was carried out following established literature procedures **[1]**. All other reagents were sourced commercially and used without additional purification unless otherwise noted. The polymer-supported base (diethylaminomethyl-polystyrene, 200 - 400 mesh); extent of labelling: ~3.2 mmol/g loading, purchased from Sigma Aldrich. The diastereomeric ratios (*dr*) were determined from the ^{1}H NMR spectra of the crude reaction mixtures.

General procedure for synthesis of N-aryl substituted maleimides. The amine (10 mmol) was added to a stirred solution of maleic anhydride (2.5 equiv.) in acetic acid (15 mL) and the mixture was heated at reflux for 6 hours. The solvent was evaporated under reduced pressure. The residue was extracted with ethyl acetate (20 mL) and the extract was washed with saturated sodium bicarbonate solution (2 × 30 mL), followed by a wash with brine (30 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified using column chromatography on silica gel (100–200 mesh) with a gradient of 15–20% ethyl acetate in hexane, yielding the corresponding maleimides in 70–95% yield.

General procedure for synthesis of N-aryl substituted itaconimides 1.[33] The *N*-aryl-substituted maleimide (1.0 mmol, 1.0 equiv.) was dissolved in ethanol (10 mL) at room temperature (25°C). Triphenylphosphine (1.0 equiv.) was added to the reaction mixture, which was stirred under ambient conditions. After 15 minutes, the appropriate aldehyde (1.0 equiv.) was added, and the reaction was continued with stirring for 10–12 hours, with progress monitored by thin-layer chromatography (TLC). Upon completion, the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (DCM) and washed sequentially with water (100 mL) and brine (3 × 20 mL). The combined organic extract was dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by flash column chromatography using silica gel (100–200 mesh) as the stationary phase and with a gradient of 20–40% ethyl acetate in hexane as eluent, affording the target *N*-aryl-substituted itaconimide or substituted pyrrolidine-2,5-dione derivatives **1**.

General procedure for synthesis of N-aryl substituted thiosuccinimides 3. A mixture of the *N*-substituted pyrrolidine-2,5-dione derivative **1** (0.2 mmol, 1 equiv.) and thiol **2** (0.22 mmol, 1.1 equiv.) in CH_3CN (1 mL) was stirred at 0 °C for 10 min. Triethylamine (0.2 mmol, 1.0 equiv.) was added slowly to the reaction mixture. Subsequently, the progress of the reaction was monitored by TLC. After reaction completion (7-16 h), the mixture was concentrated under vacuum, and the residue was purified by column chromatography on silica gel (100–200 mesh) with a gradient of 8–20% ethyl acetate in hexane to obtain **3** (68-94%).

Note: In the spectral data reported below, only the signals of the major diastereomer are described to avoid unnecessary complexity in the assignments, although both sets of signals were usually visible in the spectra.

3-((Benzylthio)(phenyl)methyl)-1-(4-methoxyphenyl)pyrrolidine-2,5-dione (3aa). Pale yellow viscous liquid; yield = 88% (74 mg); *dr* = 9:1 (after purification); *dr* = 5:1 (crude reaction mixture); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 4.2 Hz, 4H), 7.33 – 7.26 (m, 3H), 7.25 – 7.22 (m, 1H), 7.22 – 7.15 (m, 4H), 6.99 (d, *J* = 9.0 Hz, 2H), 4.48 (d, *J* = 3.5 Hz, 1H), 3.83 (s, 3H), 3.69 (d, *J* = 13.1 Hz, 1H), 3.58 (d, *J* = 13.2 Hz, 1H), 3.46 – 3.37 (m, 1H), 3.09 – 2.97 (m, 1H), 2.88 – 2.74 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.57, 176.21, 159.99, 137.19, 135.92, 129.83, 129.77, 129.16, 129.11, 128.01, 127.90, 127.61, 124.53, 114.85, 55.89, 48.21, 40.98, 36.47, 35.22; IR (Neat)**:** ν 3017, 2891, 2831, 1944, 1778, 1712, 1588, 1512, 1452, 1393, 1294, 1253, 1214, 1185, 1111, 1076, 1029, 913, 827, 747, 665; HRMS (ES+) calc. for $C_{25}H_{23}NO_3S$ $[M+H]^+$: 418.1471, found: 418.1473.

3-((Benzylthio)(4-fluorophenyl)methyl)-1-(4-methoxyphenyl)pyrrolidine-2,5-dione (3ba). White solid; yield = 73% (64 mg); *dr* > 20:1 (after purification); *dr* = 4:1 (crude reaction mixture); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (s, 5H), 7.06 (d, *J* = 8.9 Hz, 2H), 6.96 (d, *J* = 9.0 Hz, 2H), 6.86 (t, *J* = 8.6 Hz, 2H), 6.79 – 6.74 (m, 2H), 4.27 (d, *J* = 13.7 Hz, 1H), 3.82 (s, 3H), 3.80 (d, *J* = 13.7 Hz, 1H), 3.23 (d, *J* = 4.6 Hz, 1H), 3.14 – 3.05 (m, 1H), 2.94 – 2.86 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.09, 175.92, 162.04 ($J_{(C-F)}$ = 243.8 Hz), 159.78, 136.96, 131.41 ($J_{(C-F)}$ = 2.5

Hz), 131.08 ($J_{(C-F)}$ = 7.5 Hz), 129.54, 128.87, 127.69, 127.68, 124.19, 115.77 ($J_{(C-F)}$ = 21.3 Hz), 114.63, 55.65, 47.82, 40.35, 36.20, 33.96; ^{19}F NMR (471 MHz, $CDCl_3$) δ -115.17; IR (Neat): ν 3037, 2916, 2831, 1712, 1611, 1512, 1455, 1385, 1298, 1255, 1185, 1037; HRMS (ES+) calc. for $C_{25}H_{23}FNO_3S$ $[M+H]^+$: 436.1377, found: 436.1372; M. P.: 118–120 °C.

3-((Benzylthio)(4-chlorophenyl)methyl)-1-(4-methoxyphenyl)pyrrolidine-2,5-dione (3ca). White solid; yield = 80% (72 mg); *dr* > 20:1 (after purification); *dr* = 5:1 (crude reaction mixture); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.33 (m, 5H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 8.9 Hz, 2H), 6.96 (d, *J* = 8.9 Hz, 2H), 6.73 (d, *J* = 8.4 Hz, 2H), 4.27 (d, *J* = 13.7 Hz, 1H), 3.82 (s, 3H), 3.80 (d, *J* = 13.7 Hz, 1H), 3.20 (d, *J* = 4.5 Hz, 1H), 3.09 – 3.03 (m, 1H), 2.93 – 2.88 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.23, 176.14, 160.04, 137.16, 134.46, 133.48, 131.72, 131.08, 129.77, 129.28, 129.12, 127.94, 124.41, 114.89, 55.90, 47.89, 40.59, 36.46, 34.38; IR (Neat): ν 3010, 2932, 2856, 1712, 1514, 1492, 1455, 1385, 1298, 1253, 1179, 1090, 829; HRMS (ES+) calc. for $C_{25}H_{23}ClNO_3S$ $[M+H]^+$: 452.1082 , found: 452.1044; M. P.: 108–110 °C.

3-((Benzylthio)(4-bromophenyl)methyl)-1-(4-methoxyphenyl)pyrrolidine-2,5-dione (3da). White solid; yield = 82% (81 mg); *dr* > 20:1 (after purification); *dr* = 5:1 (crude reaction mixture); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.33 (m, 5H), 7.28 (d, *J* = 8.3 Hz, 2H), 7.08 (d, *J* = 9.0 Hz, 2H), 6.96 (d, *J* = 9.0 Hz, 2H), 6.67 (d, *J* = 8.4 Hz, 2H), 4.27 (d, *J* = 13.7 Hz, 1H), 3.82 (s, 3H), 3.80 (d, *J* = 13.9 Hz, 1H), 3.19 (d, *J* = 4.7 Hz, 1H), 3.08 – 3.02 (m, 1H), 2.95 – 2.85 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.95, 175.88, 159.79, 136.90, 134.73, 131.99, 131.18, 129.52, 128.88, 127.70, 127.69, 124.16, 121.34, 114.64, 55.65, 47.56, 40.34, 36.22, 34.20; IR (Neat): ν 3032, 2914, 2826, 1712, 1607, 1518, 1451, 1391, 1292, 1245, 1183, 1032, 694; HRMS (ES+) calc. for $C_{25}H_{22}BrNO_3S$ $[M+H]^+$: 496.0577, found: 496.0533; M. P.: 104–106 °C.

3-((Benzylthio)(4-nitrophenyl)methyl)-1-(4-methoxyphenyl)pyrrolidine-2,5-dione (3ea). White solid; yield = 76% (70 mg); *dr* > 20:1 (after purification); *dr* = 6:1 (crude reaction mixture); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.7 Hz, 2H), 7.40 – 7.33 (m, 3H), 7.33 – 7.29 (m, 2H), 7.11 (d, *J* = 9.0 Hz, 2H), 7.01 – 6.93 (m, 4H), 4.29 (d, *J* = 13.7 Hz, 1H), 3.83 (s, 3H), 3.77 (d, *J* = 13.8 Hz, 1H), 3.16 – 3.08 (m, 3H), 2.98 – 2.90 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.58, 175.43, 159.87, 147.16, 143.61, 136.85, 130.28, 129.54, 128.90, 127.83, 127.59, 124.02, 114.69, 55.67, 47.26, 40.28, 36.18, 34.61; IR (Neat): ν 3027, 2842, 1776, 1712, 1603, 1512, 1452, 1385, 1347, 1300, 1253,1183, 1031; HRMS (ES+) calc. for $C_{25}H_{23}N_2O_5S$ $[M+H]^+$: 463.1322, found: 463.1317; M. P.**:** 121–123 °C.

3-((benzylthio)(2,3-dichlorophenyl)methyl)-1-(4-methoxyphenyl)pyrrolidine-2,5-dione (3fa). White solid; yield = 81% (79 mg); *dr* > 20:1 (after purification); *dr* = 5:1 (crude reaction mixture); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.32 (m, 1H), 7.27 – 7.20 (m, 5H), 7.16 (d, *J* = 9.0 Hz, 2H), 7.02 (t, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 9.0 Hz, 2H), 6.94 – 6.90 (m, 1H), 4.17 (d, *J* = 13.4 Hz, 1H), 3.81 (s, 3H), 3.74 (d, *J* = 13.4 Hz, 1H), 3.50 – 3.42 (m, 1H), 3.29 (d, *J* = 4.4 Hz, 1H), 3.07 – 2.99 (m, 1H), 3.00 – 2.91 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.11, 175.71, 160.04, 137.04, 136.82, 133.95, 132.98, 129.89, 129.60, 129.47, 129.04, 127.95, 127.91, 127.77, 124.49, 114.90, 55.92, 46.72, 42.09, 36.34, 34.87; IR (Neat): ν 3010, 2936, 2848, 1784, 1712, 1615, 1512,1450, 1422, 1385, 1298, 1251, 1179, 1031, 833; HRMS (ES+) calc. for $C_{25}H_{22}Cl_2NO_3S$ $[M+H]^+$: 486.0692, found: 486.0685; M. P.: 110–112 °C.

3-((Benzylthio)(3,4-dichlorophenyl)methyl)-1-(4-methoxyphenyl)pyrrolidine-2,5-dione (3ga). White solid; yield = 80% (78 mg); *dr* > 20:1 (after purification); *dr* = 5:1 (crude reaction mixture); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.33 (m, 1H), 7.28 – 7.20 (m, 5H), 7.16 (d, *J* = 8.9 Hz, 2H), 7.02 (t, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 9.1 Hz, 2H), 6.94 – 6.89 (m, 1H), 4.17 (d, *J* = 13.5 Hz, 1H), 3.81 (s, 3H), 3.74 (d, *J* = 13.5 Hz, 1H), 3.49 – 3.42 (m, 1H), 3.29 (d, *J* = 4.4 Hz, 1H), 3.08 – 3.00 (m, 1H), 2.99 – 2.91 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.85, 175.45, 159.78, 136.78, 136.56, 133.69, 132.72, 129.63, 129.34, 129.21, 128.78, 127.69, 127.65, 127.51, 124.23, 114.65, 55.66, 46.46, 41.83, 36.08, 34.61; IR (Neat): ν 3006, 2938, 2837, 1712, 1611, 1512,1450, 1422, 1385, 1302, 1251, 1179, 1037, 833; HRMS (ES+) calc. for $C_{25}H_{22}Cl_2NO_3S$ $[M+H]^+$: 486.0692, found: 486.0686; M. P.**:** 106–108 °C.

3-((Benzylthio)(5-bromo-2-fluorophenyl)methyl)-1-(4-methoxyphenyl)pyrrolidine-2,5-dione (3ha). White solid; yield = 69% (71 mg), *dr* = 3:1 (after purification); *dr* = 6:1 (crude reaction mixture); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 6H), 7.24 – 7.22 (m, 1H), 7.17 – 7.14 (m, 2H), 7.00 – 6.97 (m, 2H), 6.89 (t, 1H), 4.21 (d, *J* = 13.5 Hz, 1H), 3.83 (s, 3H), 3.51 – 3.29 (m, 1H), 3.28 – 3.22 (m, 2H), 2.98 – 2.86 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.71, 175.24, 160.31($J_{(C-F)}$ = 245 Hz), 159.76, 136.46, 133.86 ($J_{(C-F)}$ = 3.75 Hz), 132.16 ($J_{(C-F)}$ = 8.75 Hz), 129.22, 128.75, 127.67 ($J_{(C-F)}$ = 7.5 Hz), 125.76 ($J_{(C-F)}$ = 17.5 Hz), 124.13, 117.45 ($J_{(C-F)}$ = 23.75 Hz), 114.62, 55.60, 46.78, 41.93, 36.12, 29.22; ^{19}F NMR (471 MHz, $CDCl_3$) δ -118.69; IR (Neat): ν 3033, 2917, 2830, 1715, 1604, 1512, 1455, 1391, 1292, 1245, 1179, 1034, 936, 695; HRMS (ES+) calc. for $C_{25}H_{22}BrFNO_3S$ $[M+H]^+$: 514.0482, found: 514.0477; M. P.: 107–112 °C.

3-((Benzylthio)(p-tolyl)methyl)-1-(4-methoxyphenyl)pyrrolidine-2,5-dione (3ia). Colorless viscous liquid; yield = 70% (60 mg); *dr* > 20:1 (after purification); *dr* = 3:1 (crude reaction mixture); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.29 (m, 5H), 7.25 – 7.20 (m, 6H), 7.02 (d, 2H), 4.47 (d, *J* = 3.5 Hz, 1H), 3.86 (s, 3H), 3.70 (d, *J* = 13.1 Hz, 1H), 3.60 (d, *J* = 13.2 Hz, 1H), 3.46 – 3.38 (m, 1H), 3.12 – 3.04 (m, 1H), 2.86 – 2.77 (m, 1H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.76, 175.51, 159.72, 137.83, 137.25, 136.63, 129.75, 129.16, 128.63, 127.97, 127.87, 127.41, 124.65, 114.66, 55.64, 49.20, 46.86, 36.24, 31.61, 21.22; IR (Neat): ν 3012, 2895, 2826, 1712, 1689, 1520, 1460, 1395, 1300, 1215, 1179, 1038, 918, 824, 748; HRMS (ES+) calc. for $C_{26}H_{25}NO_3S$ $[M+H]^+$: 432.1628, found: 432.1642.

3-((Benzylthio)(4-(tert-butyl)phenyl)methyl)-1-(4-methoxyphenyl)pyrrolidine-2,5-dione (3ja). Colorless viscous liquid; yield = 68% (65 mg); *dr* > 20:1 (after purification); *dr* = 3:1 (crude reaction mixture); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.34 (m, 2H), 7.32 – 7.29 (m, 1H), 7.28 – 7.24 (m, 4H), 7.23 (d, *J* = 7.0 Hz, 1H), 7.21 – 7.17 (m, 3H), 6.98 (d, *J* = 8.9 Hz, 1H), 6.83 – 6.52 (m, 1H), 4.55 – 4.45 (m, 1H), 3.76 (s, 3H), 3.68 (t, *J* = 11.4 Hz, 1H), 3.63 – 3.53 (m, 1H), 3.46 – 3.35 (m, 1H), 3.13 – 3.01 (m, 1H), 2.89 – 2.73 (m, 1H), 1.33 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.89, 175.56, 159.74, 150.98, 137.35, 136.65, 129.17, 128.75, 128.62, 127.90, 127.68, 127.40, 125.95, 114.67, 55.65, 49.25, 46.84, 36.46, 34.70, 31.67, 31.46; IR (Neat): ν 3014, 2951, 1714, 1615, 1597, 1512, 1465, 1393, 1306, 1253, 1181, 1037; HRMS (ES+) calc. for $C_{29}H_{31}NO_3S$ $[M+H]^+$: 474.2097, found: 474.2085.

3-((Benzylthio)(phenyl)methyl)-1-phenylpyrrolidine-2,5-dione (3ka). Pale yellow viscous liquid; yield = 82% (64 mg); *dr* = 3:1 (after purification); *dr* = 4:1 (crude reaction mixture); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.44 (m, 2H), 7.43 – 7.40 (m, 1H), 7.40 – 7.35 (m, 4H), 7.34 – 7.31 (m, 1H), 7.31 – 7.27 (m, 3H), 7.27 – 7.21 (m, 2H), 7.21 – 7.16 (m, 2H), 4.49 (d, 1H), 3.68 (t, *J* = 12.9 Hz, 1H), 3.61 – 3.51 (m, 1H), 3.46 – 3.38 (m, 1H), 3.10 – 2.97 (m, 1H), 2.89 – 2.76 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.61, 175.28, 139.93, 137.36, 135.73, 132.26, 129.51, 129.35, 129.27, 129.04, 128.85, 128.27, 127.65, 126.85, 49.69, 47.07, 36.54, 31.84; IR (Neat): ν 2887, 2835, 1942, 1771, 1712, 1586, 1514, 1455, 1395, 1297, 1216, 1182, 1078, 1027, 911, 824, 745, 668; HRMS (ES+) calc. for $C_{24}H_{21}NO_2S$ $[M+H]^+$: 388.1366, found: 388.1053.

3-((Benzylthio)(phenyl)methyl)-1-(4-fluorophenyl)pyrrolidine-2,5-dione (3la). White solid; yield = 92% (75 mg); *dr* = 1:1 (after purification); *dr* = 5:1 (crude reaction mixture); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.31 (m, 5H), 7.29 – 7.23 (m, 4H), 7.21 – 7.14 (m, 3H), 7.02 (t, *J* = 8.6 Hz, 1H), 6.80 – 6.70 (m, 1H), 4.59 – 4.40 (m, 1H), 3.73 – 3.63 (m, 1H), 3.61 – 3.50 (m, 1H), 3.48 – 3.36 (m, 1H), 3.12 – 2.96 (m, 1H), 2.90 – 2.74 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.33, 174.99, 162.42 ($J_{(C-F)}$ = 247.5 Hz), 139.55, 137.08, 129.22, 129.13, 129.02, 128.72 ($J_{(C-F)}$ = 13.75 Hz), 128.46, 128.43 ($J_{(C-F)}$ = 23.75 Hz), 128.07, 127.50, 116.36 ($J_{(C-F)}$ = 22.5 Hz), 49.50, 46.89, 36.30, 31.56; ^{19}F NMR (471 MHz, $CDCl_3$) δ -112.18; IR (Neat): ν 3087, 3027, 2932, 1778, 1710, 1605, 1508, 1455, 1382, 1232, 1183, 1053; HRMS (ES+) calc. for $C_{24}H_{21}FNO_2S$ $[M+H]^+$: 406.1272, found: 406.1266. M. P.: 112–116 °C

3-((Benzylthio)(phenyl)methyl)-1-(4-bromophenyl)pyrrolidine-2,5-dione (3ma). White solid; yield = 85% (79 mg); *dr* > 20:1 (after purification); *dr* = 6:1 (crude reaction mixture); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.6 Hz, 2H), 7.37 (d, *J* = 4.2 Hz, 4H), 7.34 – 7.31 (m, 1H), 7.30 – 7.26 (m, 2H), 7.25 – 7.21 (m, 1H), 7.18 (d, *J* = 8.7 Hz, 4H), 4.46 (d, *J* = 3.6 Hz, 1H), 3.71 – 3.63 (m, 1H), 3.59 – 3.53 (m, 1H), 3.45 – 3.36 (m, 1H), 3.09 – 3.01 (m, 1H), 2.84 – 2.73 (m, 1H); 13C NMR (125 MHz, $CDCl_3$) δ 175.81, 174.45, 139.27, 136.81, 132.25, 130.74, 128.88, 128.87, 128.42, 127.90, 127.81, 127.27, 127.26, 122.46, 49.24, 46.68, 36.06, 31.34; IR (Neat): ν 3025, 2922, 2826, 1716, 1607, 1492, 1450, 1381, 1232,1183, 1074, 686; HRMS (ES+) calc. for $C_{24}H_{21}BrNO_2S$ $[M+H]^+$: 466.0471, found: 466.0464; M. P.**:** 111–113 °C.

3-((Benzylthio)(phenyl)methyl)-1-(3-chlorophenyl)pyrrolidine-2,5-dione (3na). White solid; yield = 90% (76 mg); *dr* = 1:1 (after purification); *dr* = 5:1 (crude reaction mixture); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 5H), 7.32 – 7.29 (m, 1H), 7.29 – 7.21 (m, 4H), 7.21 – 7.09 (m, 3H), 6.83 – 6.58 (m, 1H), 4.47 (dd, *J* = 30.6, 3.9 Hz, 1H), 3.72 – 3.61 (m, 1H), 3.53 (dd, *J* = 20.8, 13.4 Hz, 1H), 3.45 – 3.35 (m, 1H), 3.09 – 2.95 (m, 1H), 2.89 – 2.72 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.96, 174.58, 139.51, 137.04, 135.41, 134.81, 133.03, 130.21, 129.12, 129.00, 128.76, 128.66, 128.04, 127.50, 126.90, 124.81, 49.45, 46.89, 36.29, 31.58; IR (Neat): ν 3081, 3022, 2940, 1771, 1712, 1601, 1508, 1447, 1381, 1232, 1183, 825; HRMS (ES+) calc. for $C_{24}H_{21}ClNO_2S$ $[M+H]^+$: 422.0976, found: 422.0970. M. P.**:** 109–114 °C.

3-((Benzylthio)(phenyl)methyl)-1-(2-nitrophenyl)pyrrolidine-2,5-dione (3oa). White solid; yield = 72% (62 mg); *dr* = 4:1 (after purification); *dr* = 6:1 (crude reaction mixture); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.4 Hz, 1H), 7.76 (t, *J* = 7.7 Hz, 1H), 7.61 (t, *J* = 7.9 Hz, 1H), 7.39 (d, *J* = 5.5 Hz, 4H), 7.34 (t, *J* = 3.0 Hz, 2H), 7.29 – 7.22 (m, 4H), 7.20 (s, 1H), 4.50 (d, *J* = 3.7 Hz, 1H), 3.69 (d, *J* = 13.1 Hz, 1H), 3.60 (s, 1H), 3.57 – 3.49 (m, 1H), 3.09 (dd, *J* = 18.5, 5.1 Hz, 1H), 2.88 (dd, *J* = 18.5, 9.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.22, 173.82, 144.98, 139.02, 136.76, 134.24, 130.36, 130.01, 128.87, 128.84, 128.39, 127.90, 127.77, 127.24, 125.84, 125.69, 48.96, 47.19, 36.02, 31.53; IR (Neat): ν 3025, 2845, 2783, 1778, 1713, 1599, 1510, 1448, 1389, 1337, 1304, 1289,1188, 1036, 932, 818; HRMS (ES+) calc. for $C_{24}H_{21}N_2O_4S$ $[M+H]^+$: 433.1217, found: 433.1257. M. P.**:** 115–120 °C.

3-((Benzylthio)(phenyl)methyl)-1-(3,4-dimethylphenyl)pyrrolidine-2,5-dione (3pa). Pale yellow viscous liquid; yield = 70% (58 mg); *dr* = 4:1 (after purification); *dr* = 3:1 (crude reaction mixture); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.34 (m, 4H), 7.34 – 7.26 (m, 2H), 7.25 – 7.22 (m, 2H), 7.22 (s, 1H), 7.20 – 7.14 (m, 2H), 7.14 – 6.93 (m, 2H), 4.48 (d, *J* = 3.5 Hz, 1H), 3.67 (dd, *J* = 17.6, 13.2 Hz, 1H), 3.56 (dd, 1H), 3.45 – 3.34 (m, 1H), 3.05 (dd, *J* = 18.4, 5.0 Hz, 1H), 2.77 (dd, *J* = 18.3, 9.3 Hz, 1H), 2.28 (d, *J* = 2.4 Hz, 3H), 2.18 (d, *J* = 13.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.40, 175.12, 139.57, 137.64, 137.50, 136.92, 130.23, 129.02, 128.89, 128.78, 128.37, 127.78, 127.72, 127.37, 127.16, 123.80, 49.22, 46.64, 36.13, 31.36, 19.74, 19.42; IR (Neat): ν 3013, 2955, 1711, 1616, 1593, 1514, 1466, 1390, 1308, 1278, 1185, 1041, 955; HRMS (ES+) calc. for $C_{26}H_{26}NO_2S$ $[M+H]^+$: 416.1679, found: 416.1681.

3-((Benzylthio)(phenyl)methyl)-1-methylpyrrolidine-2,5-dione (3qa). Colorless viscous liquid; yield=82% (53 mg), *dr* = 12:1 (after purification); *dr* = 5:1 (crude reaction mixture); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.25 (m, 5H), 7.23 – 7.20 (m, 2H), 7.18 – 7.14 (m, 1H), 7.13 – 7.08 (m, 2H), 4.32 (d, *J* = 3.7 Hz, 1H), 3.59 – 3.45 (m, 2H), 3.22 – 3.14 (m, 1H), 2.93 (s, 3H), 2.87 – 2.80 (m, 1H), 2.62 – 2.56 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.36, 176.14, 139.90, 137.20, 130.29, 129.11, 129.02, 128.63, 127.99, 127.42, 49.14, 46.86, 36.20, 31.47, 25.12; IR (Neat): ν 3013, 2948, 1712, 1612, 1594, 1510, 1468, 1397, 1301, 1255, 1178, 1039; HRMS (ES+) calc. for $C_{19}H_{20}NO_2S$ $[M+H]^+$: 326.1209, found: 326.1202.

3-((Ethylthio)(phenyl)methyl)-1-(4-methoxyphenyl)pyrrolidine-2,5-dione (3ab). Pale yellow viscous liquid; yield = 75% (53 mg); *dr* = 4:1 (after purification); *dr* = 3:1 (crude reaction mixture); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.1 Hz, 2H), 7.40 – 7.29 (m, 3H), 7.23 – 6.97 (m, 3H), 6.78 (dd, *J* = 83.0, 8.9 Hz, 1H), 4.64 (d, *J* = 3.3 Hz, 1H), 3.83 (s, 3H), 3.55 – 3.40 (m, 1H), 3.09 (dd, *J* = 18.5, 5.0 Hz, 1H), 2.94 – 2.71 (m, 1H), 2.55 – 2.40 (m, 2H), 1.32 – 1.15 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.26, 175.79, 159.95, 140.75, 135.57, 130.62, 129.53, 129.29, 128.09, 114.89, 55.86, 50.13, 47.46, 31.39, 26.65, 14.92; IR (Neat): ν 3014, 2899, 2828, 1941, 1772, 1709, 1698, 1511, 1445, 1389, 1256, 1214, 1175, 1116, 1072, 1035, 917, 822, 756, 655; HRMS (ES+) calc. for $C_{20}H_{22}NO_3S$ $[M+H]^+$: 356.1315, found: 356.1321.

Procedure for the oxidation of 3aa. An oven-dried round-bottom flask was charged with compound **3aa** (50 mg, 0.12 mmol), in methanol (3 mL) to afford a homogeneous solution. Under a nitrogen atmosphere, *m*CPBA (62 mg, 0.36 mmol) was added, and the mixture was stirred at 0 °C for 4 hours. Upon complete consumption of 3aa, as monitored by TLC, the reaction mixture was quenched with water and extracted with dichloromethane. The combined organic extracts were dried, concentrated under reduced pressure, and the crude product was purified by flash chromatography (hexane/ethyl acetate, 10:2; silica gel, 100–200 mesh), affording **3-((benzylsulfonyl)(phenyl)methyl)-1-(4-methoxyphenyl)pyrrolidine-2,5-dione** (**4aa**) as a pale yellow viscous liquid; yield = 78% (42 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 6.2 Hz, 2H), 7.53 – 7.42 (m, 3H), 7.40 – 7.31 (m, 3H), 7.17 – 7.11 (m, 2H), 6.85 (d, *J* = 8.9 Hz, 2H), 6.72 (d, *J* = 9.0 Hz, 2H), 4.74 (d, *J* = 2.9 Hz, 1H), 4.14 (d, *J* = 2.1 Hz, 2H), 4.09 – 4.03 (m, 1H), 3.77 (s, 3H), 3.31 (dd, *J* = 19.0, 4.7 Hz, 1H), 3.14 (dd, *J* = 19.1, 9.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.64, 174.55, 159.53, 130.68, 130.09, 130.04, 129.50, 129.22, 128.87, 128.44, 127.79, 127.34, 126.59, 114.33, 63.48, 58.15, 55.34, 39.08, 30.44; IR (Neat): ν 3054, 2934, 2856, 1924,1773, 1712, 1613, 1514, 1459, 1399, 1323, 1253, 1187, 1127, 1024, 895, 835, 689; HRMS (ES+) calc. for $C_{25}H_{24}NO_5S$ $[M+H]^+$: 450.1370, found: 450.1386.

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Supplementary Material

The data supporting this article have been included as part of the Supplementary Information.

References

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