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Cu/Ag cocatalyzed aerobic oxidative amination and $CuCl_2$ mediated aerobic oxidative chloroamination of maleimides

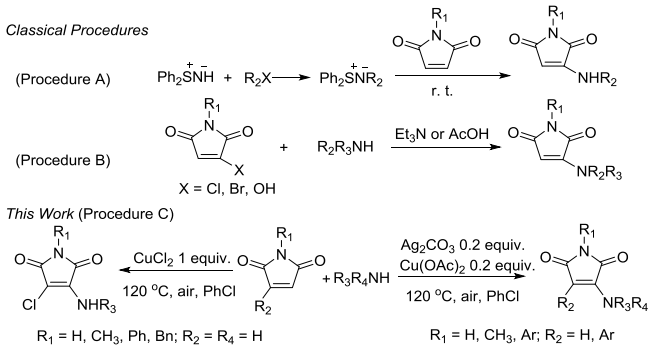
Yu-Long an,[a] He-Hui Zhang,[a] Zhen-Hua Yang,[a] Long Lin,[a] and Sheng-Yin Zhao*[a,b]

Oxidative amination and chloroamination

Abstract: An efficient $Cu(OAc)_2/Ag_2CO_3$ cocatalyzed approach for the synthesis of 3-aminomaleimides and 3-amino-4-indolylmaleimides has been developed with satisfied yields. A series of primary and secondary amines are compatible with this reaction. In addition, the treatment of maleimides with primary amines using one equivalent of $CuCl_2$ leads to the formation of chloroamination products such as 3-amino-4-chloromaleimides by a radical-type mechanism.

Introduction

3-Aminomaleimides and their derivatives have a wide range of applications in the fields of natural products,[1] pharmaceuticals,[2] and material sciences.[3] Therefore, a certain attention has been paid to their synthesis. To date, several synthetic methods have been established, and could be summarized as the following procedures: 1) Reactions of N-benzyldiphenylsulfilimines, which were prepared by treating diphenylsulfilimine with alkyl halides in refluxing chloroform, with maleimides (Scheme 1, Procedure A).[4] 2) Dehydrohalogenation or dehydration coupling of 3-substituted maleimides with amines in the presence of triethylamine or acetic acid, respectively (Scheme 1, Procedure B).[5]



Scheme 1. Synthesis of 3-aminomaleimides

Procedure A is limited to the synthesis of the secondary enamine products; the tertiary enamine products cannot be prepared via this method.[4] Although procedure B is an efficient way to synthesize a wide range of 3-aminomaleimides, continuing exploration is of great significance considering that the starting materials should be halogenated and hydroxylated from maleimides. Therefore, the development of efficient synthetic methods to access these 3-aminomaleimides are attractive for organic chemists.

In recent years, transition metal-catalyzed oxidative amination of arenes[6] and alkenes[7] has attracted considerable attention because it provides an efficient synthesis for various nitrogen-containing products. Several transition metals have been studied as catalysts and oxidants such as Pd, Ru, Rh, Co and so on.[8] However, these reactions suffer from the limitations such as pre-functionalization, high catalyst loadings, long reaction times, expensive and hazardous reagents.[7d-7e] Furthermore, most of the reaction substrates were focused on styrene and α,β-unsaturated carbonyl compounds such as acrylic esters. Nevertheless, to the best of our knowledge, an efficient directly synthesis of 3-aminomaleimides and 3-amino-4-chloromaleimides has not yet been explored. The maleimides are unstable in the presence of strong acids and bases, and are apt to polymerize and decompose. Thus, an efficient, economical and environmentally benign Lewis acid catalyst is highly desirable for this process. Recently, our group has been interested in the synthesis of indolylmaleimides and related derivatives.[9] Herein, we report an efficient synthetic strategy toward 3-aminomaleimides and 3-amino-4-indoylmaleimides through Cu/Ag cocatalyzed aerobic oxidative amination of maleimides. In addition, the treatment of maleimides with primary amines using one equivalent of $CuCl_2$ leads to the formation of 3-amino-4-chloromaleimides (Scheme 1, Procedure C).

Results and Discussion

Initially, N-phenylmaleimide **1a** and piperidine **2a** were chosen as model substrates to optimize the reaction conditions. Ag_2CO_3 or $Cu(OAc)_2$ were chosen as catalysts. The reactions were performed at 120℃ for 12 hours (monitoring by TLC) opening to the air. The results were shown in Table 1. Fortunately, with solely 0.2 equivalent of Ag_2CO_3 or $Cu(OAc)_2$ in the system, both of oxidative amination and Michael addition reactions could proceed. 1-Phenyl-3-(piperidin-1-yl)-1*H*-pyrrole-2,5-dione **3a** and 1-phenyl-3-(piperidin-1-yl)pyrrolidine-2,5-dione **4a** were obtained in moderate yields (entries 1, 3). None of $Cu(OAc)_2.H_2O$, CuI, $CuCl_2$, $FeCl_3$, I_2, $FeCl_2.4H_2O$, $CoCl_2.6H_2O$ or $NiCl_2.6H_2O$ could give much better selectivity for the synthesis of **3a** (entries 5-12). Several parameters were altered in an attempt to improve the

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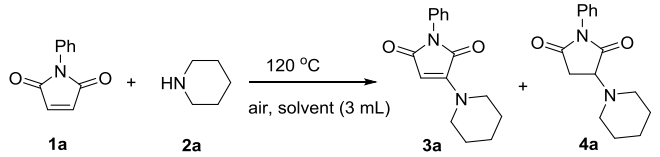
yield of desired product. We found that increasing the dosage of Ag_2CO_3 or $Cu(OAc)_2$ to 1 equivalent, the oxidative amination product **3a** yielded 83% and 85%, respectively. Michael addition product **4a** could hardly be isolated (entries 2, 4). When the reaction was performed under a N_2 atmosphere in the presence of 0.2 equivalent of $Cu(OAc)_2$, the yield of product **4a** could be improved, while the oxidative amination product **3a** was obtained with 18% yield (entry 13). It could be indicated that oxygen played an important role in the oxidative amination reactions (entries 13, 14). Interestingly, when 0.2 equivalent of $Cu(OAc)_2$ worked with 0.2 equivalent of Ag_2CO_3, only the oxidative amination product **3a** could be obtained with 92% yield and the reaction could be completed within 2 hours (entry 15). Taking the place of Ag_2CO_3 with 0.4 equivalent of $AgNO_3$, the yield of **3a** reduced to 78% (entry 16). Reducing the temperature to 80℃ leads to long reaction time and decreased the yield of product **3a** (entry 17). The reactions proceeded in DMF, DMSO and 1,4-dioxane lead to lower yields (entries 18-20). The above result demonstrated that $Cu(OAc)_2/Ag_2CO_3$ are more effective catalysts. It should be noted that, without any catalyst or oxidant, only Michael addition product **4a** could be obtained in about 80% (entry 21).

Table 1. Optimization of reaction conditions [a]

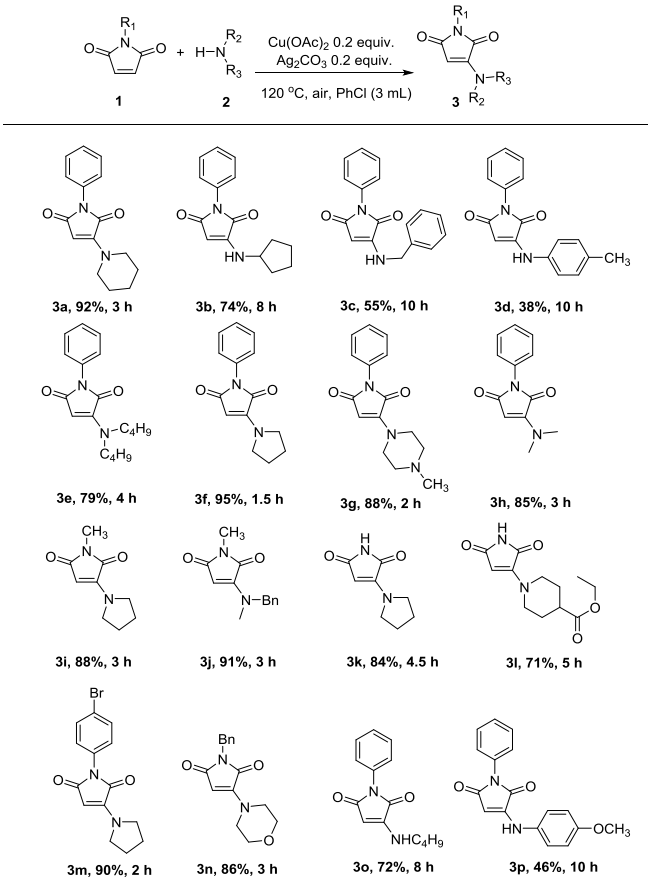


Entry	Catalyst [equiv.]	Time [h]	Solvent	Yield[b][%] 3a	4a
1	Ag_2CO_3(0.2)	12	PhCl	35	46
2	Ag_2CO_3(1)	12	PhCl	83	trace
3	$Cu(OAc)_2$(0.2)	12	PhCl	72	15
4	$Cu(OAc)_2$(1)	12	PhCl	85	trace
5	$Cu(OAc)_2.H_2O$(0.2)	12	PhCl	65	20
6	CuI(0.2)	12	PhCl	28	55
7	$CuCl_2$(0.2)	12	PhCl	42	50
8	$FeCl_3$ (0.2)	12	PhCl	50	10
9	I_2 (0.2)	12	PhCl	32	trace
10	$FeCl_2.4H_2O$ (0.2)	12	PhCl	0	72
11	$CoCl_2.6H_2O$ (0.2)	12	PhCl	0	75
12	$NiCl_2.6H_2O$ (0.2)	12	PhCl	10	65
13[c]	$Cu(OAc)_2$(0.2)	12	PhCl	18	68
14	$Cu(OAc)_2$(0.2)/O_2(ball)	8	PhCl	88	trace
15	$Cu(OAc)_2$(0.2)/Ag_2CO_3(0.2)	2	PhCl	92	0
16	$Cu(OAc)_2$(0.2)/$AgNO_3$(0.4)	5	PhCl	78	trace
17[d]	$Cu(OAc)_2$(0.2)/Ag_2CO_3(0.2)	12	PhCl	80	trace
18	$Cu(OAc)_2$(0.2)/Ag_2CO_3(0.2)	8	DMF	83	trace
19	$Cu(OAc)_2$(0.2)/Ag_2CO_3(0.2)	8	DMSO	81	trace
20	$Cu(OAc)_2$(0.2)/Ag_2CO_3(0.2)	12	Dioxane	66	trace
21		2	PhCl	0	80

[a] Reaction conditions: N-phenylmaleimide **1a** (1.0 mmol), piperidine **2a** (1.1 mmol). [b] Isolated Yield. [c] Under a N_2 atmosphere. [d] 90℃, 12 h.

With the optimized conditions in hand, we set out to investigate the scope of the present Cu/Ag cocatalyzed aerobic oxidative amination of maleimides. A series of 3-aminomaleimides were synthesized from maleimides and amines. All products had been isolated and characterized (see the Supporting Information). The yields and reaction time were summarized in Scheme 2.

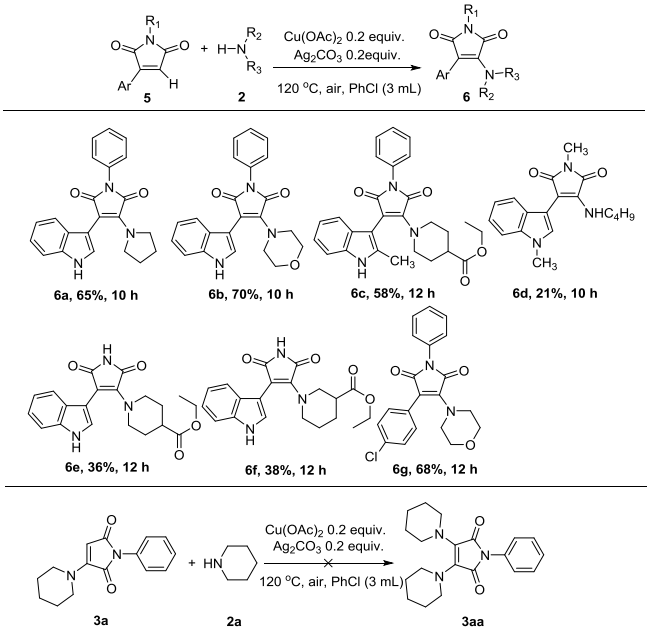
As shown in Scheme 2, various amines, such as secondary amines, primary alkylamines and arylamines, were examined under the optimized reaction conditions. Satisfied yields were obtained from the secondary amines (71%-95%; **3a**, **3e**-**3n**). For the primary alkylamines, this reaction gave moderate yields (55%-74%; **3b**, **3c**, **3o**). But poor yields were obtained using arylamines as substrates (38%-46%; **3d**, **3p**). What's more, these reactions took shorter time using the secondary amines (1.5-5 h) than primary alkyl amines (8-10 h) and arylamines (10 h). And the better yields were obtained using N-substituted maleimides as substrates compared to maleimide (NH) (71%-84%; **3k**-**3l**).



Scheme 2. Scope of Cu/Ag-cocatalyzed oxidative amination of maleimides. Optimal reaction condition: maleimide (1.5 mmol), amine (1.6 mmol), $Cu(OAc)_2$ (0.3 mmol), Ag_2CO_3 (0.3 mmol), PhCl (3 mL), air, 120℃ (isolated yields are given).

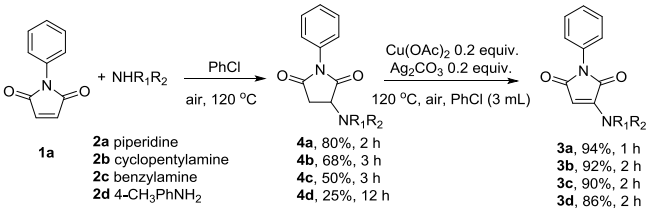
Since the 3-amino-4-indolylmaleimides[1,2c-d] and 3-amino-4-phenylmaleimides[2a-b] exist widely in both natural products and pharmaceuticals, we next explored the scope of this reaction for 3-arylmaleimides **5**, which were synthesized according to our previous work[9] (see the Supporting Information for detail). The corresponding products were also obtained with

moderate yields (21%-70%; **6a**-**6g**, Scheme 3). In addition, the product **3a** could not react with piperidine to yield the corresponding product **3aa** in the protocol (Scheme 3).



Scheme 3. Scope of Cu/Ag-cocatalyzed oxidative amination of 3-arylmaleimides. Optimal reaction condition: maleimide (1.5 mmol), amine (1.6 mmol), $Cu(OAc)_2$ (0.3 mmol), Ag_2CO_3 (0.3 mmol), PhCl (3 mL), air, 120℃ (isolated yields are given).

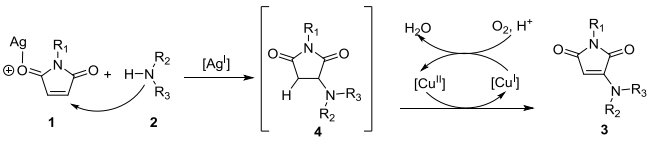
To understand the reaction mechanism, additional experiments were carried out (Scheme 4). Michael addition reactions of amines to maleimides could occur without any catalyst.[10] Michael addition product **4a** was obtained with 80% yields when N-phenylmaleimides was treated with piperidine without any catalyst in the reaction (Table 1, entry 21). Next, we investigated the reactions of cyclopentylamine, benzylamine and 4-methylaniline with N-phenylmaleimide at 120 ℃ in PhCl. Products **4a**-**4d** were isolated in moderate yields after 2-12 h (Scheme 4). They could be further oxidized to products **3a**-**3d** for 1-2 h in good yields (86%-94%) with the optimized protocol.



Scheme 4. Control experiments.

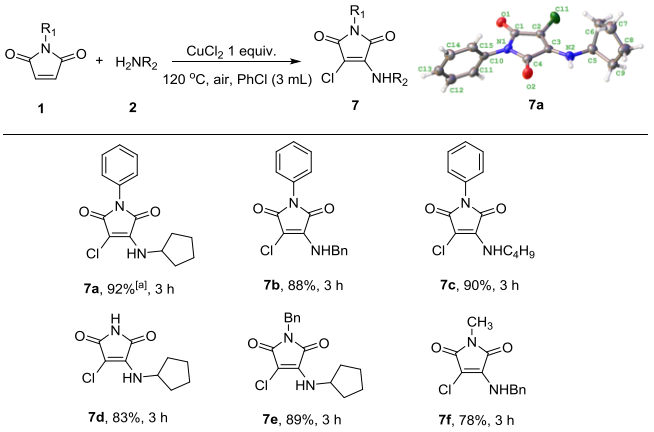
The results suggested Michael addition products **4** could be the intermediates in the aerobic amination reaction. They could be also isolated with Ag_2CO_3 (0.2 equiv) or $Cu(OAc)_2$ (0.2 equiv) as catalyst (Table 1, entry 1, 3). However, this reaction completed within 2 h under Cu/Ag cocatalyzed protocol (Table 1, entry 15). These results indicate (i) a directly aerobic oxidative amination of maleimides possibly proceeds through the sequential reactions; (ii) Michael addition and dehydrogenation oxidative process exist in this reaction.

Based on above evidence, the plausible pathway is proposed in Scheme 5. Initially, Ag(I) coordinated to activate the double bond of maleimides (**1**) followed by the rapid nucleophilic 1,4-addition.[11] The azo-Michael addition of amines (**2**) with malimeids under Ag(I) catalysis would generate intermediates **4**, which are oxidized to the aimed products **3** quickly in the presence of $Cu(OAc)_2$. Cu(I) species in this reaction could be converted into Cu(II) system by O_2 oxidation in the air[12,7f].



Scheme 5. Proposed reaction mechanism for oxidative amination.

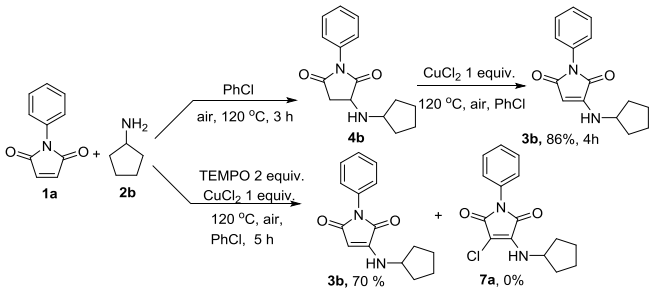
Interestingly, when treatment of maleimide **1** with primary amines **2** in the presence of $CuCl_2$ (1 equiv.) in PhCl at 120℃ for 3 h, chloroamination products **7** were obtained in good yields (Scheme 6). The structure of **7a** was further clearly confirmed by single-crystal X-ray diffraction.



Scheme 6. $CuCl_2$ mediated oxidative chloroamination of maleimides. Optimal reaction conditions: maleimide (1.5 mmol), amine (1.6 mmol), $CuCl_2$ (1.5 mmol), PhCl (3 mL), air, 120℃ (isolated yields are given). [a] In the presence of $CuCl_2$ (0.3 mmol) / Ag_2CO_3 (0.3 mmol) yield **7a** and **3b** 15% and 68%, respectively.

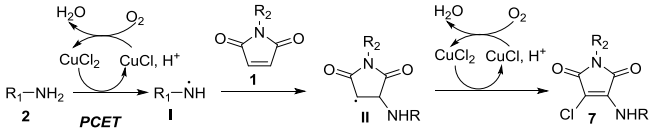
$CuCl_2$ could work as Lewis acid, oxidant and chloride source.[13] However, both oxidative amination and chloroamination products could be isolated in the presence of $CuCl_2$ and Ag_2CO_3 (Scheme 6, Note: a, **7a**, **3b**, 15% and 68%, respectively). Using the secondary amine as substrate in the $CuCl_2$ catalyzed protocol,

only oxidative amination and Michael addition products could be obtained (Table 1, entry 7, **3a**, **4a**, 42% and 50%, respectively). It seems that the nucleophilicity of the amines has an important influence in the $CuCl_2$ mediated chloroamination. And strong nucleophilic agents are apt to the Michael addition in the protocol for oxidative amination products. Only the oxidative amination product **3b** could be isolated from both the azo-Michael addition product **4b** in the $CuCl_2$ mediated protocol and maleimide **1a** and amine **2b** in the $CuCl_2$ mediated protocol in the presence of TEMPO (Scheme 7). It suggested that a general $CuCl_2$ promoted radical procedure occurred in the oxidative chloroamination. [13c-e, 14a] What is more, arylamines mainly provided the aromatic azo products in the presence of $CuCl_2$ and had awful reactivity in the chloroamination protocol.[14]



Scheme 7. Control experiments.

A plausible mechanism for oxidative chloroamination is proposed in Scheme 8. First, the proton-coupled electron transfer from amine **2** to $CuCl_2$ generates radical **I**. [13c-e, 14a] Then, Michael addition occurs to form the intermediate **II**, followed by the oxidative reaction by $CuCl_2$ to provide the final product **7**. Cu(I) species could be converted into Cu(II) system by O_2 in the air[12,7f].



Scheme 8. Proposed reaction mechanism for oxidative choroamination.

Conclusions

In summary, we have successfully developed a novel aerobic oxidative amination of maleimides catalyzed by Cu/Ag cocatalysts. A series of 3-aminomaleimides and 3-amino-4-arylmaleimides could be synthesized in moderate to good yields. However, using one equivalent of $CuCl_2$ in the reaction leads to the formation of 3-amino-4-chloromaleimides by a radical-type mechanism. This method offers the important motifs for the synthesis of 3-aminemaleimides and 3-amino-4-arylmaleimides as natural products, biologically active compounds, and pharmaceutical agents.

Experimental Section

General

Unless otherwise noted, all the materials were purchased from commercial suppliers and used without further purification. Petroleum ether (PE) refers to a hydrocarbon mixture with a boiling range of 60-90℃. TLC was performed on silica gel polygram SILG/UV 254 plates and visualized by quenching of UV fluorescence (λmax = 254 nm). Silica gel (100-200 microns) was used for all chromatographic separations. Melting points were determined with RY-1 apparatus and uncorrected. IR spectra were recorded as KBr pellets on a Shimadzu model 470 spectrophotometer. NMR (^1H and ^{13}C) spectra were recorded using a Bruker AV 400 MHz spectrometer in DMSO-d_6 and $CDCl_3$ with TMS as internal standard. Chemical shifts (δ) were recorded in ppm. Mass spectra were acquired on Waters micromass GCT premier, Agilent technologies 5973N and thermo Fisher scientific LTQ FT Ultra. The X-ray crystal-structure determination of **7a** was obtained on a Bruker SMART APEX II CCD system. All of the products were known compounds, and the data of m.p. and ^1H NMR were in accord with those reported in the literature.

General procedure for oxidative amination of maleimides and amines (synthesis of compound 3a-p and 6a-g).

A mixture of maleimides **1** or **5** (1.5 mmol), amines **2** (1.6 mmol), $Cu(OAc)_2$ (0.3 mmol) and Ag_2CO_3 (0.3 mmol) in 3 mL of PhCl was stirred at 120 ℃ under air. After the reaction completed (monitoring by TLC), the solvent was removed. The residue was fully dissolved in ethyl acetate (30 mL). Filtering out the insoluble substances, the organic phases were washed with H_2O (20 mL×3), dried over Na_2SO_4, concentrated and purified by silica gel column chromatography to yield the pure products **3** or **6**.

1-phenyl-3-(piperidin-1-yl)-1*H*-pyrrole-2,5-dione (3a).[15] Yellow solid; yield: 0.38 g, 92%; R_f = 0.15 (Petrumlem ether/Ethyl acetate 12:1); m.p. 100-102 ℃; IR(KBr): 3100, 2929, 2847, 1701, 1611, 1494, 1445, 1379, 1202, 1113, 741, 697cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.71 (s, 6H), 3.71 (brs, 4H), 5.04 (brs, 1H), 7.32 (t, *J* = 7.6 Hz, 3H), 7.43 (t, *J* = 7.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 24.03(2C), 25.72(2C), 48.79, 88.30, 126.47(2C), 127.31, 128.86(2C), 131.96, 150.00, 166.12, 169.83; MS (ESI): m/z = 257.1 $[M+H]^+$. HRMS (ESI): m/z $[M+H]^+$ calcd $C_{15}H_{17}N_2O_2$ for 257.1285, found 257.1284.

3-(cyclopentylamino)-1-phenyl-1*H*-pyrrole-2,5-dione (3b). Yellow solid; yield: 0.28 g, 74%; R_f = 0.15 (Petrumlem ether/Ethyl acetate 20:1); m.p. 108-110 ℃; IR(KBr): 3326, 3122, 3040, 2953, 2868, 1708, 1644, 1502, 1448, 1392, 1200, 902, 765, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.63–1.85 (m, 6H), 2.06 (dd, *J* = 14.4, 7.4 Hz, 2H), 3.82 (m, 1H), 5.00 (s, 1H),5.52 (s, 1H), 7.36 (dd, *J* = 18.9, 7.7 Hz, 3H), 7.47 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 23.87(2C), 32.54(2C), 55.81, 84.70, 125.94(2C), 127.31, 128.95(2C), 131.91, 148.36, 166.48, 171.14; MS (ESI): m/z = 257.1 $[M+H]^+$. HRMS (ESI): m/z $[M+H]^+$ calcd $C_{15}H_{17}N_2O_2$ for 257.1285, found 257.1284.

3-(benzylamino)-1-phenyl-1*H*-pyrrole-2,5-dione (3c).[4] Yellow solid; yield: 0.23 g, 55%; R_f = 0.15 (Petrumlem ether/Ethyl acetate 15:1); m.p. 110-112 ℃; IR(KBr): 3340, 3116, 3055, 2933, 2866, 1705, 1639, 1497,

1444, 1392, 1203, 1117, 1027, 973, 874, 784, 742, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.39 (d, *J* = 5.0 Hz, 2H), 5.01 (s, 1H), 5.90 (s, 1H), 7.38-7.45 (m, 10H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 48.52, 85.71, 125.90(2C), 127.38, 127.79(2C), 128.39, 128.97(2C), 129.08(2C), 131.82, 135.56, 148.74, 166.35, 171.01; MS (ES): m/z = 278 $[M]^+$, 249, 216, 187, 173, 157, 146, 129, 91, 68.

1-phenyl-3-(p-tolylamino)-1*H*-pyrrole-2,5-dione (3d). Yellow solid; yield: 0.16 g, 38%; R_f = 0.15 (Petrumlem ether/Ethyl acetate 20:1); m.p. 220-222 ℃; IR(KBr): 3314, 3252, 3062, 2930, 1759, 1698, 1619, 1533, 1444, 1404, 1200, 1105, 1029, 910, 811, 777, 737, 686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 5.61 (s, 1H), 7.10 (d, *J* = 7.6 Hz, 2H), 7.23 (d, *J* = 7.7 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 7.5 Hz, 2H), 7.47 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 20.92, 88.46, 119.06(2C), 125.89(2C), 127.57, 129.06(2C), 130.35(2C), 131.68, 134.76, 135.66, 142.67, 167.10, 171.38; MS (ESI): m/z = 279.1 $[M+H]^+$. HRMS (ESI): m/z $[M+H]^+$ calcd $C_{17}H_{15}N_2O_2$ for 279.1128, found 279.1126.

3-(di-n-butylamino)-1-phenyl-1*H*-pyrrole-2,5-dione (3e). Yellow solid; yield: 0.35 g, 79%; R_f = 0.15 (Petrumlem ether/Ethyl acetate 30:1); m.p. 42-44 ℃; IR(KBr): 3114, 3032, 2957, 2868, 1750, 1705, 1613, 1498, 1457, 1381, 1200, 1160, 1115, 926, 767, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.96 (t, *J* = 6.8 Hz, 6H), 1.36 (dd, *J* = 13.9, 6.8 Hz, 4H), 1.64 (s, 4H), 3.23 (s, 2H), 3.82 (s, 2H), 4.95 (s, 1H), 7.32 (dd, *J* = 15.2, 7.6 Hz, 3H), 7.44 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 13.85(2C), 20.13(2C), 27.88, 31.48, 50.16, 53.09, 86.83, 126.44(2C), 127.25, 128.87(2C), 132.03, 149.38, 165.70, 169.96; MS (ESI): m/z = 301.2 $[M+H]^+$. HRMS (ESI): m/z $[M+H]^+$ calcd $C_{18}H_{25}N_2O_2$ for 301.1911, found 301.1910.

1-phenyl-3-(pyrrolidin-1-yl)-1*H*-pyrrole-2,5-dione (3f).[15] Yellow solid; yield: 0.34 g, 95%; R_f = 0.15 (Petrumlem ether/Ethyl acetate 10:1); m.p. 98-100 ℃; IR(KBr): 3100, 3058, 2981, 2875, 1700, 1625, 1501, 1450, 1380, 1344, 1203, 1113, 1034, 947, 774, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.02 (s, 4H), 3.35 (s, 2H), 3.94 (s, 2H), 4.89 (s, 1H), 7.32 (dd, J = 18.4, 7.7 Hz, 3H), 7.43 (t, J = 7.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 24.08, 26.35, 49.11, 50.45, 86.04, 126.30(2C), 127.18, 128.86(2C), 132.12, 148.18, 165.60, 170.42; MS (EI): m/z = 242 $[M]^+$, 213, 186, 170, 158, 145, 119, 95, 77, 69.

3-(4-methylpiperazin-1-yl)-1-phenyl-1*H*-pyrrole-2,5-dione (3g). Yellow solid; yield: 0.36 g, 88%; R_f = 0.15 (Petrumlem ether/Ethyl acetate 1:5); m.p. 120-122 ℃; IR(KBr): 3124, 3045, 2966, 2853, 2793, 1703, 1617, 1498, 1449, 1387, 1293, 1255, 1205, 1129, 1001, 918, 768, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.36 (s, 3H), 2.55 (brs, 4H), 3.78 (brs, 4H), 5.09 (s, 1H),7.32 (d, *J* = 7.3 Hz, 3H), 7.44 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 46.05, 47.10(2C), 54.40(2C), 89.65, 126.45(2C), 127.46, 128.92(2C), 131.77, 149.75, 166.06, 169.60; MS (ESI): m/z = 272.1 $[M+H]^+$. HRMS (ESI): m/z $[M+H]^+$ calcd $C_{15}H_{18}N_3O_2$ for 272.1394, found 272.1393.

3-(dimethylamino)-1-phenyl-1*H*-pyrrole-2,5-dione (3h).[15] Yellow solid; yield: 0.27 g, 85%; R_f = 0.15 (Petrumlem ether/Ethyl acetate 10:1); m.p. 132-134 ℃; IR(KBr): 3100, 3051, 2930, 2805, 1745, 1689, 1624, 1494, 1384, 1303, 1216, 1165, 1110, 934, 781, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.25 (brs, 6H), 4.97 (s, 1H), 7.33 (d, *J* = 7.5 Hz, 3H), 7.44 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 39.69(2C), 87.71, 126.43(2C), 127.33, 128.88(2C), 131.96, 150.47, 165.74, 169.68; MS (EI): m/z = 216 $[M]^+$, 201, 187, 173, 159, 144, 117, 106, 91, 82, 69.

1-methyl-3-(pyrrolidin-1-yl)-1*H*-pyrrole-2,5-dione (3i). Yellow solid; yield: 0.24 g, 88%; R_f = 0.15 (Petrumlem ether/Ethyl acetate 15:1); m.p. 90-92 ℃; IR(KBr): 3102, 2961, 2914, 2874, 1719, 1601, 1444, 1384, 1239, 1132, 943, 861, 768, 681cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.00 (s, 4H), 2.97 (s, 3H), 3.28 (s, 2H), 3.89 (s, 2H), 4.72 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 23.28, 24.08, 26.30, 48.93, 50.21, 85.55, 148.64, 166.92, 171.92; MS (ESI): m/z = 181.1 $[M+H]^+$. HRMS (ESI): m/z $[M+H]^+$ calcd $C_9H_{13}N_2O_2$ for 181.0927, found 181.0927.

3-(benzyl(methyl)amino)-1-methyl-1*H*-pyrrole-2,5-dione (3j). Yellow solid; yield: 0.31 g, 91%; R_f = 0.15 (Petrumlem ether/Ethyl acetate 15:1); m.p. 36-38 ℃; IR(KBr): 2930, 1751, 1699, 1614, 1439, 1384, 1245, 1030, 937, 760, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.98 (s, 3H), 3.20 (s, 3H), 4.90 (s, 2H), 7.21 (d, *J* = 7.1 Hz, 2H), 7.33 (dt, *J* = 21.9, 7.2 Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 23.42, 29.71, 38.84, 88.23, 127.41(2C), 127.86, 128.87(3C), 150.72, 167.18, 171.03; MS (ESI): m/z = 231.1 $[M+H]^+$. HRMS (ESI): m/z $[M+H]^+$ calcd $C_{13}H_{15}N_2O_2$ for 231.1128, found 231.1128.

3-(pyrrolidin-1-yl)-1*H*-pyrrole-2,5-dione (3k). Yellow solid; yield: 0.21 g, 84%; R_f = 0.15 (Petrumlem ether/Ethyl acetate 8:1); m.p. 212-214 ℃; IR(KBr): 3167, 3100, 3019, 2955, 2920, 2866, 1744, 1686, 1617, 1453, 1403, 1331, 1223, 1109, 964, 911, 780, 739, 662 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.01 (s, 4H), 3.30 (s, 2H), 3.89 (s, 2H), 4.73 (s, 1H), 7.29 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 24.09, 26.28, 48.93, 50.31, 86.95, 148.77, 166.99, 171.42; MS (ESI): m/z = 167.1 $[M+H]^+$. HRMS (ESI): m/z $[M+H]^+$ calcd $C_8H_{11}N_2O_2$ for 167.0815, found 167.0815.

Ethyl-1-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)piperidine-4-carboxylate (3l). Yellow solid; yield: 0.27 g, 71%; R_f = 0.15 (Petrumlem ether/Ethyl acetate 3:1); m.p. 110-112 ℃; IR(KBr): 3154, 3106, 3039, 2975, 2869, 2747, 1724, 1622, 1456, 1350, 1312, 1199, 1122, 1039, 975, 889, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.27 (t, *J* = 7.1 Hz, 3H), 1.82 (td, *J* = 14.2, 3.7 Hz, 2H),2.02 (dd, *J* = 13.5, 2.9 Hz, 2H), 2.58 (td, *J* = 10.2, 5.0 Hz, 1H), 3.18 (t, *J* = 11.7 Hz, 2H), 4.17 (q, *J* = 7.1 Hz, 4H), 4.93 (s, 1H),7.37 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.23, 27.63, 40.24(2C), 46.59, 60.86(2C), 90.32, 150.33, 167.41, 170.41, 173.84; MS (ESI): m/z = 253.1 $[M+H]^+$. HRMS (ESI): m/z $[M+H]^+$ calcd $C_{12}H_{17}N_2O_4$ for 253.1183, found 253.1183.

1-(4-bromophenyl)-3-(pyrrolidin-1-yl)-1*H*-pyrrole-2,5-dione (3m). Yellow solid; yield: 0.43 g, 90%; R_f = 0.15 (Petrumlem ether/Ethyl acetate 10:1); m.p. 150-152 ℃; IR(KBr): 3116, 2971, 2875, 1703, 1622, 1486, 1455, 1375, 1278, 1206, 1107, 1037, 943, 820, 754, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.03 (s, 4H), 3.35 (s, 2H),3.95 (s, 2H), 4.89 (s, 1H),7.28 (d, *J* = 8.3 Hz, 2H), 7.56 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 24.09, 26.33, 49.17, 50.54, 86.06, 120.62, 127.59(2C), 131.24, 131.93(2C), 148.16, 165.22, 169.87; MS (ESI): m/z = 321.0 $[M+H]^+$, 323.0$[M+2+H]^+$. HRMS (ESI): m/z $[M+H]^+$ calcd $C_{14}H_{14}N_2O_2Br$ for 321.0233, found 321.0233.

1-benzyl-3-(4-morpholinyl)-1*H*-pyrrole-2,5-dione (3n).[5a] Yellow solid; yield: 0.35 g, 86%; R_f = 0.15 (Petrumlem ether/Ethyl acetate 6:1); m.p. 120-122 ℃; IR(KBr): 3173, 3098, 3016, 2975, 2862, 1743, 1685, 1613, 1449, 1400, 1329, 1216, 1108, 964, 910, 781, 660 cm^{-1}; ^1H NMR (400 MHz, CDCl3): δ 3.70 (s, 4H), 3.79 (s, 4H),4.64 (s, 2H), 4.98 (s, 1H),7.30 (d, *J* = 12.6 Hz, 2H),7.37 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 40.99(2C), 47.14(2C), 66.28, 89.76, 127.59, 128.36(2C), 128.59(2C), 136.83, 150.06, 166.90, 170.34; MS (EI): m/z = 272 $[M]^+$, 254, 241, 229, 215, 201, 181, 163, 151, 140, 123, 106, 91, 77.

3-(n-butylamino)-1-phenyl-1*H*-pyrrole-2,5-dione (3o).[3] Yellow solid; yield: 0.26 g, 72%; R_f = 0.15 (Petrumlem ether/Ethyl acetate 25:1); m.p. 128-130 ℃; IR(KBr): 3260, 3112, 3032, 2959, 2859, 1700, 1616, 1521, 1453, 1399, 1293, 1207, 1062, 890, 777, 694, 656 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.97 (t, *J* = 7.3 Hz, 3H), 1.48–1.38 (m, 2H), 1.70–1.62 (m,

2H), 3.24 (q, *J* = 6.7 Hz, 2H), 4.97 (s, 1H), 5.55 (s, 1H), 7.41–7.29 (m, 3H), 7.44 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 13.72, 20.06, 30.57, 44.13, 84.11, 125.92(2C), 127.34, 128.97(2C), 131.85, 149.12, 166.36, 171.19; MS (EI): m/z = 244 $[M]^+$, 215, 201, 187, 173, 160, 146, 124, 106, 97, 77, 68.

3-((4-methoxyphenyl)amino)-1-phenyl-1*H*-pyrrole-2,5-dione (3p). Yellow solid; yield: 0.20 g, 46%; R_f = 0.15 (Petrumlem ether/Ethyl acetate 15:1); m.p. 184-186 ℃; IR(KBr): 3305, 3257, 3066, 2914, 2839, 1755, 1699, 1618, 1549, 1508, 1450, 1404, 1247, 1112, 1031, 823, 767, 739, 687 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.84 (s, 3H), 5.55 (s, 1H), 6.96 (d, *J* = 8.5 Hz, 2H), 7.16 (d, *J* = 8.2 Hz, 2H), 7.30 (s, 1H), 7.36 (t, *J* = 7.3 Hz, 1H), 7.41 (d, *J* = 7.8 Hz, 2H), 7.48 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 55.62, 87.46, 115.02(2C), 120.83(2C), 125.91(2C), 127.59, 129.09(2C), 131.17, 131.64, 143.14, 156.90, 167.03, 171.46; MS (ESI): m/z = 295.1 $[M+H]^+$. HRMS (ESI): m/z $[M+H]^+$ calcd $C_{17}H_{15}N_2O_3$ for 295.1077, found 295.1077.

3-(1*H*-indol-3-yl)-1-phenyl-4-(pyrrolidin-1-yl)-1*H*-pyrrole-2,5-dione (6a). Orange solid; yield: 0.35 g, 65%; R_f = 0.15 (Petrumlem ether/Ethyl acetate 8:1); m.p. 208-210 ℃; IR(KBr): 3315, 3054, 2965, 2874, 1749, 1694, 1627, 1538, 1495, 1440, 1387, 1244, 1198, 1100, 938, 742, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.78 (s, 4H), 3.61 (s, 4H), 7.20–7.08 (m, 3H), 7.32 (d, *J* = 7.9 Hz, 2H),7.45 (d, *J* = 4.1 Hz, 4H), 7.53 (d, *J* = 7.5 Hz, 1H), 8.47 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 25.26(2C), 50.65(2C), 94.01, 105.98, 111.29, 119.95, 120.08, 122.12, 125.73, 126.25(2C), 127.03, 128.82(2C), 129.87, 132.41, 135.45, 143.42, 166.45, 171.16; MS (ESI): m/z = 358.2 $[M+H]^+$. HRMS (ESI): m/z $[M+H]^+$ calcd $C_{22}H_{20}N_3O_2$ for 358.1550, found 358.1548.

3-(1*H*-indol-3-yl)-4-(4-morpholinyl)-1-phenyl-1*H*-pyrrole-2,5-dione (6b). Orange solid; yield: 0.39 g, 70%; R_f = 0.15 (Petrumlem ether/Ethyl acetate 4:1); m.p. 124-126 ℃; IR(KBr): 3356, 3056, 2965, 2917, 2855, 1754, 1700, 1628, 1532, 1497, 1386, 1268, 1235, 1111, 1020, 927, 851, 744, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.67 (s, 8H), 7.20 (dd, *J* = 16.9, 8.3 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 7.43 (dt, *J* = 14.8, 7.1 Hz, 5H), 7.59 (d, *J* = 7.6 Hz, 1H), 8.54 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 48.53(2C), 67.06(2C), 101.44, 105.43, 111.55, 120.30, 120.51, 122.65, 125.68, 126.31(2C), 127.35, 127.70, 128.92(2C), 132.02, 135.72, 142.08, 167.30, 170.28; MS (ESI): m/z = 374.1 $[M+H]^+$. HRMS (ESI): m/z $[M+H]^+$ calcd $C_{22}H_{20}N_3O_3$ for 374.1499, found 374.1497.

Ethyl-1-(4-(2-methyl-1*H*-indol-3-yl)-2,5-dioxo-1-phenyl-2,5-dihydro-1*H*-pyrrol-3-yl)piperidine-4-carboxylate (6c). Orange solid; yield: 0.40 g, 58%; R_f = 0.15 (Petrumlem ether/Ethyl acetate 5:1); m.p. 88-90 ℃; IR(KBr): 3353, 3054, 2975, 2933, 2950, 1697, 1625, 1551, 1496, 1455, 1387, 1318, 1185, 1105, 1040, 920, 861, 744, 691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 1.24 (t, J = 6.9 Hz, 3H), 1.92–1.62 (m, 5H), 2.39 (s, 3H), 3.17–2.99 (m, 2H), 4.02 (d, *J* = 11.2 Hz, 1H), 4.12 (dd, *J* = 13.8, 6.8 Hz, 2H), 4.45 (d, *J* = 10.3 Hz, 1H), 7.12 (dd, *J* = 13.7, 6.7 Hz, 2H), 7.27 (s, 1H), 7.41–7.33 (m, 2H), 7.46 (s, 4H), 8.23 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 13.18, 14.18, 28.52, 40.53, 47.36, 60.60, 99.49, 102.90, 110.55, 119.02, 120.12, 121.56, 126.24, 127.15, 128.84, 129.30, 132.20, 135.13, 135.39, 144.44, 167.06, 169.94, 174.21; MS (ESI): m/z = 458.2 $[M+H]^+$. HRMS (ESI): m/z $[M+H]^+$ calcd $C_{27}H_{28}N_3O_4$ for 458.2074, found 458.2072.

3-(n-butylamino)-1-methyl-4-(1-methyl-1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (6d). Orange solid; yield: 0.10 g, 21%; R_f = 0.15 (Petrumlem ether/Ethyl acetate 10:1); m.p. 134-136 ℃; IR(KBr): 3330, 3100, 3052, 2952, 2869, 1753, 1700, 1655, 1546, 1449, 1384, 1337, 1294, 1241, 1104, 1055, 995, 819, 746, 686 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.72 (t, *J* = 7.2 Hz, 3H), 1.20–1.07 (m, 2H), 1.42–1.32 (m, 2H), 3.09 (s, 3H), 3.16 (t, *J* = 6.7 Hz, 2H), 3.85 (s, 3H), 5.19 (s, 1H), 7.21–7.10 (m, 2H),7.28–7.23 (m, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.52 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 13.49, 19.58, 23.92, 32.20, 33.02, 43.40, 93.61, 103.35, 109.38, 119.69, 120.15, 121.89, 129.02, 129.40, 136.57, 142.82, 168.62, 173.08; MS (ESI): m/z = 312.2 $[M+H]^+$. HRMS (ESI): m/z $[M+H]^+$ calcd $C_{18}H_{22}N_3O_2$ for 312.1707, found 312.1705.

Ethyl-1-(4-(1*H*-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl) piperidine-4-carboxylate (6e). Orange solid; yield: 0.19 g, 36%; R_f = 0.15 (Petrumlem ether/Ethyl acetate 1:3); m.p. 164-166 ℃; IR(KBr): 3320, 3052, 2969, 2857, 1700, 1623, 1533, 1444, 1343, 1184, 1097, 1039, 938, 895, 746, 659 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, *J* = 7.0 Hz, 3H), 1.86–1.70 (m, 4H), 2.44 (d, *J* = 8.5 Hz, 1H), 3.07 (t, *J* = 12.0 Hz, 2H), 4.23–4.08 (m, 4H), 7.28–7.09 (m, 3H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 7.5 Hz, 1H) , 7.58 (s, 1H), 8.69 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.18, 28.36(2C), 40.52, 47.58(2C), 60.63, 101.32, 105.60, 111.53, 120.07, 120.29, 122.42, 125.40, 127.82, 135.81, 143.48, 168.52, 171.49, 174.28; MS (EI): m/z = 367 $[M]^+$, 338, 322, 294, 266, 252, 238, 227, 212, 195, 184, 168, 155, 140, 128. HRMS (EI): m/z $[M]^+$ calcd $C_{20}H_{21}N_3O_4$ for 367.1532, found 367.1530.

Ethyl-1-(4-(1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)piperidine-3-carboxylate (6f). Orange solid; yield: 0.20 g, 38%; R_f = 0.15 (Petrumlem ether/Ethyl acetate 1:2); m.p. 182-184 ℃; IR(KBr): 3312, 3051, 2939, 2856, 1700, 1624, 1533, 1442, 1343, 1267, 1232, 1183, 1106, 1018, 915, 861, 745, 659 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (t, *J* = 6.9 Hz, 3H), 1.50 (dd, *J* = 22.4, 10.8 Hz, 1H), 1.70–1.59 (m, 2H), 2.00 (d, *J* = 11.4 Hz, 1H), 2.59 (s, 1H), 3.08 (t, *J* = 11.6 Hz, 1H), 3.30 (t, *J* = 11.4 Hz, 1H), 3.84 (d, *J* = 12.7 Hz, 1H), 4.09 (q, *J* = 6.7 Hz, 2H), 4.28 (d, *J* = 13.1 Hz, 1H), 7.24–7.12 (m, 3H), 7.34 (d, *J* = 7.7 Hz, 1H) , 7.49 (d, *J* = 7.5 Hz, 1H),7.66 (s, 1H), 8.77 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.09, 24.67, 26.82, 41.68, 48.68, 49.88, 60.64, 101.79, 105.44, 111.55, 120.01, 120.24, 122.36, 125.48, 127.74, 135.86, 143.57, 168.52, 171.62, 173.10; MS (EI): m/z = 367 $[M]^+$, 338, 322, 294, 266, 252, 238, 227, 212, 195, 184, 168, 155, 140, 128. HRMS (EI): m/z $[M]^+$ calcd $C_{20}H_{21}N_3O_4$ for 367.1532, found 367.1535.

3-(4-chlorophenyl)-4-(4-morpholinyl)-1-phenyl-1*H*-pyrrole-2,5-dione (6g). Orange solid; yield: 0.37 g, 68%; R_f = 0.15 (Petrumlem ether/Ethyl acetate 12:1); m.p. 134-136 ℃; IR(KBr): 3056, 2965, 2901, 2855, 1751, 1702, 1623, 1495, 1430, 1388, 1276, 1162, 1109, 1021, 950, 915, 851, 787, 749, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.60 (s, 4H), 3.74 (s, 4H), 7.35 (dd, *J* = 20.3, 7.0 Hz, 6H), 7.45 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 49.37(2C), 66.79(2C), 104.41, 126.29(2C), 127.57, 128.45(2C), 128.95(3C), 131.49(2C), 131.68, 133.91, 143.09, 166.50, 169.39; MS (ESI): m/z = 369.1 $[M+H]^+$, 371.1 $[M+2+H]^+$. HRMS (ESI): m/z $[M+H]^+$ calcd $C_{20}H_{18}N_2O_3Cl$ for 369.1000, found 369.1000.

General procedure for Michael addition of malmeimides with amines (synthesis of compounds 4a-d).

A mixture of N-phenylmaleimide **1a** (0.34 g, 2.0 mmol) and amines 2 (2.1 mmol) in 3 mL of PhCl was stirred at 120 ℃ under air condition. After the reaction completed (monitoring by TLC), the solvent was removed. The residue was fully dissolved in ethyl acetate (30 mL). Filtering out the insoluble substances, the organic phases were washed with H_2O (20 mL×3), dried (Na_2SO_4), concentrated and purified by silica gel column chromatography (eluent: ethyl acetate–PE, 1: 3) to yield the pure product **4**.

1-phenyl-3-(piperidin-1-yl)-2,5-pyrrolidinedione (4a).[10] White solid; yield: 0.41 g, 80%; R_f = 0.15 (Petrumlem ether/Ethyl acetate 1:1); m.p. 116-118 ℃; IR(KBr): 3059, 2926, 2846, 2804, 1777, 1696, 1597, 1494, 1448, 1377, 1273, 1202, 1159, 1107, 897, 847, 746, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.51 (d, *J* = 3.9 Hz, 2H), 1.66 (d, *J* = 4.7 Hz, 4H),

2.68–2.53 (m, 2H), 2.85 (dd, *J* = 17.6, 3.9 Hz, 3H), 3.05 (dd, *J* = 18.6, 9.1 Hz, 1H), 3.96 (dd, *J* = 8.7, 4.3 Hz, 1H), 7.29 (d, *J* = 7.0 Hz, 2H), 7.42 (t, *J* = 7.3 Hz, 1H), 7.49 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 24.02, 26.03, 32.04, 50.25, 63.15, 126.51, 128.72, 129.20, 131.56, 174.50, 175.39; MS (ESI): m/z = 259.1 $[M+H]^+$. HRMS (ESI): m/z $[M+H]^+$ calcd $C_{15}H_{19}N_2O_2$ for 259.1441, found 259.1441.

3-(cyclopentylamino)-phenyl-2,5-pyrrolidinedione (4b). White solid; yield: 0.35 g, 68%; R_f = 0.15 (Petrumlem ether/Ethyl acetate 3:1); m.p. 114-116 ℃; IR(KBr): 3283, 3060, 2950, 2901, 2861, 1702, 1543, 1500, 1457, 1392, 1178, 883, 746, 695, 626 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (d, *J* = 4.8 Hz, 2H), 1.59 (s, 2H), 1.74 (s, 2H), 1.93 (s, 2H), 2.03 (s, 1H), 2.76 (dd, *J* = 17.6, 2.4 Hz, 1H), 3.11 (dd, *J* = 17.8, 8.1 Hz, 1H), 3.30–3.18 (m, 1H), 3.97 (s, 1H), 7.28 (d, *J* = 7.6 Hz, 2H), 7.40 (d, *J* = 6.7 Hz, 1H), 7.47 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 23.61, 23.88, 32.79, 33.65, 37.55, 55.80, 59.08, 126.36(2C), 128.73, 129.22(2C), 131.63, 174.40, 177.20; MS (ESI): m/z = 259.1 $[M+H]^+$. HRMS (ESI): m/z $[M+H]^+$ calcd $C_{15}H_{19}N_2O_2$ for 259.1441, found 259.1440.

3-(benzylamino)-1-phenyl-2,5-pyrrolidinedione (4c).[16] White solid; yield: 0.28 g, 50%; R_f = 0.15 (Petrumlem ether/Ethyl acetate 4:1); m.p. 92-94 ℃; IR(KBr): 3320, 3071, 3026, 2930, 2849, 1783, 1712, 1596, 1495, 1455, 1383, 1325, 1185, 1030, 747, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.44 (s, 1H), 2.72 (d, *J* = 17.9 Hz, 1H), 3.04 (dd, *J* = 17.9, 8.3 Hz, 1H), 4.02–3.88 (m, 3H), 7.28 (d, *J* = 7.3 Hz, 3H), 7.43–7.34 (m, 5H), 7.47 (t, *J* = 6.7 Hz, 2H); ^{13}C NMR (101 MHz, CDCl3): δ 36.63, 51.97, 55.60, 126.34(2C), 127.67, 128,37(2C), 128.76(3C), 129.23(2C), 131.57, 138.60, 174.20, 176.92; MS (ESI): m/z = 281.1 $[M+H]^+$. HRMS (ESI): m/z $[M+H]^+$ calcd $C_{17}H_{17}N_2O_2$ for 281.1285, found 281.1282.

3-[(4-methylphenyl)amino]-1-phenyl-2,5-pyrrolidinedione (4d). White solid; yield: 0.14 g, 25%; R_f = 0.15 (Petrumlem ether/Ethyl acetate 8:1); m.p. 188-190 ℃; IR(KBr): 3369, 3335, 2920, 1770, 1699, 1620, 1510, 1450, 1398, 1289, 1194, 1117, 1005, 944, 866, 806, 739, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.31 (s, 3H), 2.87 (dd, *J* = 17.9, 5.2 Hz, 1H), 3.44 (dd, *J* = 17.9, 8.2 Hz, 1H), 4.55 – 4.44 (m, 1H), 6.63 (d, *J* = 7.5 Hz, 2H), 7.10 (d, *J* = 7.5 Hz, 2H), 7.36 (d, *J* = 7.5 Hz, 2H), 7.46 (d, *J* = 8.2 Hz, 1H), 7.53 (t, *J* = 7.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 20.48, 38.39, 53.39, 114.19(2C), 126.32(2C), 128.94(2C), 129.15, 129.32(2C), 130.08(2C), 131.49, 143.67, 173.64, 176.09; MS (ESI): m/z = 281.1 $[M+H]^+$. HRMS (ESI): m/z $[M+H]^+$ calcd $C_{17}H_{17}N_2O_2$ for 281.1285, found 281.1283.

General procedure for chloroamination of malmeimides with primary amines (synthesis of compounds 7a-f).

A mixture of maleimide **1** (1.5 mmol), primary amines **2** (1.6 mmol), and $CuCl_2$ (0.20 g, 1.5 mmol) in 3 mL of PhCl was stirred at 120 ℃ under air condition. After the reaction completed (monitoring by TLC), the solvent was removed. The residue was fully dissolved in ethyl acetate (30 mL). Filtering out the insoluble substances, the organic phases were washed with H_2O (20 mL× 3), dried over Na_2SO_4, concentrated and purified by silica gel column chromatography (eluent: ethyl acetate–PE, 1: 30) to yield the pure product **7**.

3-chloro-4-(cyclopentylamino)-1-phenyl-1*H*-pyrrole-2,5-dione (7a). Yellow solid; yield: 0.40 g, 92%; R_f = 0.15 (Petrumlem ether/Ethyl acetate 25:1); m.p. 130-132 ℃; IR(KBr): 3322, 2961, 2870, 1768, 1717, 1664, 1594, 1500, 1451, 1402, 1266, 1211, 1098, 992, 788, 739, 691 cm^{-1}; ^{1}H NMR (400 MHz, CDCl3): δ 1.72 (ddd, *J* = 33.6, 16.2, 6.7 Hz, 6H), 2.18–2.09 (m, 2H), 4.51 (dd, *J* = 12.8, 6.3 Hz, 1H), 5.46 (d, *J* = 6.3 Hz, 1H), 7.43–7.32 (m, 3H), 7.47 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 23.90(2C), 34.86(2C), 54.68, 89.36, 125.76(2C), 127.67, 129.06(2C), 131.48, 139.72, 164.68, 166.63; MS (ESI): m/z = 293.1$[M+2+H]^+$, 291.1 $[M+H]^+$. HRMS (ESI): m/z $[M+H]^+$ calcd $C_{15}H_{16}N_2O_2Cl$ for 291.0895, found 291.0895.

3-chloro-4-(benzylamino)-1-phenyl-1*H*-pyrrole-2,5-dione (7b). Yellow solid; yield: 0.41 g, 88%; R_f = 0.15 (Petrumlem ether/Ethyl acetate 20:1); m.p. 106-108 ℃; IR(KBr): 3333, 3034, 2933, 1772, 1720, 1665, 1591, 1503, 1448, 1394, 1264, 1214, 1101, 1038, 929, 786, 741, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.87 (d, *J* = 6.3 Hz, 2H), 5.71 (s, 1H), 7.38–7.32 (m, 5H), 7.76–7.39 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 47.14, 90.59, 125.74(2C), 127.70(2C), 127.76, 128.36, 129.10(2C), 129.13(2C), 131.37, 136.90, 139.79, 164.55, 166.45; MS (ESI): m/z = 315.1$[M+2+H]^+$, 313.1 $[M+H]^+$. HRMS (ESI): m/z $[M+H]^+$ calcd $C_{17}H_{14}N_2O_2Cl$ for 313.0738, found 313.0738.

3-(butylamino)-4-chloro-1-phenyl-1*H*-pyrrole-2,5-dione (7c). Yellow solid; yield: 0.37 g, 90%; R_f = 0.15 (Petrumlem ether/Ethyl acetate 35:1); m.p.: 82-84 ℃; IR(KBr): 3326, 3055, 2957, 2866, 1715, 1668, 1517, 1460, 1402, 1271, 1219, 1099, 984, 915, 783, 740, 687, 628 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, J = 7.1 Hz, 3H), 1.50–1.39 (m, 2H), 1.72–1.63 (m, 2H), 3.67 (q, *J* = 6.5 Hz, 2H), 5.50 (s, 1H), 7.41–7.29 (m, 3H), 7.44 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 13.71, 19.70, 32.86, 43.03, 89.39, 125.72(2C), 127.66, 129.05(2C), 131.47, 140.24, 164.62, 166.58; MS (EI): m/z = 280$[M+2]^+$, 278$[M]^+$, 251, 249, 237, 235, 222, 207, 194, 180, 164, 146, 131, 119, 104, 88, 77, 57; HRMS (EI): m/z $[M]^+$ calcd $C_{14}H_{15}N_2O_2Cl$ for 278.0822, found 278.0827.

3-chloro-4-(cyclopentylamino)-1*H*-pyrrole-2,5-dione (7d). Yellow solid; yield: 0.27 g, 83%,; R_f = 0.15 (Petrumlem ether/Ethyl acetate 10:1); m.p.: 140-142 ℃; IR(KBr): 3319, 3171, 3055, 2962, 2866, 1766, 1709, 1650, 1508, 1350, 1163, 1034, 966, 912, 741, 710, 646 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63–1.52 (m, 2H), 1.81–1.64 (m, 4H), 2.08 (d, *J* = 6.0 Hz, 2H), 4.43 (d, *J* = 5.8 Hz, 1H), 5.29 (s, 1H), 7.48 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 23.86(2C), 34.81(2C), 54.49, 89.79, 140.39, 165.36, 167.36; MS (EI): m/z = 216$[M+2]^+$, 214$[M]^+$, 187, 185, 172, 146, 108, 87, 68; HRMS (EI): m/z $[M]^+$ calcd $C_9H_{11}N_2O_2Cl$ for 214.0509, found 214.0507.

1-benzyl-3-chloro-4-(cyclopentylamino)-1*H*-pyrrole-2,5-dione (7e). Yellow solid; yield: 0.40 g, 89%; R_f = 0.15 (Petrumlem ether/Ethyl acetate 50:1); m.p.: 84-86 ℃; IR(KBr): 3324, 3026, 2957, 2870, 1766, 1713, 1656, 1507, 1438, 1403, 1350, 1258, 1171, 1077, 895, 738, 698, 623 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (dd, *J* = 12.1, 5.8 Hz, 2H), 1.68 (dt, *J* = 24.3, 11.8 Hz, 4H), 2.05 (dd, *J* = 11.9, 5.6 Hz, 2H), 4.39 (dd, *J* = 13.0, 6.5 Hz, 1H), 4.64 (s, 2H), 5.25 (s, 1H), 7.38–7.26 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 23.85(2C), 34.80(2C), 41.90, 54.55, 88.83, 127.85, 128.49(2C), 128.66(2C), 136.22, 139.92, 165.45, 167.54; MS (EI): m/z = 306$[M+2]^+$,304$[M]^+$, 275, 236, 213, 197, 173, 159, 106, 91, 69, 51; HRMS (EI): m/z $[M]^+$ calcd $C_{16}H_{17}N_2O_2Cl$ for 304.0979, found 304.0978.

3-(benzylamino)-4-chloro-1-methyl-1*H*-pyrrole-2,5-dione (7f).[17] Yellow solid; yield: 0.29 g, 78%; R_f = 0.15 (Petrumlem ether/Ethyl acetate 30:1); m.p.: 122-124 ℃; IR(KBr): 3318, 2937, 1713, 1656, 1512, 1447, 1383, 1261, 1167, 1088, 985, 908, 860, 739, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.02 (s, 3H), 4.80 (d, *J* = 6.2 Hz, 2H), 5.54 (s, 1H), 7.31 (d, *J* = 7.2 Hz, 2H), 7.37 (dt, *J* = 13.0, 6.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.28, 47.06, 127.61(2C), 90.03, 128.27, 129.08(2C), 137.02, 140.08, 165.73, 167.81; MS (EI): m/z = 252 $[M+2]^+$, 250$[M]^+$, 215, 183, 156, 125, 103, 91, 77, 65, 51.

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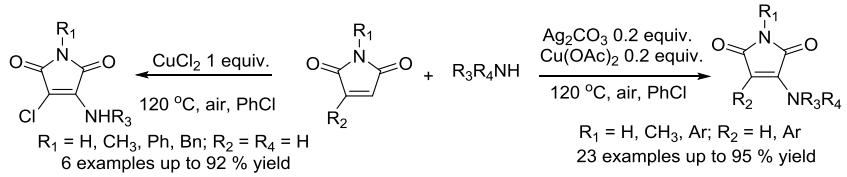

A novel aerobic oxidative amination of maleimides catalyzed by Cu/Ag cocatalysts and aerobic oxidative chloroamination of maleimides mediated by $CuCl_2$ have been developed. A series of 3-aminomaleimides, 3-amino-4-indolylmaleimides and 3-amino-4-chloromaleimides have been synthesized with satisfied yields.

*Oxidative amination and chloroamination

*Yu-Long an, He-Hui Zhang, Zhen-Hua Yang, Long Lin, and Sheng-Yin Zhao**

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Cu/Ag cocatalyzed aerobic oxidative amination and $CuCl_2$ mediated aerobic oxidative chloroamination of maleimides