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ARTICLE

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γ-Al_2O_3/triflic acid as cooperative catalysts for the tandem Michael addition/carbocyclization: An easy access to 2-substituted pyrrolo[2,1-*a*]isoquinolines and 3-substituted pyrrolidine-2,5-diones

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Abstract

A tandem Michael addition/carbocyclization of 3,4-dimethoxyphenethyl maleimide with carbon and sulfur nucleophiles is accomplished via a relay catalysis using γ-Al_2O_3/TfOH binary system. The X-ray Photoelectron Spectroscopy (XPS) analysis of binary system indicates the presence of AlF_3, AlO(OH) species. This approach provides an easy access to 2-aryl or 2-thio aryl pyrrolo[2,1-*a*]isoquinolines in good yields in a tandem fashion. With suitable ratio of γ-Al_2O_3/TfOH binary system, the Michael addition of N/C/S nucleophiles to *N*-benzyl maleimide is also achieved. A key to the success of these reactions would be the generation of AlF_3, AlO(OH) species from γ-Al_2O_3 and TfOH, which might have delineated the disadvantageous background reactions usually displayed by a strong Brønsted acid such as TfOH.

KEYWORDS

3-substituted pyrrolidine-2,5-diones, carbocyclization, Michael addition, pyrrolo[2,1-*a*]isoquinolines, γ-Al_2O_3/TfOH binary system

1 | INTRODUCTION

Pyrrolo[2,1-*a*]isoquinolines are fused tricyclic subunits occur widely in natural products. (−)-Trolline, (+)-oleracein E, and (+)-crispine A are some of the pyrrolo[2,1-*a*]isoquinoline skeleton containing alkaloids (Figure 1). These alkaloids display remarkable biological activities such as antibacterial activity, radical scavenging property, and anticancer property.[1] Erythrina alkaloids are well-known for their sedative, hypotensive, anticonvulsive, hypnotic, CNS depressing, and curare-like properties.[2] Owing to their structural diversity and the spectrum of biological activities, efforts have been directed to develop an efficient methodologies utilizing Bischler–Napierlski, Parham-type cyclization, *6-exo-trig* cyclization through imide carbonyl group activation, and so on, to synthesize pyrroloisoquinoline skeletons.[1,3] Recently, our group also contributed toward the synthesis of this class of alkaloids via imide carbonyl group activation and cyclization strategy from phenethyl imides in the presence of either $AlBr_3$ or TfOH (Scheme 1).[4] The synthesis of at 2-substituted pyrrolo[2,1-*a*]isoquinoline requires pre-installed substituents in unsymmetrical succinimides.[4a] Therefore, the additional steps are indeed required for the preparation of *N*-phenethyl unsymmetrical succinimides. Unlike succinimides, due to the presence of α,β-unsaturated system, the maleimide is prone to be attacked by two nucleophiles in the presence of Lewis acid or Brønsted acids. Thus by modulating the reactivity of maleimide toward two nucleophiles in an intra- and intermolecular fashion would lead to the formation of 2-substituted pyrroloisoquinoline skeletons (Scheme 1).

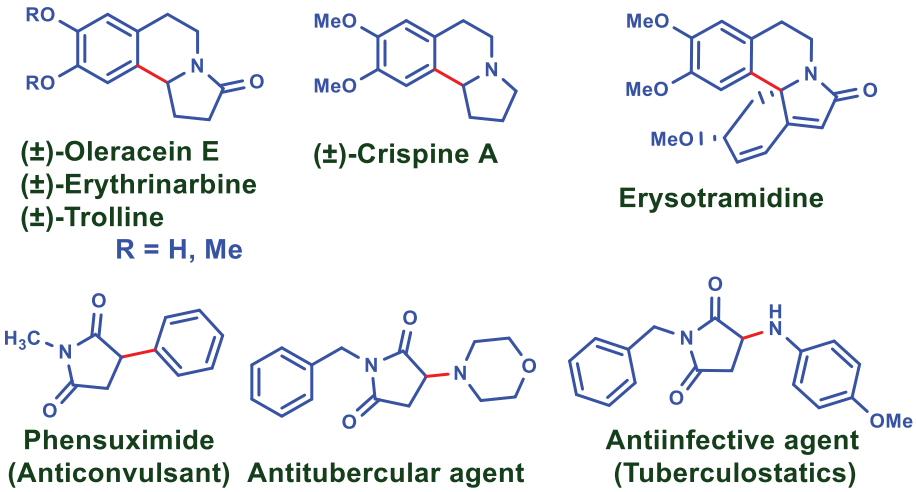
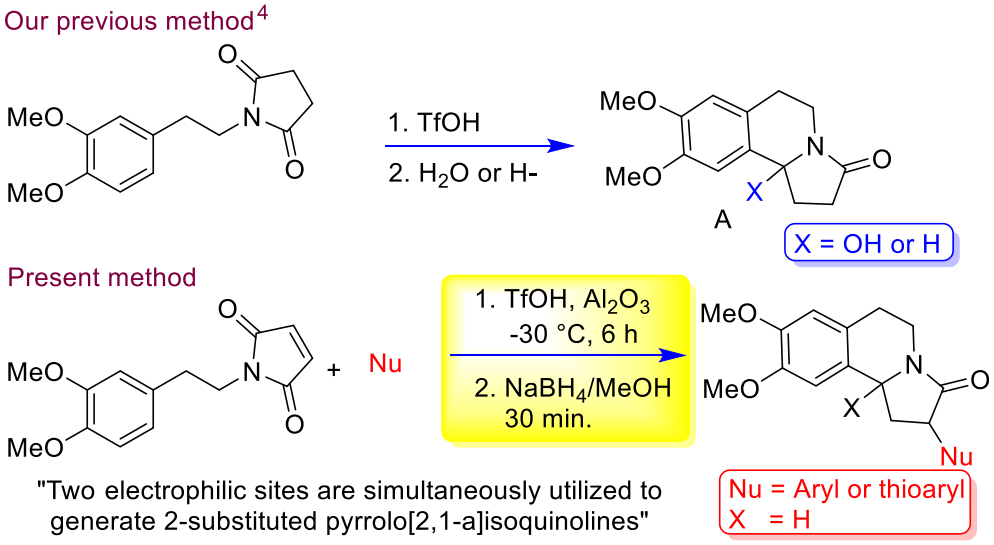


FIGURE 1 Selected pyrroloisoquinoline based alkaloids and pyrrolidine-2,5-diones



SCHEME 1 Synthesis of 2-substituted pyrroloisoquinolines

Furthermore, the maleimides persist to attract synthetic chemists due to their intrinsic chemical reactivity toward various nucleophiles to generate natural products,[5] pharmaceuticals,[6] functional materials,[7] antidepressant,[8] anticonvulsant,[9] anti-tubercular agents,[10] cyclopeptide alkaloids,[11] neurotoxic fungal metabolites,[12] anti-filarial,[13] and anti-emetic agents[14] as well as antibiotics of the quinolone carboxylic acid series.[15]

In pursuit of exploring the TfOH mediated *6-exo-trig* cyclization, we herein, report the construction of 2-aryl/2-thioarylpyrroloisoquinoline units by exploiting the dual reaction site nature of maleimide involving Michael addition/carbocyclization strategy.

2 | RESULTS AND DISCUSSION

We commenced our work to examine the cyclization reaction of 3,4-dimethoxyphenethyl maleimide with TfOH (8 equiv. as adopted for succinimides) at 0 °C, followed by reduction using $NaBH_4$/MeOH. The desired product pyrroloisoquinoline (**A**) was obtained only in 10% yield (Scheme 1). This is perhaps the intrinsic property of maleimides undergoing side reactions, for example, polymerization in the presence of strong Brønsted acid.

It is well known that the maleimides can exist as dicationic species (Figure 2, dicationic species I and II)[16] in the presence of strong Brønsted acid (TfOH). Therefore, we intend to modulate the reactivity of dicationic species of maleimide with nucleophiles and that may lead to 2-substituted pyrrolo-isoquinolines. Hence, the systematic investigation on trapping the dicationic species with external and internal nucleophiles may produce the desired product (Scheme 1). Accordingly, 3,4-dimethoxy-phenethyl maleimide was treated with 1,3,5-trimethoxy benzene in the presence of TfOH, which failed to give the expected product.

This may be due to the super acid's ability to protonate not only maleimide but also trimethoxy benzene.[17] Hence, controlling the reactivity of TfOH has become essential. Presence of excess acid also favors the

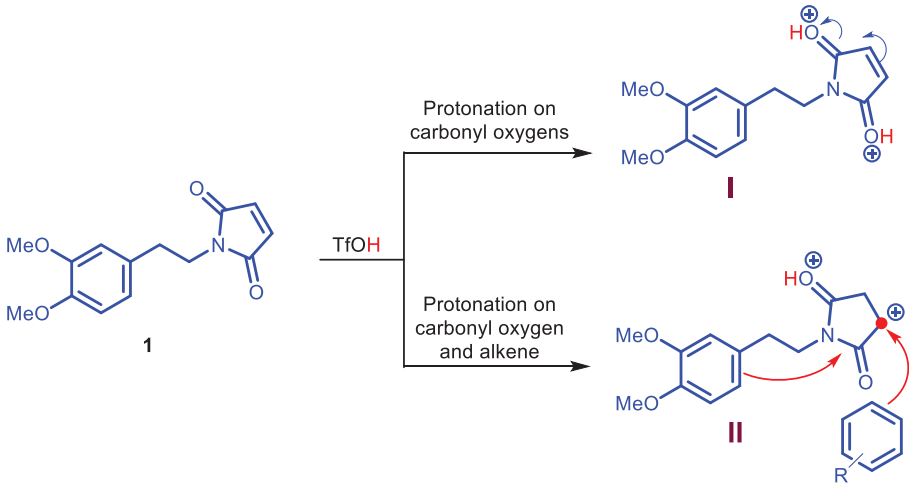


FIGURE 2 Possible dicationic species I and II of maleimides with TfOH

polymerization reaction instead of Michael addition.[18] The *6-exo-trig* cyclization essentially requires excess TfOH, whereas, the Michael addition requires catalytic quantity of either Brønsted acid or Lewis acid.[19] γ-Al_2O_3 is known to display multifunctional characteristics (Lewis acidic and basic sites) upon treatment with super acid[20] and consequently it could moderate the reactivity of excess super acid. To test this hypothesis, the reaction of 3,4-dimethoxyphenethyl maleimide along with external nucleophile 1,3,5-trimethoxy benzene was carried out with TfOH (8 equiv.) in the presence of γ-Al_2O_3 (1 equiv.) in dichloromethane at −30 °C. After 6 h, the expected 2-aryl substituted pyrroloisoquinoline 3a was obtained in 27% yield. Encouraged by this observation, the experiments were performed by varying the equivalents of both γ-Al_2O_3 and TfOH. The results are summarized in Table 1. While decreasing the equivalents of γ-Al_2O_3 the formation of tandem product is favored with eight equivalents of TfOH (Table 1, entries 1–5). In the presence of γ-Al_2O_3 (0.1 equiv.), the expected product 3a was obtained in 80% yield (Table 1, entry 5). With 0.1 equivalents of γ-Al_2O_3, the reactions were carried out by varying the equivalents of TfOH (8 to 12 equiv.). While increasing the TfOH equivalents, the decrease in tandem product formation was observed (Table 1, entries 6–7). On the other hand, by retaining the equivalents of γ-Al_2O_3 (0.1) constant and decreasing the equivalent of TfOH, lead to the formation of Michael addition product (Table 1, entry 8). This observation not only ascertains the involvement of relay catalytic process but also the essential role played by γ-Al_2O_3. The first step involves the Michael addition of 1,3,5-trimethoxy benzene on to maleimide ring in 3,4-dimethoxyphenethyl maleimide triggered by Lewis acid AlF_3 generated from alumina.

Subsequently, the precursor generated in situ underwent regioselective cyclization in the presence of available TfOH to furnish the tandem product, 2-aryl pyrroloisoquinoline **3a**.

TABLE 1 Optimization of reaction conditions [a]

S. No.	TfOH (equiv.)	Al_2O_3 (equiv.)	Yield (%)[b]
1.	8	1	27
2.	8	0.5	52
3.	8	0.2	67
4.	8	0.15	72
5.	**8**	**0.1**	**80**
6.	10	0.1	27
7.	12	0.1	21
8.	4	0.1	68[c]

[a]Reaction conditions: maleimide 1 (1 mmol), 1,3,5-trimethoxybenzene (1 mmol), DCE (3 mL), −30 °C.
[b]Yields are isolated product.
[c]Michael addition product (**5**).

The present method enabled the generation of 2-aryl substituted phenyl succinimide **5** (Scheme 2), and thus allowing efficient synthesis of fused 2-aryl pyrroloisoquinolines from readily accessible 3,4-dimethoxyphenethyl maleimide **1** with various C-nucleophiles in a relay catalytic process (Figure 3). With this condition in hand, the scope of aromatic and heteroaromatic nucleophiles have been examined in presence of TfOH/γ-Al_2O_3 (8:0.1 ratio) and they smoothly delivered the expected product in good to excellent yields (Figure 3; **3a**–**3g**). To prove the versatility of this tandem process, the hetero nucleophiles such as thiol and amine were examined. Interestingly, the sulfur nucleophile was installed at C-2 carbon in pyrroloisoquinolines through tandem process (Figure 3, entry **3h**).

Unfortunately, the nitrogen nucleophile failed to undergo this transformation. This may be due to the protonation of amine nucleophile by excess TfOH. Synthesis of 3-substituted succinimides, for example, 3-aryl succinimides, are usually accomplished from maleimides

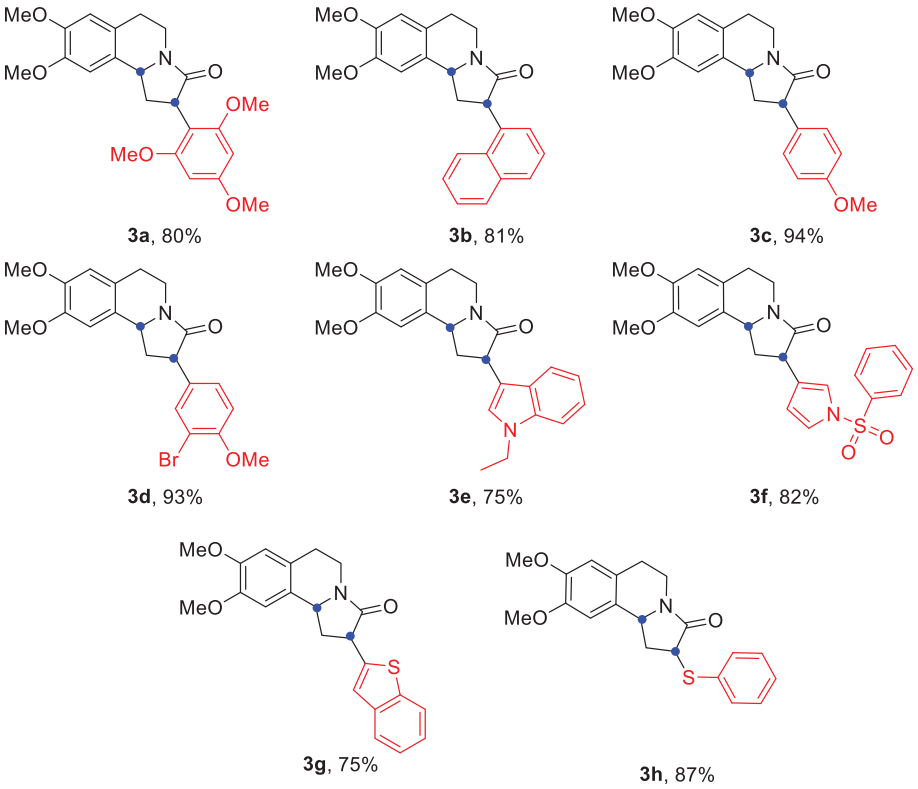
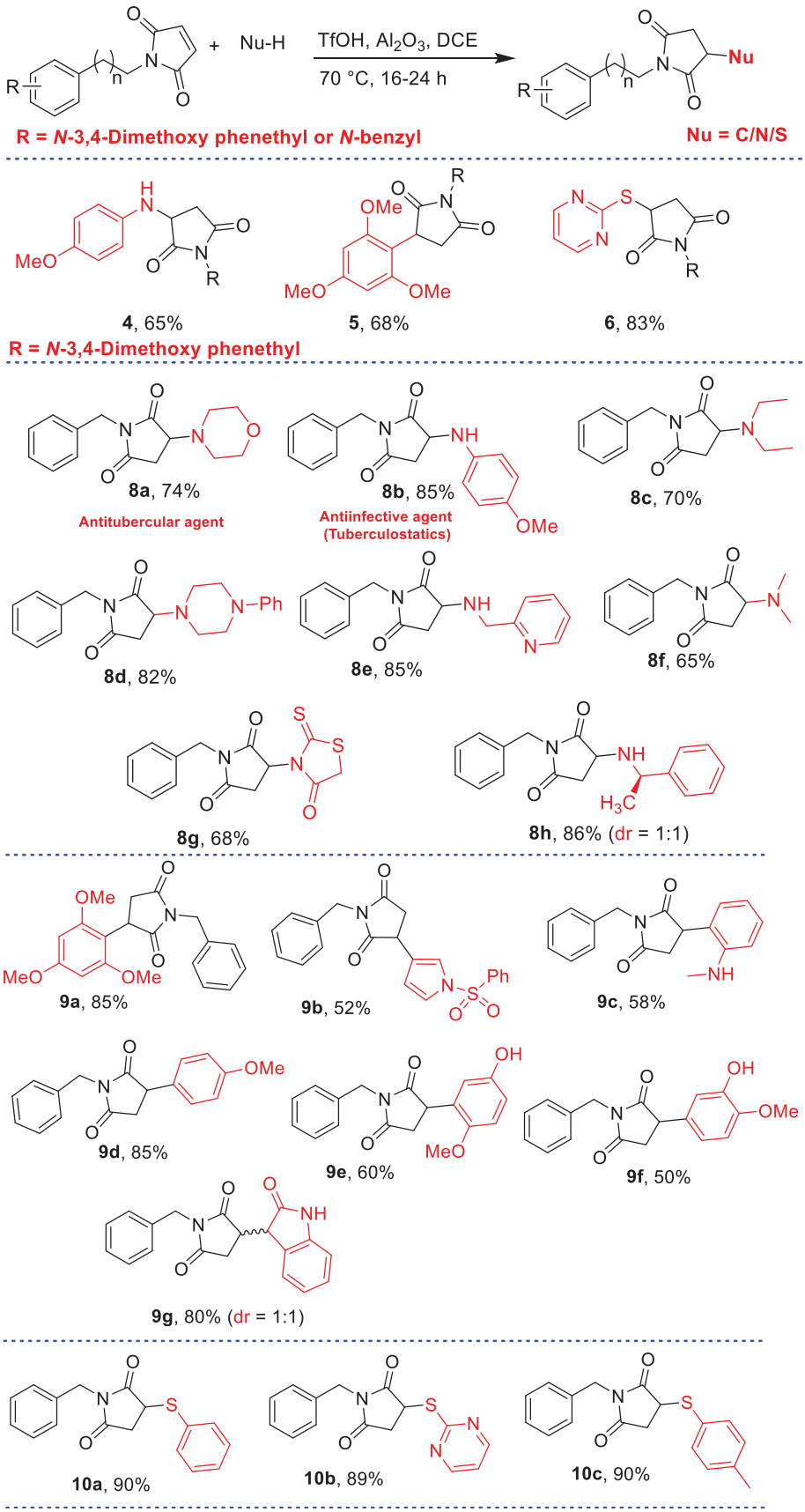


FIGURE 3 Synthesis of 2-substituted pyrroloisoquinolines

through Michael addition[21] or transition metal catalyzed reactions.[22] All these reactions are mainly utilized to synthesize 3-aryl succinimides. Whereas, aza-Michael addition was promoted by various Lewis acids.[23] On the other hand, S-nucleophile is usually attached at C-3 position in succinimide via Michael addition with maleimide by using base mediated reactions.[24] The aza-Michael addition is possible only when free amines are available in the reaction medium and that is not feasible with excess TfOH. Therefore, the equivalents of TfOH gradually reduced to one equivalent at room temperature to witness again no Michael addition product. While increasing the temperature of the reaction from room temperature to 70 °C in 1,2-dichloroethane, the formation of Michael adduct **4** was realized (Scheme 2, entry **4**). This may be due to the generation of free amine from ammonium triflate salt with reagent system γ-Al_2O_3/TfOH (0.1/1) at 70 °C. Since, the reaction at elevated temperature in presence of γ-Al_2O_3 (0.1 equiv.) and TfOH (1 equiv.) facilitated the Michael adduct formation with nitrogen nucleophile, we intend to find out the outcome of this condition with carbon and sulfur nucleophiles as well and in both cases the expected Michael adducts were obtained in good yields (Scheme 2, entries **4–6**). To generalize this condition, the model substrate N-benzylmaleimide was successfully employed to demonstrate the Michael addition reaction with various nitrogen nucleophiles (1°/2° amines), carbon nucleophiles (arenes, heteroarenes, and active methylene compounds), and sulfur nucleophiles (aryl thiols). This reaction generated 3-aryl pyrrolidine-2,5-diones, 3-amino pyrrolidine-2,-5-diones, and 3-mercapto pyrrolidine-2,5-diones in good yields (Scheme 2, entries **8a–8h**, **9a–9g**, and **10a–10c**, respectively). Chiral primary amine, *R*-(+)-α-methyl benzylamine, smoothly furnished the Michael adduct with 1:1 diastereomeric ratio (Scheme 2, entry 8 h). Similarly, an active methylene compound, oxindole, also underwent this reaction to form the diastereomeric mixture in equal ratio (Scheme 2, entry **9g**).

The active species involved in binary system have been investigated through systematic analysis of materials generated from γ-Al_2O_3 and TfOH by using pyridine IR (PY-IR) spectroscopy and X-ray Photoelectron Spectroscopy (XPS). The commercial γ-Al_2O_3 (Merck) was pre-heated at 300 °C (Al_2O_3) to avoid moisture contamination and used for analysis as well as the preparation of Al_2O_3-Tf sample [prepared from TfOH (1 mL) and pre-heated γ-Al_2O_3 (100 mg) at room temperature] and Al_2O_3-Tf-1 sample [obtained from pre-heated γ-Al_2O_3 (100 mg) and TfOH (0.1 mL) at 70 °C]. The generation of Lewis acidic sites (LPy) and Brønsted acidic sites (BPy) were ascertained with help of Fourier Transform Infrared (FT-IR) spectroscopy after pyridine adsorption (Py-PAS). Pyridine was adsorbed on these samples at 423 K, and the FT-IR spectra of pyridine-loaded and unloaded samples were recorded at room temperature (Figure 4).

SCHEME 2 Synthesis of 3-substituted 1-phenethyl/benzyl pyrrolidine-2,5-diones



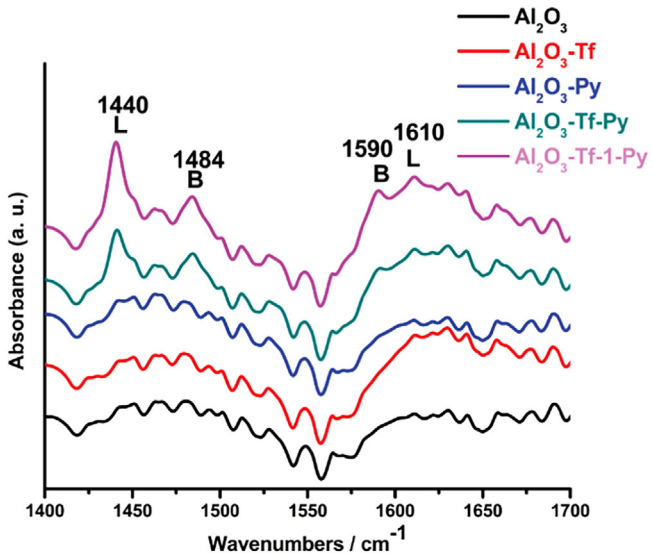


FIGURE 4 Pyridine-IR spectrum

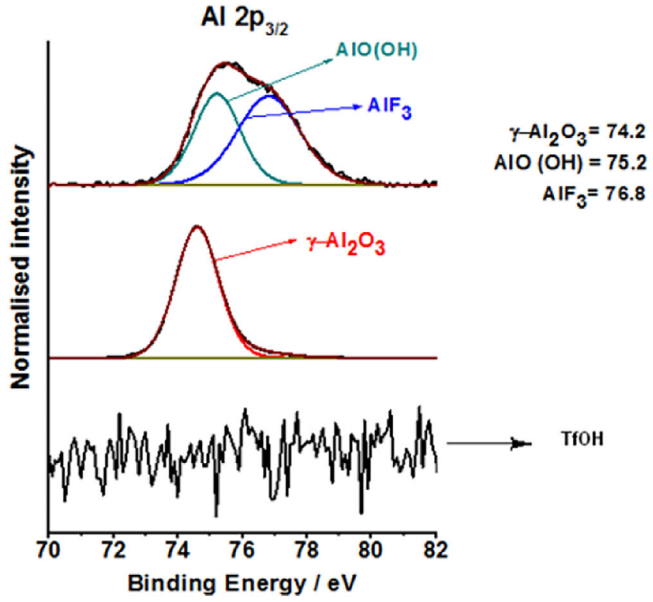


FIGURE 5 Deconvoluted Al(2P) XPS spectra of treated sample Al_2O_3-Tf (top) along with standard γ-Al_2O_3

The intensities of bands at about 1440 cm^{-1} (LPy), 1484 cm^{-1} (LPy + BPy), 1590 cm^{-1} (BPy), and 1610 cm^{-1} (LPy) in the normalized spectra were used to determine the type of acidic sites semi-quantitatively.[25]

From PY-IR spectroscopy it is clear that the addition of TfOH to the pre-heated γ-Al_2O_3 at room temperature, the Lewis, and Brønsted acidic strength has got increased when compared to the normal γ-Al_2O_3, which was further enhanced when heated at 70 °C. Due to this, the binary system displayed co-operative catalysis to furnish tandem and Michael addition products. Super acids are known to etch the γ-Al_2O_3 layer and leads to the formation of matrix. To understand this, the TfOH treated alumina (Al_2O_3-Tf) was analyzed using XPS (Figure 5). The Al 2p spectrum of untreated and treated samples (γ-Al_2O_3 and Al_2O_3-Tf) could be deconvoluted to three species corresponding to 74.2 eV as in Al_2O_3, 75.2 eV as in AlO(OH), and 76.8 eV, which is the position of Al 2p in AlF_3. These binding energy values correlated well with the literature reports.[26] Based on these results, a plausible mechanism for the Michael addition and cyclization reaction is proposed (Scheme 3).

The presence of species Al(O)—OH may probably facilitate the Michael addition of nucleophiles such as amines and thiols to maleimides (Scheme 4).

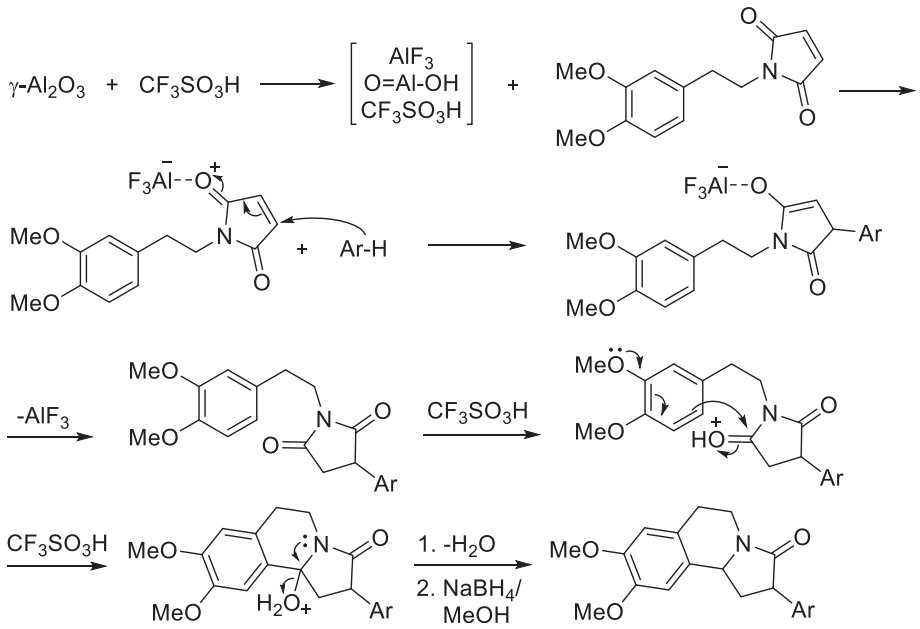
3 | CONCLUSION

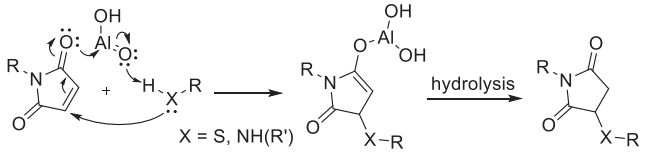
In conclusion, we have demonstrated a tandem Michael addition/carbocyclization sequence using γ-Al_2O_3/TfOH (0.1/8) binary catalytic system. Using this strategy, 2-aryl or 2-thioaryl pyrroloisoquinoline derivatives are obtained in good to excellent yields at low temperature. Whereas, the binary system γ-Al_2O_3/TfOH (0.1/1 ratio) furnished 3-substituted succinimide derivatives with C/N/S nucleophiles at elevated temperature in good yields. The active species involved in binary system were confirmed through XPS, which are found to be AlO(OH), AlF_3 along with TfOH. Furthermore, PY-IR analysis reveals the Lewis and Brønsted acidic nature of the binary system. Exploration of the synthetic utility of this binary system in other organic transformations is in progress in this laboratory.

4 | EXPERIMENTAL

Melting points reported in this paper are uncorrected and were determined using BUCHI M-560, Buchi Labortechnik AG, Switzerland. Infrared spectra were recorded on Thermo Nicolet 6700 FT-IR Spectrophotometer and are reported in frequency of absorption (cm^{-1}). Mass spectra were measured with Agilent-6530 B Q-TOF (ESI-HRMS), ^1H and ^{13}C NMR were recorded on Bruker AVANCE 400 spectrometer. NMR spectra for all the samples were measured in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard. The chemical shifts are expressed in δ ppm down field from the signal of internal TMS. Pyridine (FT-IR) spectroscopy recorded with Nicolet iS50 spectrometer equipped with DTGS KBR detector. XPS was analyzed through Perkin-Elmer PHI 5300Thermo Scientific Kalpha+ XPS spectrometer. Trifluoromethanesulfonic acid purchased from M/s. Sigma-Aldrich and used without further purification. Aromatic/

SCHEME 3 Plausible mechanism for the formation of 2-aryl pyrroloisoquinoline derivatives





SCHEME 4 Plausible mechanism for the formation of 2-substituted pyrrolidine-2,5-diones

hetero nucleophiles were also purchased from M/s. Sigma-Aldrich and purified (liquid sample) by distillation under reduced pressure. *N*-Benzyl[27] and 3,4-dimethoxy *N*-phenethyl maleimides[4] were prepared from maleic anhydride with benzyl amine and 3,4-dimethoxy *N*-phenethyl amine, respectively, using the reported procedures.[27] Solvents used for the reactions were dried using standard procedures. Analytical Thin Layer Chromatographic (TLC) tests were carried out using precoated aluminum TLC plates. The spots were visualized by short exposure to iodine vapor or UV light. Column chromatography was carried out using M/s. Merck silica gel (100–200 mesh). All the glassware were pre-dried at 120 °C for 6 h and assembled while hot and cooled under stream of dry nitrogen gas. In all experiments, round bottom flasks of appropriate size were used.

4.1 | Pyridine FT-IR spectroscopy

Lewis acid sites (LPy) and Brønsted acid sites (BPy) were studied with Nicolet iS50 spectrometer equipped with DTGS KBR detector. The spectra were recorded in DRIFT mode with 4 cm^{-1} resolution and 32 scans. Before recording the samples, a background spectrum was recorded with KBr. The samples were diluted with KBr in the 195:5 wt% ratio. The samples were mixed with 20 μL Pyridine. Then spectra were recorded between 4000 and 400 cm^{-1} before and after Py adsorption at RT.

4.2 | XPS analysis

XPS experiments were performed in an ultrahigh vacuum (UHV) chamber equipped with a Perkin-Elmer PHI 5300 Thermo Scientific K-alpha+ XPS spectrometer with a position-sensitive detector and a hemispherical energy analyzer. The Al Kα (beam energy = 1486.6 eV) X-ray source of the XPS spectrometer was operated at 350 W with 15 kV acceleration voltage used for photoemission.

4.3 | General procedure to synthesize 2-substituted pyrroloisoquinolinone derivatives (3a–3h)

An oven-dried schlenk tube with side arm was fitted with nitrogen balloon, septum, and equipped with stir bar was cooled down to room temperature under a steady stream of nitrogen gas flow. After reaching room temperature, the septum was opened under nitrogen atmosphere and the schlenk tube was charged with 3,4-dimethoxyphenethyl maleimide 1 (1 mmol), π-nucleophile (or) thiophenol (1 mmol), γ-Al_2O_3 (10 mol%), and dry dichloromethane (5 mL). The contents were closed with septum under nitrogen atmosphere and stirred at −30 °C followed by addition of TfOH (0.71 mL, 8 mmol). After stirring for 3 h at −30 °C, the reaction mixture was brought to room

temperature and quenched with $NaBH_4$ (2 mmol) and MeOH (2.5 mL), and stirring was continued until the color disappears. The contents were transferred to round bottom flask and the schlenk tube was washed with dichloromethane (2 × 20 mL). The solvent was evaporated under reduced pressure. The trace amount of solvents dichloromethane and methanol were removed under high vacuum. The residue was then quenched with water and then extracted with dichloromethane (2 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and filtered and the solvent was removed under reduced pressure. The crude reaction mixture was purified through silica gel column chromatography using ethyl acetate and hexane (50:50) as eluent to furnish 2-aryl pyrroloisoquinolinone derivatives 3a-3 h in pure form.

4.4 | 8,9-Dimethoxy-2-(2,4,6-trimethoxyphenyl)-1,5,6,10b-tetrahydro pyrrolo[2,1-*a*]isoquinolin-3(2H)-one (3a)

Yellow liquid, yield: 330 mg (80%), IR (KBr, cm^{-1}): 2922, 2851, 1686, 1609, 1506, 1452, 1261, 1173, 1113, 1050, 1016, 872, 820, 722, 596; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.64 (s, 1H), 6.54 (s, 1H), 6.12 (d, J = 2.0 Hz, 1H), 6.04 (d, J = 2.4 Hz, 1H), 4.77–4.73 (m, 1H), 4.38–4.33 (m, 2H), 3.87 (s, 3H), 3.82 (s, 3H), 3.79 (s, 3H), 3.76 (s, 3H), 3.49 (s, 3H), 3.06–3.00 (m, 1H), 2.95–2.87 (m, 1H), 2.85–2.80 (m, 1H), 2.72–2.38 (m, 1 H), 2.04–1.96 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.6, 160.5, 159.3, 159.0, 148.2, 147.7, 130.5, 125.7, 111.7, 108.5, 107.9, 91.6, 90.9, 56.0, 55.5, 55.47, 54.9, 38.7, 37.9, 34.8, 28.5; HRMS-ESI (m/z): $(M+H)^+$ calcd for $C_{23}H_{27}NO_6$: 414.1917; found: 414.1918.

4.5 | 8,9-Dimethoxy-2-(naphthalen-1-yl)-1,5,6,10b-tetrahydropyrrolo-[2,1-a] isoquinolin-3(2H)-one (3b)

Colorless liquid, yield: 243 mg (68%), IR (KBr, cm^{-1}): 2925, 2850, 1688, 1609, 1508, 1454, 1263, 876, 821, 724, 597; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99–7.97 (m, 1H), 7.87–7.85 (m, 1H), 7.77–7.74 (m, 1H), 7.49–7.46 (m, 2H), 7.44–7.40 (m, 2H), 6.68 (s, 1H), 6.55 (s, 1H), 4.91-4.87 (m, 1H), 4.65–4.60 (m, 1H), 4.51–4.46 (m, 1H), 3.88 (s, 3H), 3.80 (s, 3H), 3.29–3.16 (m, 2H), 3.09–3.01 (m, 1H), 2.83–2.79 (m, 1H), 2.08–2.00 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1, 148.3, 148.2, 135.3, 134.2, 132.1, 129.2, 129.1, 127.1, 126.2, 126.1, 125.9, 125.6, 123.2, 111.9, 107.7, 56.1, 54.8, 46.4, 38.1, 37.8, 28.4; HRMS-ESI (m/z): $(M+H)^+$ calcd for $C_{24}H_{24}NO_3$: 374.1756; found: 374.1720.

4.6 | 8,9-Dimethoxy-2-(4-methoxyphenyl)-1,5,6,10b-tetrahydropyrrolo-[2,1-a]isoquinolin-3(2H)-one (3c)

Colorless liquid, yield: 332 mg (94%), IR (KBr, cm^{-1}): 2925, 2850, 1688, 1609, 1508, 1454, 1263, 1171, 1115, 1051, 1018, 876, 821, 724, 597; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17–7.15 (m, 2H), 6.87–6.84 (m, 2H), 6.66 (s, 1H), 6.59 (s, 1H), 4.76–4.72 (m, 1H), 4.40–4.35 (m, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.81–3.79 (m, 1H), 3.78 (s, 3H), 3.14–3.02 (m, 2H), 2.99–2.91 (m, 1H), 2.77–2.73 (m, 1H), 1.96–1.88 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7, 155.2, 148.4, 148.3, 133.1, 132.5, 128.8, 128.7, 125.7, 112.2, 112.0, 111.9, 107.8, 56.4, 56.2, 54.5, 48.3, 38.0, 37.6, 28.4; HRMS-ESI (m/z): $(M+H)^+$ calcd for $C_{21}H_{24}NO_4$: 354.1705; found: 354.1702.

4.7 | 2-(3-Bromo-4-methoxyphenyl)-8,9-dimethoxy-1,5,6,10b-tetra-hydropyrrolo [2,1-*a*]isoquinolin-3(2H)-one (3d)

Colorless liquid, yield: 401 mg (93%), IR (KBr, cm^{-1}): 2925, 2850, 1688, 1609, 1508, 1454, 1263, 1171, 1115, 1051, 1018, 876, 821, 778, 724, 597; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (d, J = 2.0 Hz, 1H), 7.19–7.16 (m, 1H), 6.85 (d, J = 8.4 Hz, 1H), 6.66 (s, 1H), 6.58 (s, 1H), 4.76–4.72 (m, 1H), 4.38–4.34 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.81–3.76 (m, 1H), 3.13–3.03 (m, 2H), 3.00–2.91 (m, 1H), 2.74 (d, J = 14.0 Hz, 1H), 1.90 (dd, J = 21.6, 12.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7, 155.2, 148.4, 148.3, 133.1, 132.5, 128.8, 128.7, 125.7, 112.3, 112.0, 111.9, 107.8, 56.5, 56.2, 56.1, 48.3, 38.1, 37.7, 28.4; HRMS-ESI (m/z): $(M+H)^+$ calcd for $C_{21}H_{22}BrNO_4$: 432.0810; found: 432.0795.

4.8 | 2-(1-Ethyl-1H-indol-3-yl)-8,9-dimethoxy-1,5,6,10b-tetrahydro-pyrrolo [2,1-*a*]isoquinolin-3(2H)-one (3e)

Colorless liquid, yield: 292 mg (75%), IR (KBr, cm^{-1}): 2926, 2852, 1691, 1611, 1515, 1451, 1362, 1261, 1223, 1177, 1118, 1057, 1016, 865, 725, 690, 607; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.47 (m, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.20–7.15 (m, 2H), 7.07–7.03 (m, 1H), 6.66 (s, 1H), 6.58 (s, 1H), 4.81 (dd, J = 9.6, 6.8 Hz, 1H), 4.45–4.40 (m, 1H), 4.20–4.15 (m, 1H), 4.14–4.08 (m, 2H), 3.88 (s, 3H), 3.83 (s, 3H), 3.22–3.11 (m, 1H), 3.04–2.97 (m, 1H), 2.80–2.75 (m, 1H), 2.06–1.97 (m, 2H), 1.45–1.42 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.3, 139.7, 134.0, 133.6, 129.7, 126.7, 125.4, 123.1, 113.8, 112.7, 111.8, 107.6,

56.2, 56.1, 54.3, 42.4, 39.2, 37.7, 31.3, 28.3; HRMS-ESI (m/z): $(M+H)^+$ calcd for $C_{24}H_{27}N_2O_3$: 391.2022; found: 391.2016.

4.9 | 8,9-Dimethoxy-2-(1-[phenylsulfonyl]-1H-pyrrol-3-yl)-1,5,6,10b-tetrahydropyrrolo[2,1-*a*] isoquinolin-3(2H)-one (3f)

Green color liquid, yield: 370 mg (82%), IR (KBr, cm^{-1}): 2928, 2846, 1687, 1609, 1515, 1458, 1363, 1266, 1221, 1116, 1019, 861, 742, 468; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.83–7.81 (m, 2H), 7.62–7.58 (m, 1H), 7.54–7.50 (m, 2H), 7.22 (dd, J = 3.6, 1.6 Hz, 1H), 6.63 (s, 1H), 6.54 (s, 1H), 6.26–6.24 (m, 1H) 6.18–6.16 (m, 1H), 4.74–4.69 (m, 1H), 4.41–4.31 (m, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.27–3.21 (m, 1H), 3.11–3.04 (m, 1H), 2.97–2.89 (m, 1H), 2.72 (dd, J = 13.6, 2.0 Hz, 1H), 1.81–1.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4, 148.3, 148.1, 136.4, 129.3, 127.4, 125.6, 125.3, 121.6, 119.3, 119.0, 111.8, 109.6, 107.7, 56.1, 54.7, 41.1, 40.1, 37.6, 37.5, 28.4; HRMS-ESI (m/z): $(M+H)^+$ calcd for $C_{24}H_{25}N_2O_5S$: 453.1484; found: 453.1483.

4.10 | 2-(Benzo[b]thiophen-2-yl)-8,9-dimethoxy-1,5,6,10b-tetrahydro-pyrrolo[2,1-*a*]isoquinolin-3(2H)-one (3g)

Yellow color liquid, yield: 285 mg (75%), IR (KBr, cm^{-1}): 2923, 2855, 1687, 1514, 1422, 1264, 1171, 1113, 1021, 773, 725, 601; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.85–7.83 (m, 1H), 7.71–7.69 (m, 1H), 7.34 (t, J = 3.6 Hz, 3H), 6.67 (s, 1H), 6.57 (s, 1H), 4.87–4.83 (m, 1H), 4.46–4.41 (m, 1H), 4.31–4.26 (m, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.22–3.13 (m, 2H), 3.05–2.96 (m, 3H), 2.08–2.01 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1, 148.4, 140.8, 138.4, 133.2, 128.9, 125.6, 124.4, 124.1, 123.7, 123.1, 121.9, 111.9, 107.7, 56.1, 54.7, 43.6, 37.7, 36.5, 28.4; HRMS-ESI (m/z): $(M+H)^+$ calcd for $C_{22}H_{22}NO_3S$: 380.1320; found: 380.1310.

4.11 | 8,9-Dimethoxy-2-(phenylthio)-1,5,6,10b-tetrahydro-pyrrolo[2,1-*a*] isoquinolin-3(2H)-one (3h)

Yellow color liquid, yield: 309 mg (87%), IR (KBr, cm^{-1}): 3060, 2928, 2841, 1771, 1694, 1611, 1515, 1434, 1361, 1326, 1263, 1220, 1166, 1115, 1019, 863, 740, 696, 559, ^1H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.49 (m, 2H), 7.25–7.20 (m, 3H), 6.56 (s, 1H), 6.46 (s, 1H), 4.65 (t, J = 8.0 Hz, 1H), 4.33–4.28 (m, 1H), 4.06 (dd, J = 10.0, 8.8 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.06–2.98 (m, 2H), 2.84–2.76 (m, 1H), 2.64 (dd, J = 15.6, 2.4 Hz, 1H), 1.91–1.83 (m, 1H), ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4, 148.3, 148.1, 133.6, 132.6, 129.0, 128.3, 127.7, 125.5, 111.8, 107.6, 56.0, 54.4, 49.3, 37.8, 36.2, 28.0; HRMS-ESI (m/z): $(M+H)^+$ calcd for $C_{20}H_{22}NO_3S$: 356.1320; found: 356.1322.

4.12 | General procedure for the synthesis of 3-substituted pyrrolidine-2,5-diones, 4–6, and 8a–8h, 9a–9h, 10a–10c

An oven-dried schlenk tube with side arm was fitted with nitrogen balloon, septum, and equipped with stir bar was cooled down to room temperature under a steady stream of nitrogen gas flow. After reaching room temperature, the septum was opened under nitrogen atmosphere and the schlenk tube was charged with 3-methoxyphenethyl maleimide (1 mmol) or *N*-benzyl maleimide (1 mmol), N/C/S-nucleophile (1 mmol), γ-Al_2O_3 (10 mol%), and dry 1,2-dichloroethane (3 mL). The contents were closed with septum under nitrogen atmosphere and stirred at room temperature followed by the addition of TfOH (1 mmol). The reaction mixture was stirred at 70 °C. After the consumption of the starting material (16 to 24 h), the reaction mixture was cooled to room temperature and quenched with water (10 mL). Organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic layer was washed with brine solution (2 × 10 mL), dried over anhydrous Na_2SO_4, filtered and the solvent was removed *in vacuo*. The crude reaction mixture was purified through silica gel column chromatography using hexane and ethyl acetate (80:20) as eluent to give 3-substituted 1-phenethyl/benzyl pyrrolidine-2,5-diones **4**, **5** and **6**/**8a-8h**, **9a–9g** and **10a–10c**.

4.13 | 1-(3,4-Dimethoxyphenethyl)-3-((4-methoxyphenyl) amino)-pyrrolidine-2,5-dione (4)

Yellow color liquid, yield: 249 mg (65%), IR (KBr, cm^{-1}): 3035, 2839, 1704, 1514, 1452, 1404, 1346, 1242, 1151, 1028, 817, 761; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.81–6.78 (m, 3H), 6.75–6.73 (m, 2H), 6.56 (d, J = 8.8 Hz, 2H), 4.17–4.13 (dd, J = 8.0, 5.2 Hz, 2H), 3.86 (s, 3H), 3.84 (s, 1H), 3.78 (d, J = 7.2 Hz, 2H), 3.74 (s, 3H), 3.16–3.09 (m, 1H), 2.89–2.85 (m, 2H), 2.56 (dd, J = 17.6, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.0, 174.7, 153.6, 149.0, 147.9, 140.0, 130.0, 121.0, 115.6, 115.1, 112.1, 111.3, 55.9, 55.7, 53.6, 40.3, 38.0, 33.1; HRMS-ESI (m/z): $(M+H)^+$ calcd for $C_{21}H_{25}N_2O_5$: 385.1763; found: 385.1781.

4.14 | 1-(3,4-Dimethoxyphenethyl)-3-(2,4,6-trimethoxyphenyl) pyrolidine-2,5-dione (5)

Yellow oily liquid, yield: 291 mg (68%), IR (KBr, cm^{-1}): 2942, 1700, 1602, 1510, 1406, 1344, 1233, 1153, 1116, 1028, 811, 757; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.85–6.80 (m, 3H), 6.12 (d, J = 20.0 Hz, 2H), 4.45–4.41 (m, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.81–3.78 (m, 6H), 3.77–3.74 (m, 2 H), 3.65 (s, 3H), 3.00–2.93 (m, 1H), 2.88–2.84 (m, 2H), 2.65–2.59 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.8, 177.4, 161.1, 149.1, 147.8, 130.8, 120.9, 112.0, 111.4, 106.6, 91.1, 90.9, 56.0, 55.6, 55.5, 40.3, 36.0, 35.4, 33.5; HRMS-ESI (m/z): $(M+H)^+$ calcd for $C_{23}H_{28}NO_7$: 430.1866; found: 430.1885.

4.15 | 1-(3,4-Dimethoxyphenethyl)-3-(pyrimidin-2-ylthio) pyrrolidine-2,5-dione (6)

Colorless liquid, yield: 310 mg (83%), IR (KBr, cm^{-1}): 2938, 1775, 1705, 1557, 1514, 1450, 1388, 1234, 1153, 1027, 808, 758; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.37 (d, J = 4.8 Hz, 2H), 6.96 (t, J = 4.8 Hz, 1H), 6.75 (d, J = 4.8 Hz, 3H), 4.15 (dd, J = 9.6, 5.6 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.76–3.72 (m, 2H), 3.24–3.17 (m, 1H), 2.91 (d, J = 5.6 Hz, 1H), 2.87–2.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.2, 175.0, 169.8, 157.4, 148.9, 147.7, 130.2, 120.8, 117.4, 111.9, 111.3, 55.9, 41.1, 40.7, 36.2, 33.0; HRMS-ESI (m/z): $(M+H)^+$ calcd for $C_{18}H_{20}N_3O_4S$: 374.1175; found: 374.1190.

4.16 | 1-Benzyl-3-morpholinopyrrolidine-2,5-dione (8a)

Yellow color liquid, yield: 203 mg (74%), IR (KBr, cm^{-1}): 2925, 2854, 1771, 1704, 1440, 1394, 1344, 1161, 1116, 1006, 944, 706; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.35 (m, 2H), 7.33–7.25 (m, 3H), 4.66 (dd, J = 16.8, 14.0 Hz, 2H), 3.76–3.73 (m, 1H), 3.70 (t, J = 4.8 Hz, 4H), 2.87–2.76 (m, 3H), 2.66 (dd, J = 18.4, 4.8 Hz, 1H), 2.50–2.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.7, 174.6, 135.7, 129.0, 128.8, 128.2, 66.9, 62.6, 49.6, 42.4, 31.5; HRMS-ESI (m/z): $(M+H)^+$ calcd for $C_{15}H_{19}N_2O_3$: 275.1396; found: 275.1407.

4.17 | 1-Benzyl-3-((4-methoxyphenyl) amino)pyrrolidine-2,5-dione (8b)

Yellow color liquid, yield: 360 mg (90%); IR (KBr, cm^{-1}): 3368, 2940, 2836, 1779, 1706, 1633, 1515, 1438, 1399, 1343, 1243, 1167, 1033, 936, 822, 107, 628; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.38 (m, 2H), 7.33–7.28 (m, 3H), 6.77 (d, J = 8.8 Hz, 2H), 6.53 (d, J = 8.8 Hz, 2H), 4.66 (s, 2H), 4.30 (bs, 1H), 4.17 (dd, J = 8.4, 5.2 Hz, 1H), 3.72 (s, 3H), 3.08 (dd, J = 18.0, 8.4 Hz, 1H), 2.54 (dd, J = 18.0, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.8, 174.4, 153.2, 139.9, 135.4, 128.8, 128.6, 128.0, 115.3, 114.8, 55.5, 53.4, 42.5, 37.4; HRMS-ESI (m/z): $(M+H)^+$ calcd for $C_{18}H_{18}N_2O_3$: 311.1396; found: 311.1421.

4.18 | 1-Benzyl-3-(diethylamino) pyrrolidine-2,5-dione (8c)

Yellow color liquid, yield: 182 mg (70%), IR (KBr, cm^{-1}): 3029, 2927, 2858, 1772, 1706, 1612, 1459, 1392, 1346, 1161, 1079, 810,757, 632, ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, J = 6.5 Hz, 2H), 7.32–7.28 (m, 3H), 4.70–4.61 (m, 2H), 4.02 (dd, J = 8.9, 5.2 Hz, 1H), 2.84–2.78 (m, 1H), 2.67–2.61 (m, 1H), 2.59–2.50 (m, 4H), 1.09–1.05 (m, 6H), ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.3, 175.2, 135.9, 129.0, 128.8, 128.1, 59.2, 44.8, 42.3, 32.1, 13.6, HRMS-ESI (m/z): $(M+H)^+$ calcd for $C_{15}H_{20}N_2O_2$: 261.1603; found: 261.1619.

4.19 | 1-Benzyl-3-(4-phenylpiperazin-1-yl) pyrrolidine-2,5-dione (8d)

Yellow color liquid, yield: 286 mg (82%), IR (KBr, cm^{-1}): 3032, 2937, 2827, 1773, 1707, 1595, 1499, 1443, 1391, 1343, 1152, 1007, 930, 757, 702, 412, ^1H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.37 (m, 2H), 7.33–7.23 (m, 5H), 6.90–6.84 (m, 3H), 4.66 (d, J = 4.0 Hz, 2H), 3.80 (dd, J = 8.8, 4.8 Hz, 1H), 3.18–3.16 (m, 4H), 2.94–2.91 (m, 2H), 2.84 (m, 1H), 2.71–2.61 (m, 3H), ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.7, 174.7, 151.1, 135.8, 129.2, 128.9, 128.8, 128.1, 120.1, 116.3, 62.4, 49.3, 49.2, 42.3, 31.6, HRMS-ESI (m/z): $(M+H)^+$ calcd for $C_{21}H_{24}N_3O_2$: 350.1869; found: 350.1894.

4.20 | 1-Benzyl-3-([pyridin-2-ylmethyl] amino)pyrrolidine-2,5-dione (8e)

Yellow color liquid, yield: 251 mg (85%), IR (KBr, cm^{-1}): 3316, 2924, 2856, 1775, 1703, 1591, 1461, 1395, 1344, 1163, 754, 702; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.56 (d, J = 4.4 Hz, 1H), 7.65 (td, J = 7.6, 2.0 Hz, 1H), 7.38–7.36 (m, 2H), 7.33–7.28 (m, 4H), 7.21–7.18 (m, 1H), 4.66 (s, 2H), 4.01 (d, J = 0.4 Hz, 2H), 3.82 (dd, J = 8.0, 4.0 Hz, 1H), 2.93 (dd, J = 18.0, 8.0 Hz, 1H), 2.7 (brs, 1H), 2.57 (dd, J = 18.0, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl3):

δ = 177.5, 175.0, 158.3, 149.6, 136.8, 135.6, 129.0, 128.8, 128.2, 122.6, 122.5, 55.8, 53.1, 42.6, 36.5; HRMS-ESI (m/z): $(M+H)^+$ calcd for $C_{17}H_{18}N_3O_2$: 296.1399; found: 296.1406.

4.21 | 1-Benzyl-3-(dimethylamino) pyrrolidine-2,5-dione (8f)

Yellow color liquid, yield: 150 mg (65%), IR (KBr, cm^{-1}): 3031, 2934, 2864, 2787, 1772, 1705, 1441, 1395, 1345, 1163, 705; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.35 (m, 2H), 7.31–7.23 (m, 3H), 4.69–4.61 (m, 2H), 3.77 (dd, J = 8.8, 4.8 Hz, 1H) 2.82–2.75 (m, 1H), 2.64–2.58 (m, 1H), 2.33 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2, 174.9, 135.8, 128.9, 128.7, 128.1, 62.7, 42.2, 41.3, 31.0; HRMS-ESI (m/z): $(M+H)^+$ calcd for $C_{13}H_{17}N_2O_2$: 233.1290; found: 233.1304.

4.22 | 1-Benzyl-3-(4-oxo-2-thioxothiazolidin-3-yl)pyrrolidine-2,5-dione (8g)

Brownish liquid, yield: 217 mg (68%), IR (KBr, cm^{-1}): 2932, 2253, 1729, 1629, 1465, 1395, 1347, 1159, 989, 908, 735, 637; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.34 (m, 2H), 7.31–7.24 (m, 3H), 4.72-4.69 (m, 2H), 4.57–4.54 (m, 1H), 3.92 (s, 2H), 3.33–3.26 (m, 1H), 2.98–2.92 (m, 1H); ^{13}C NMR (100 MHz, CDCl3): δ = 198.7, 186.2, 173.5, 172.9, 135.0, 128.7, 128.6, 128.0, 43.9, 43.3, 39.9, 36.4; HRMS-ESI (m/z): $(M+H)^+$ calcd for $C_{14}H_{12}N_2O_3S_2$: 321.0368; found: 321.0382.

4.23 | 1-Benzyl-3-(([R]-1-phenylethyl) amino)pyrrolidine-2,5-dione (8h)

Colorless liquid, yield: 265 mg (86%), IR (KBr, cm^{-1}): 3315, 3029, 2966, 2927, 2858, 1774, 1706, 1489, 1440, 1399, 1345, 1165, 761, 705; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.29 (m, 10H), 7.29–7.23 (m, 10H), 4.60 (s, 4H), 4.11–4.06 (m, 1H), 3.74 (dd, J = 13.6, 6.8 Hz, 1H), 3.60 (dd, J = 8.4, 5.2 Hz, 1H), 3.47 (dd, J = 8.0, 5.2 Hz, 1H), 2.75 (dd, J = 17.6, 8.0 Hz, 1H), 2.53 (dd, J = 18.0, 5.2 Hz, 1H), 2.45 (dd, J = 18.0, 8.0 Hz, 1H), 2.25 (brs, 2H), 2.18 (dd, J = 18.0, 5.2 Hz, 1H), 1.40 (d, J = 1.2 Hz, 3H), 1.39 (d, J = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.2, 177.9, 175.0, 175.0, 144.3, 143.4, 135.6, 135.5, 129.0, 128.9, 128.9, 128.7, 128.1, 127.7, 127.2, 126.5, 58.6, 56.3, 55.7, 54.0, 42.5, 42.4, 37.7, 36.7, 24.3, 24.1; HRMS-ESI (m/z): $(M+H)^+$ calcd for $C_{19}H_{21}N_2O_2$: 309.1603; found: 309.1628.

4.24 | 1-Benzyl-3-(2,4,6-trimethoxyphenyl) pyrrolidine-2,5-dione (9a)

Colorless liquid yield: 302 mg (85%), IR (KBr, cm^{-1}): 2943, 2842, 1772, 1711, 1609, 1497, 1462, 1327, 1223, 1116, 1037, 952, 890, 815, 706, 629, 481; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.43 (d, J = 6.8 Hz, 2H), 7.24–7.16 (m, 3H), 6.05 (s, 1H), 5.94 (s, 1H), 4.64 (s, 2H), 4.41–4.37 (m, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 3.14 (s, 3H), 2.88 (dd, J = 18.0, 9.6 Hz, 1H), 2.51 (dd, J = 18.0, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.5, 177.1, 161.0, 158.8, 158.6, 136.5, 129.4, 128.5, 127.8, 106.5, 90.9, 90.7, 55.9, 55.4, 55.0, 42.9, 36.0, 35.4; HRMS-ESI (m/z): $(M+H)^+$ calcd for $C_{14}H_{22}NO_5$: 356.1498; found: 356.1487.

4.25 | 1-Benzyl-3-(1-[phenylsulfonyl]-1H-pyrrol-3-yl)pyrrolidine-2,5-dione (9b)

Colorless liquid, yield: 205 mg (52%), IR (KBr, cm^{-1}): 2924, 2856, 1776, 1704, 1583, 1359, 1176, 1083, 823, 695, 606; ^1H NMR (400 MHz, CDC_{l3}): δ = 7.74–7.24 (m, 2H), 7.64–7.60 (m, 1H), 7.53–7.49 (m, 2H), 7.41–7.38 (m, 1H), 7.34–7.24 (m, 5H), 6.71 (s, 1H), 6.24–6.22 (m, 1H), 5.99 (dd, J = 3.2, 1.6 Hz, 1H), 4.71-4.68 (m, 3H), 4.49 (dd, J = 9.6, 5.2 Hz, 1H), 3.16 (dd, J = 18.4, 9.6 Hz, 1H), 2.65 (dd, J = 18.4, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, CDC_{l3}): δ = 176.0, 175.2, 139.2, 135.6, 134.3, 131.1, 129.7, 129.0, 128.8, 128.5, 128.2, 128.0, 126.7, 124.0, 112.5, 42.9, 39.6, 38.2; HRMS-ESI (m/z): $(M+H)^+$ calcd for $C_{21}H_{19}N_2O_4S$: 395.1066; found: 395.1035.

4.26 | 1-Benzyl-3-(2-[methylamino] phenyl)pyrrolidine-2,5-dione (9c)

Colorless liquid, yield: 171 mg (58%), IR (KBr, cm^{-1}): 3315, 2928, 2856, 2818, 1778, 1706, 1597, 1500, 1440, 1395, 1343, 1168, 1125, 1081, 1042, 1003, 928, 812, 756, 694, 626, 573, 438; ^1H NMR (400 MHz, CDC_{l3}): δ = 7.39 (d, J = 7.4 Hz, 1H), 7.23–7.11 (m, 6H), 6.82 (td, J = 7.4, 1.1 Hz, 1H), 6.65 (dd, J = 8.2, 0.6 Hz, 1H), 4.62–4.51 (m, 2H), 3.91 (d, J = 9.4 Hz, 1H), 3.42 (dd, J = 11.5, 2.8 Hz, 1H), 3.30–3.24 (m, 1H), 2.97 (dd, J = 11.5, 4.6 Hz, 1H), 2.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.4, 176.5, 148.3, 135.6, 130.3, 128.74, 128.70, 128.5, 127.9, 120.0, 119.0, 112.8, 50.8, 43.6, 42.9, 42.1, 39.6; HRMS-ESI (m/z): $(M+H)^+$ calcd for $C_{18}H_{19}N_2O_2$: 295.1447; found: 295.1426.

4.27 | 1-Benzyl-3-(4-methoxyphenyl) pyrrolidine-2,5-dione (9d)

Colorless liquid yield: 251 mg (85%), IR (KBr, cm^{-1}): 2930, 2843, 1772, 1702, 1611, 1509, 1431, 1394, 1345,

1250, 1164, 1031, 889, 833, 720, 629, 524; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (d, J = 7.6 Hz, 2H), 7.26–7.19 (m, 3H), 7.00 (d, J = 8.4 Hz, 2H), 6.79 (d, J = 8.4 Hz, 2H), 4.68–4.59 (m, 2H), 3.88 (dd, J = 9.2, 4.8 Hz, 1H), 3.71 (s, 3H), 3.09 (dd, J = 18.4, 9.6 Hz, 1H), 2.69 (dd, J = 18.8, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.8, 175.9, 159.3, 135.9, 129.2, 128.9, 128.8, 128.5, 128.1, 114.6, 55.4, 45.2, 42.7, 37.3; HRMS-ESI (m/z): $(M+H)^+$ calcd for $C_{18}H_{18}NO_3$: 296.1287; found: 296.1276.

4.28 | 1-Benzyl-3-(5-hydroxy-2-methoxyphenyl)pyrrolidine-2,5-dione (9e)

Black color liquid yield: 186 mg (60%), IR (KBr, cm^{-1}): 3440, 2927, 2358, 1773, 1701, 1602, 1517, 1437, 1395, 1347, 1274, 1164, 1030, 703, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.35 (s, 1H), 7.35–7.25 (m, 5H), 6.77-6.72 (m, 3H), 4.67–4.57 (m, 2H), 4.11–4.07 (m, 1H), 3.66 (s, 3H), 3.77-3.07 (m , 1H), 2.73–2.67 (m, 1H) 2.51-2.49 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.4, 176.6, 152.0, 148.8, 136.4, 128.4, 127.3, 125.3, 116.7, 115.8, 113.7, 55.4, 43.4, 41.6, 35.7; HRMS-ESI (m/z): $(M+H)^+$ calcd for $C_{18}H_{18}NO_4$: 312.1236; found: 312.1245.

4.29 | 1-Benzyl-3-(3-hydroxy-4-methoxyphenyl)pyrrolidine-2,5-dione (9f)

Black color liquid, yield: 155 mg (50%), IR (KBr, cm^{-1}): 3441, 2930, 2854, 1772, 1708, 1602, 1517, 1437, 1394, 1347, 1273, 1162, 1077, 1030, 922, 890, 816, 703, 625; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.40 (m, 2H), 7.33–7.26 (m, 3H), 6.85 (d, J = 8.0 Hz, 1H), 6.63 (dd, J = 8.0, 2.0 Hz, 1H), 6.55 (d, J = 2.0 Hz, 1H), 5.71 (brs, 1H) 4.76–4.68 (m, 2H), 3.93 (dd, J = 9.2, 4.4 Hz, 1H), 3.75 (s, 3H), 3.21–3.14 (m, 1H), 2.80–2.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.8, 176.1, 147.1, 145.5, 136.0, 129.1, 128.9, 128.8, 128.1, 120.2, 115.0, 109.7, 55.9, 45.6, 42.8, 37.4; HRMS-ESI (m/z): $(M+H)^+$ calcd for $C_{18}H_{17}NO_4$: 312.1236; found: 312.1244.

4.30 | 11-Benzyl-3-(2-oxoindolin-3-yl) pyrrolidine-2,5-dione (9g)

Yellow color liquid, yield: 256 mg (80%), IR (KBr, cm^{-1}): 3293, 2926, 2358, 1775, 1706, 1621, 1473, 1398, 1343, 1166, 750; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.76 (s, 1H), 8.64 (s, 1H), 7.43–7.40 (m, 2H), 7.35–7.34 (m, 3H), 7.30–7.29 (m, 1H), 7.24–7.21 (m, 2H), 7.16–7.12 (m, 2H), 7.0–6.87 (m,, 1H), 6.80 (d, J = 8.0 Hz, 1H), 6.60 (t, J = 8.0 Hz, 1H), 6.37 (d, J = 7.2 Hz, 1H), 4.77 (d, J = 14.0 Hz, 1H), 4.72–4.60 (m, 2H), 4.13 (dd, J = 6.4, 1.2 Hz, 2H), 3.68–3.53 (m, 2H), 2.84–2.65 (m, 2H), 2.40–2.34 (m, 1H), 1.86 (dd, J = 17.6, 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.8, 177.5, 177.0, 176.9, 175.4, 141.9, 135.5, 129.3, 129.2, 129.2, 128.9, 128.7, 128.6, 128.3, 127.9, 126.0, 124.6, 123.9, 123.7, 123.2, 123.0, 110.5, 110.3, 46.4, 45.7, 42.9, 42.8, 40.7, 40.4, 31.8, 30.0; HRMS-ESI (m/z): $(M+H)^+$ calcd for $C_{19}H_{17}N_2O_3$: 321.1239; found: 321.1258.

4.31 | 1-Benzyl-3-(phenylthio) pyrrolidine-2,5-dione (10a)

Yellow color liquid, yield: 267 mg (90%); IR (KBr, cm^{-1}): 3062, 2935, 2857, 2250, 1960, 1776, 1718, 1577, 1484, 1394, 1347, 1162, 1079, 1028, 895, 825, 741, 698, 631; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.36 (m, 2H), 7.28–7.24 (m, 6H), 7.19–7.15 (m, 2H), 4.53 (s, 2H), 3.95 (dd, J = 9.2, 4.0 Hz, 1H), 3.06 (dd, J = 18.8, 9.2 Hz, 1H), 2.60 (dd, J = 18.8, 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.3, 174.1, 135.2, 134.2, 130.1, 129.2, 129.1, 128.8, 128.6, 127.9, 43.7, 42.6, 35.7; HRMS-ESI (m/z): $(M+H)^+$ calcd for $C_{17}H_{16}NO_2S$: 298.0902; found: 298.0919.

4.32 | 1-Benzyl-3-(pyrimidin-2-ylthio) pyrrolidine-2,5-dione (10b)

Yellow color liquid, yield: 267 mg (89%), IR (KBr, cm^{-1}): 3037, 2927, 2856, 1780, 1695, 1557, 1496, 1391, 1346, 1163, 1078, 897, 810, 759, 698, 634, 484; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, J = 4.8 Hz, 2H), 7.41–7.38 (m, 2H), 7.21 (dd, J = 6.4, 3.6 Hz, 3H), 6.74 (t, J = 4.8 Hz, 1H), 4.69 (s, 2H), 4.01 (dd, J = 8.0, 4.0 Hz, 1H), 3.23–3.16 (m, 1H), 2.83 (dd, J = 18.4, 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.1, 174.9, 169.4, 157.3, 135.7, 129.7, 128.6, 127.9, 117.1, 43.1, 41.2, 36.1; HRMS-ESI (m/z): $(M+H)^+$ calcd for $C_{15}H_{14}N_3O_2S$: 300.0807; found: 300.0801.

4.33 | 1-Benzyl-3-(p-tolylthio)pyrrolidine-2,5-dione (10c)

Yellow color liquid, yield: 280 mg (90%), IR (KBr, cm^{-1}): 3030, 2926, 2858, 1776, 1711, 1596, 1492, 1437, 1394, 1346, 1164, 1087, 1028, 897, 812, 701, 632; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.25 (m, 7H), 6.98-6.96 (m, 2H), 4.55 (s, 2H), 3.92 (dd, J = 9.2, 4.4 Hz, 1H), 3.08 (dd, J = 18.8, 9.2 Hz, 1H), 2.68-2.62 (m, 1H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.5, 174.4, 139.8, 135.4, 135.1, 130.2, 129.0, 128.7, 128.0, 126.0, 44.1, 42.8, 35.7, 21.3; HRMS-ESI (m/z): $(M+H)^+$ calcd for $C_{18}H_{18}NO_2S$: 312.1058; found: 312.1073.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in [repository name e.g "figshare"] at http://doi.org/[doi], reference number [reference number].

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