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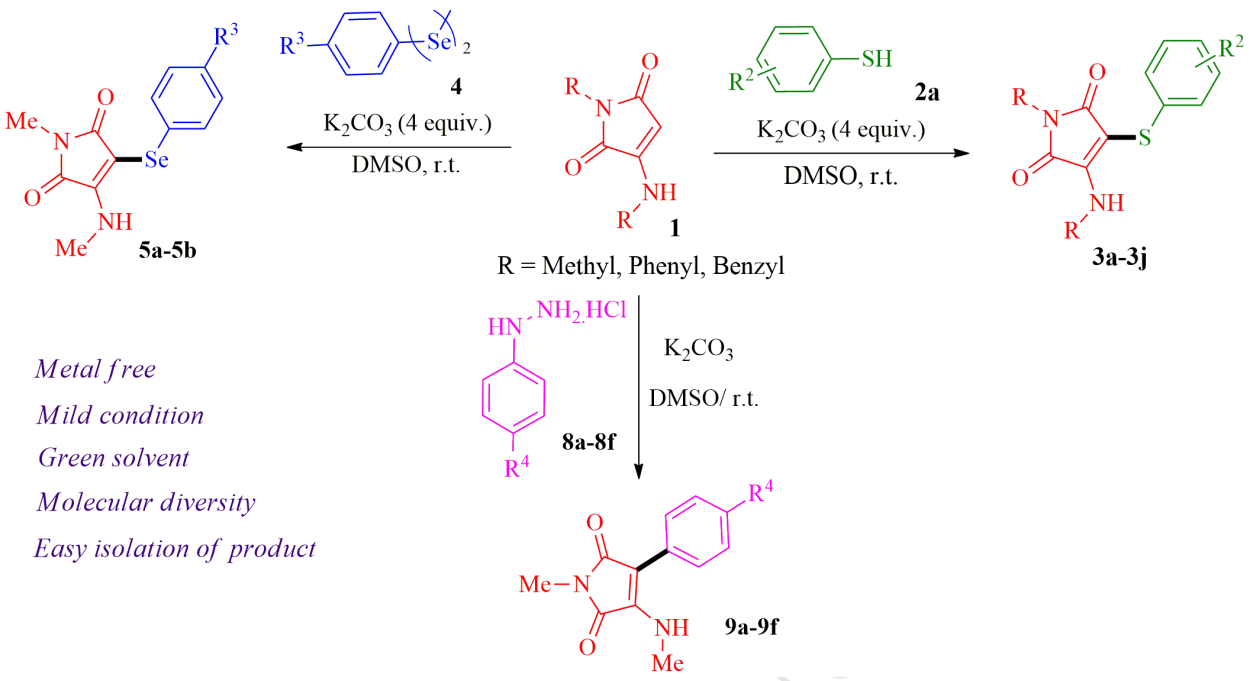

Metal free

Mild condition

Green solvent

Molecular diversity

Easy isolation of product

Transition metal free K_2CO_3 mediated thioarylation, selenoarylation and arylation of 2-aminomaleimides at ambient temperature

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Abstract

Transition metal free thioarylation, selenoarylation and arylation of 2-aminomaleimide, using thiophenols, diaryl diselenides and arylhydrazine hydrochlorides respectively, has been reported in DMSO under aerobic condition in presence of K_2CO_3 at room temperature. The reaction occurs smoothly without prerequisite N-protection of 2-aminomaleimide. The synthesis of novel, polyfunctionalized maleimides has been achieved by the direct C−H activation of enamines. Thioarylation and selenoarylation are proposed to be proceeding *via* disulfides/ diselenides and arylation has been proposed to be proceeding *via* aryl free radicals.

Keywords: 2-aminomaleimide; thioarylation; selenoarylation; arylation; thiophenols; arylhydrazine hydrochlorides; K_2CO_3/DMSO

Introduction

Maleimide is a very versatile motif in medicinal chemistry. Maleimide analogues, in conjunction with other heterocycles, have shown significant biological applications as potent selective GSK-3β inhibitors and neuroprotective agents (I),[1] anticancer drug (carboplatin) (II),[2] rhenium (I) pyridine maleimide complex for biological labeling (III),[3] PARP-1 [poly(ADP-ribose)polymerase-1] inhibitors (IV),[4] COX-2 inhibitors and anti-inflammatory agents (V) (Figure 1).[5] A variety of maleimide derivatives have also found applications as bioimaging probes for thiols and also as fluorescent & colorimetric chemosensors.[6]

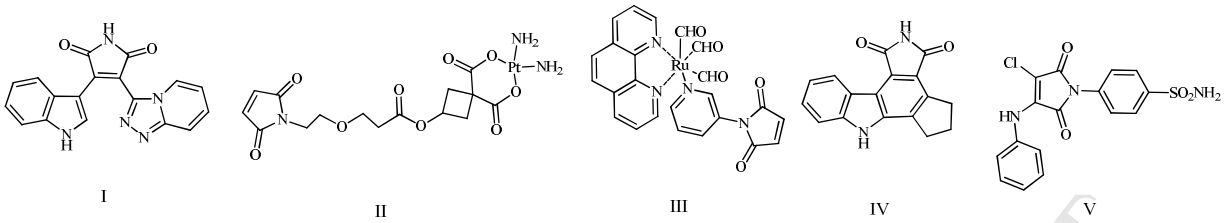


Figure 1. Some biologically active maleimides.

Over last several decades, various synthetic methods have been developed for the formation of complex molecules *via* CDC (Cross-Dehydrogenating Coupling) reaction between C–H and thiolating/ sulfenylating reagents. Di□erent thiolating/ sulfenylating reagents have been used in these protocols such as arylthiols, arylsulfonyl hydrazides, arylsulfonyl chlorides, sodium sulfinates, diaryldisulfides and 1-(substituted-phenylthio)-pyrrolidine-2,5-diones. These reactions require the synthesis of sulfenylating reagents initially.[7] Synthesis of arylsulfides *via* C–H functionalization using arylthiols as sulfenylating agents under metal-free conditions has not been explored significantly. Sulfenylation of compounds like indoles, naphthols, N,N-dimethyl aniline, 4-hydroxy coumarins, pyrazolones, 6-aminouracil, acetophenone and oxadiazoles using simple and eco-friendly reagents *viz.* I_2/BSA,[8a] K_2CO_3/DMSO,[8b] I_2/DMSO,[8c] N-chlorosuccinimide,[8d] I_2/DMSO,[8e] Cs_2CO_3[8f] and $KClO_3$/ethylactate[8g] has been reported in literature.

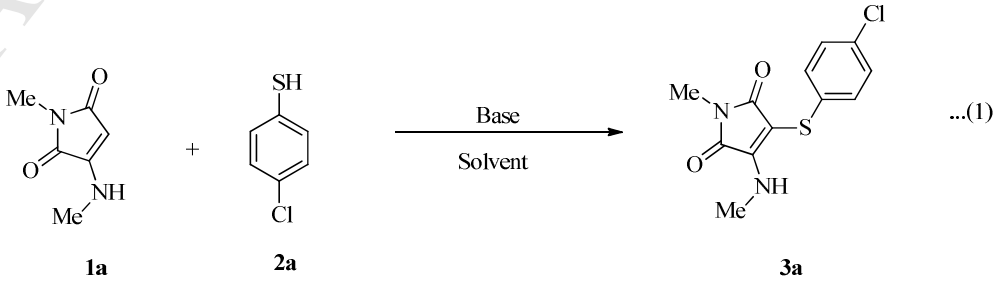
Transition metal catalyzed C-heteroatom bond formation, such as C-N, C-S and C-P bond formation *via* alkene C-H activation, has been extensively used in recent years.[9] With increasing environmental concerns, the chemists are focussing on developing sustainable novel procedures. In this direction, transition metal free arylations using phenylhydrazine in presence of base have been reported.[10] Molecular oxygen or aerial oxidation is a sustainable and mild oxidizing agent which has found application in many of these synthetic transformations.[11] To the best of our knowledge, thiolation/ arylation of 2-amino maleimide has not been explored yet. In continuation of our work aimed at development of metal free synthetic methodologies for synthesis of bioactive molecules.[12] we report herein metal free thioarylation, selenoarylation and arylation of 2-amino maleimide.

RESULTS AND DISCUSSION

Thioarylation and selenoarylation of substituted 2-aminomaleimides

In this paper, we have reported a novel transition metal free K_2CO_3 mediated thioarylation, selenoarylation and arylation of substituted 2-aminomaleimides by reaction with thiophenols, diaryl bisselenides and phenyl hydrazines, respectively in DMSO under aerobic condition at room temperature. The reactions of 1-methyl-3-(methylamino)-1*H*-pyrrole-2,5-dione (**1a**) and 4-chlorothiophenol (**2a**) were attempted by changing solvents and bases to identify appropriate conditions for the desired reaction.

Firstly, the reaction of 1-methyl-3-(methylamino)-1*H*-pyrrole-2,5-dione (**1a**) (1.0 mmol) and 4-chlorothiophenol (**2a**) (2.0 mmol) was carried out in presence of K_2CO_3 (4.0 mmol) in acetonitrile at room temperature (Table 1, entry 1). The reaction was incomplete even after 12 h as monitored by TLC but showed the formation of a new product. The product was separated and identified as 3-((4-chlorophenyl)thio)-1-methyl-4-(methylamino)-1*H*-pyrrole-2,5-dione (**3a**) (78%) (Table 1, entry 1). The reaction was then carried out in DCM, MeOH, DMF, and DMSO under otherwise identical conditions. The reactions in DCM and methanol were incomplete after 12 h and gave 72% and 55% of **3a**, respectively, after separation (Table 1, entries 2-3). The reactions carried out in DMF and DMSO were complete in 12 h and 6 h and yielded 82 % and 89% of **3a**, respectively (Table 1, entry 4-5) (eq. 1). The reactions were attempted in presence of other bases also such as NaOH, DBU and KOH under identical conditions. The reactions were complete after 12 h and no significant improvement in yield was observed (Table 1, entry 6-8). The reaction carried out using lower catalyst loading of K_2CO_3 (3 equiv.) in DMSO required longer reaction time for completion (12 h) and also gave lower yield of the product (56%) (Table 1, entry 9). The reaction of K_2CO_3 (4 equiv.) attempted at higher temperature (60 ^oC) also gave an inferior yield of the product (81%) (Table 1, entry 10).



1a **2a** **3a** ...(1)

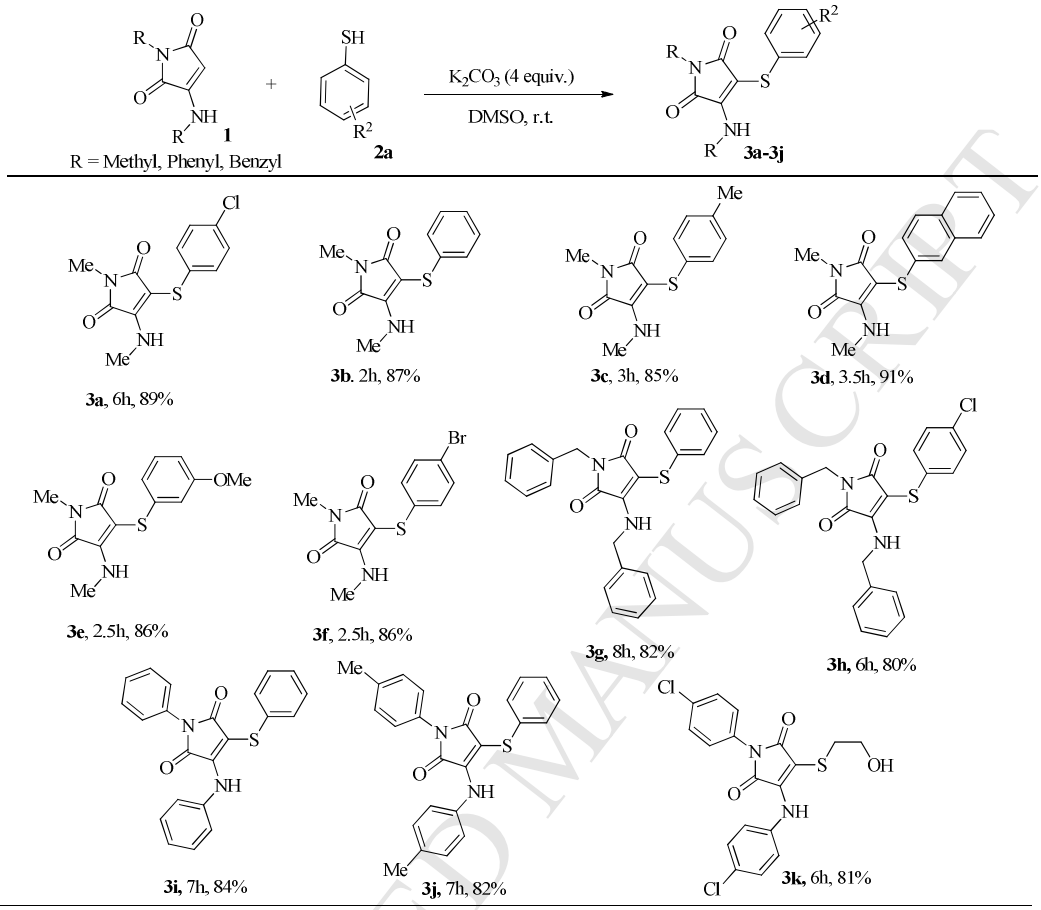
Table 1: Optimization of reaction conditions[a]

Entry	Base (equiv.)	Solvent	Temperature	Time (h)	Yield **3a** (%)
1.	K_2CO_3 (4)	CH_3CN	RT	12	78
2.	K_2CO_3 (4)	DCM	RT	12	72
3.	K_2CO_3 (4)	MeOH	RT	12	55[b]
4.	K_2CO_3 (4)	DMF	RT	12	82
5.	**K_2CO_3 (4)**	**DMSO**	**RT**	**6**	**89**
6.	NaOH (4)	DMSO	RT	12	85
7.	DBU (4)	DMSO	RT	12	86
8.	KOH (4)	DMSO	RT	12	88
9.	K_2CO_3 (3)	DMSO	RT	12	56
10.	K_2CO_3 (4)	DMSO	60 ^oC	12	81

[a]Reaction conditions: 1-Methyl-3-(methylamino)-1*H*-pyrrole-2,5-dione (1a) (1.0 mmol), 4-Chlorothiophenol (2a) (2.0 mmol), solvent (2.0 mL) [b] Incomplete reaction

It can be inferred from Table 1 that the best yield of 3-thioarylated 2-amonomethylmaleimide derivative (**3a**) was obtained when the reaction was carried out in presence of K_2CO_3 in DMSO under aerobic condition at room temperature (Table 1, entry 5). Therefore, the generality of the protocol was examined by attempting reactions of 2-aminomaleimides (**1a**) with different thiophenols *viz* thiophenol, 4-methyl thiophenol, 2-naphthylthiol, 3-methoxythiophenol and 4-bromothiophenol. All the reactions were complete in less than 8 h and gave the desired 3-thioarylated-2-aminomaleimides (**3b-3f**) in high yields (Table 2). In addition, reactions of benzyl, phenyl and 4-tolyl substituted 2-aminomaleimides were also attempted with thiophenols under identical conditions. The reactions yielded corresponding thioarylated products **3g-3j** in 80-84% yield. All the results are summarized in Table 2.

Table 2: Thioarylation of substituted 2-aminomaleimide[a]



[a] Reaction conditions: Substituted 2-aminomaleimides (1) (1.0 mmol), thiophenols/ thionaphthol (2) (2.0 mmol), K_2CO_3 (4 equiv.) and DMSO (2.0 mL)

The reaction of 2-mercaptoethanol was also attempted with 2-aminomaleimide (**1a**) under identical condition but there was no reaction. Since we had observed that reactions of thiophenols were proceeding *via* initial formation of disulphide, it was likely that 2-marcaptoethanol does not undergo aerial oxidation rapidly unlike thiophenols. Therefore, the reaction of 2-mercaptoethanol was repeated in presence of 2-3 crystals of iodine as it is known to oxidize mercaptanes to disulphides. We observed that the reaction of 2-mercaptoethanol was complete after 6 h and gave 1-(4-chlorophenyl)-3-((4-chlorophenyl)amino)-4-((2-hydroxyethyl) thio)-1*H*-pyrrole-2,5-dione (**3k**) (Table 2) in 81 % yield.

The structure of compound **3b** was confirmed by x-ray diffraction studies. The single crystal required for x-ray diffraction studies was prepared by slow evaporation of Methanol. The crystal data shows four molecule in a single crystal lattice (Figure 2).

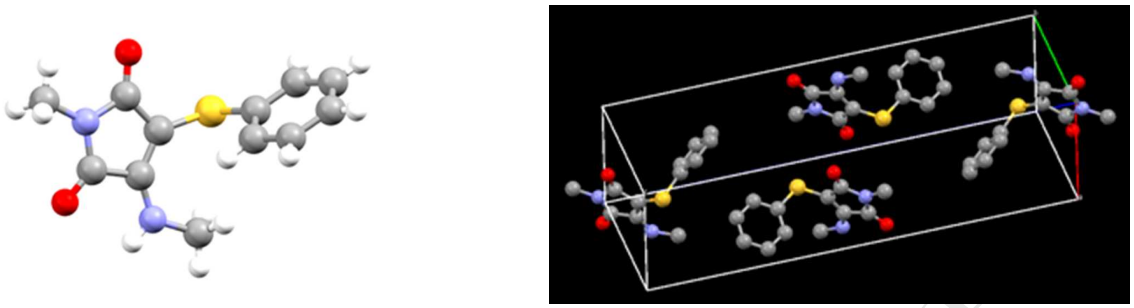
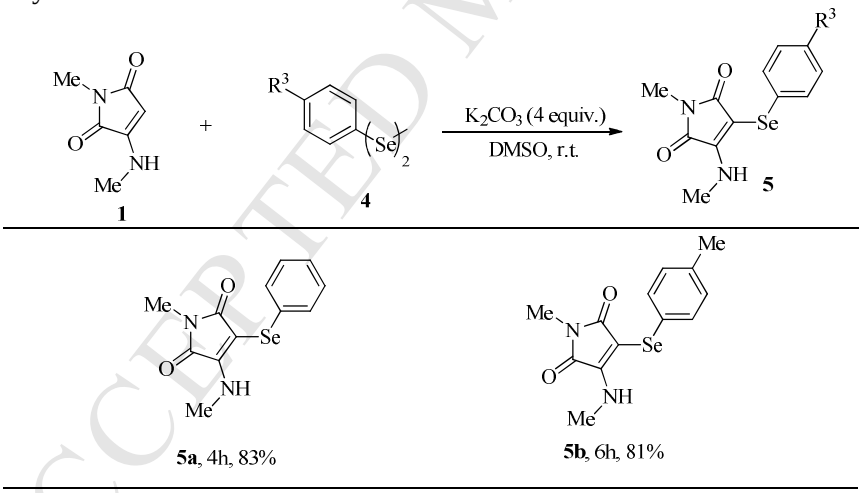


Figure 2: Crystal structure and unit cell packing of 1-methyl-3-(methylamino)-4-(phenylthio)-1*H*-pyrrole-2,5-dione **(3b)**

After successful examination of above protocol for thiophenols, we attempted selenoarylation of substituted 2-aminomaleimide (1a) with diphenyl bisselenide and di(4-tolyl) bisselenide in DMSO in presence of 4 equiv. of K_2CO_3 at room temperature as it was easier to prepare bisselenides than corresponding selenols. The reactions were complete in 4 h and 6 h and gave the corresponding 3-selenoarylated 2-aminomaleimides (5a & 5b) in 83% and 84% yield, respectively. The results are summarized in Table 3.

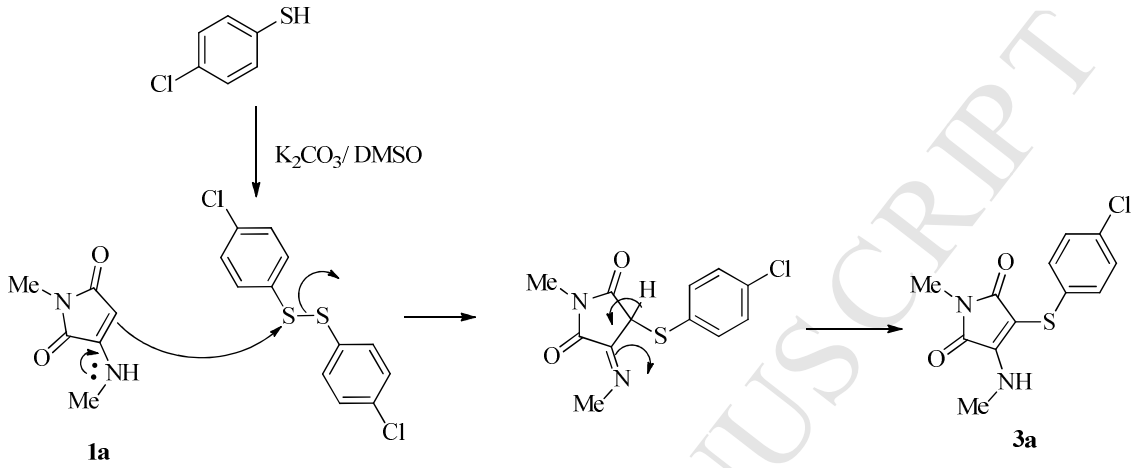
Table 3: Selenoarylation of 2-aminomaleimide[a]



[a]Reaction conditions: Substituted 2-aminomaleimide (1) (1.0 mmol), diaryl bisselenids (4) (1.2 mmol), K_2CO_3 (4 equiv.) and DMSO (2.0 mL) at room temperature

The thioarylation and selenoarylation are proposed to be proceeding by nucleophilic attack of substituted 2-aminomaleimide on disulfide/ diselenide linkage followed by loss of proton (Scheme 1). The initial formation of disulfides was observed by TLC in all the reactions and was confirmed by an independent reaction of substituted 2-aminomaleimide with 4-chlorophenyl bissulphide (1.0 mmol) under identical conditions which gave the desired product. The

thioarylation mechanism was further confirmed by reaction of 3-aryl-2-aminomaleimide and 4-chlorothiophenol which did not give any product, as expected due to non-availability of proton for abstraction, under identical condition.

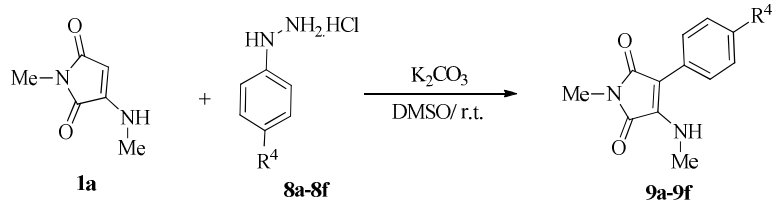


Scheme 1: Mechanism for synthesis of 3-thioarylated-2-aminomaleimide

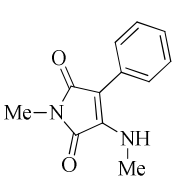
Arylation of substituted 2-aminomaleimides

After successful thioarylation and selenoarylation of 2-aminomaleimides, we decided to explore arylation of 2-aminomaleimides as arylations of different substrates have been reported with phenylhydrazine.[11] Therefore, a reaction of substituted 2-aminomaleimide (1a) (1.0 mmol) was attempted with phenylhydrazine hydrochloride (8a) (1.2 mmol) in DMSO under aerobic condition in presence of K_2CO_3 (4 equiv.) at room temperature. The reaction was complete in 5 h as monitored by TLC using ethyl acetate:petroleum ether (20:80, v/v) as eluent. After separation, the product was identified as 1-methyl-3-(methylamino)-4-phenyl-1*H*-pyrrole-2,5-dione (9a) (86%) by spectral analysis. Therefore, reactions of substituted 2-aminomaleimide (1a) were then carried out with diversely substituted arylhydrazines (8b-8f) under identical reaction conditions. All the reactions gave corresponding 3-arylated-2-aminomaleimides (9b-9f) in high yields. The results are summarized in Table 4.

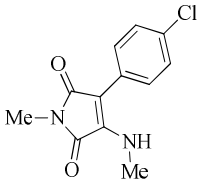
Table 4: Scope of arylation of 2-aminomaleimide[a]



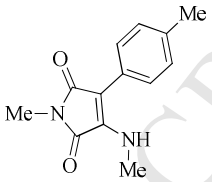
1a **8a-8f** **9a-9f**



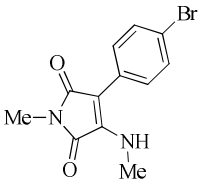
9a, 5h, 86%



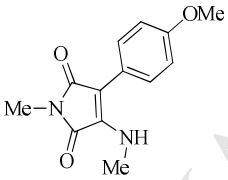
9b, 4h, 82%



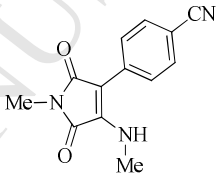
9c, 4.5h, 78%



9d, 6h, 81%



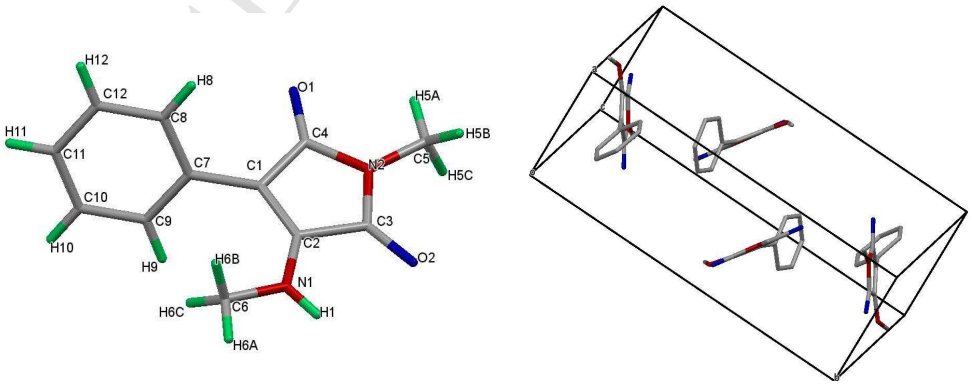
9e, 8h, 76%



9f, 3h, 83%

[a] Reaction conditions: Substituted 2-aminomaleimide (1a) (1 mmol), Arylhydrazine hydrochloride (8a-8f) (1.2 mmol), K_2CO_3 (4 equiv.) and DMSO (2.0 mL) at room temperature

The structure of compound **9a** was confirmed by X-ray diffraction studies. The single crystal required for x-ray diffraction studies was prepared by slow evaporation of methanol. The crystal data shows four molecule in a single crystal lattice and the compound **9a** also show hydrogen bonding between C=O of maleimide and NH (Figure 3).



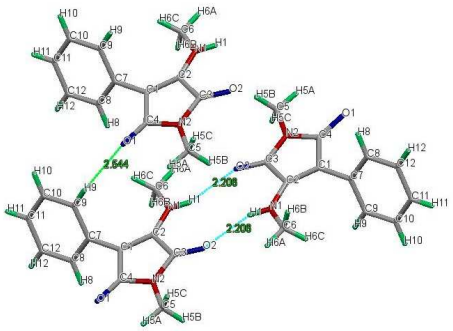
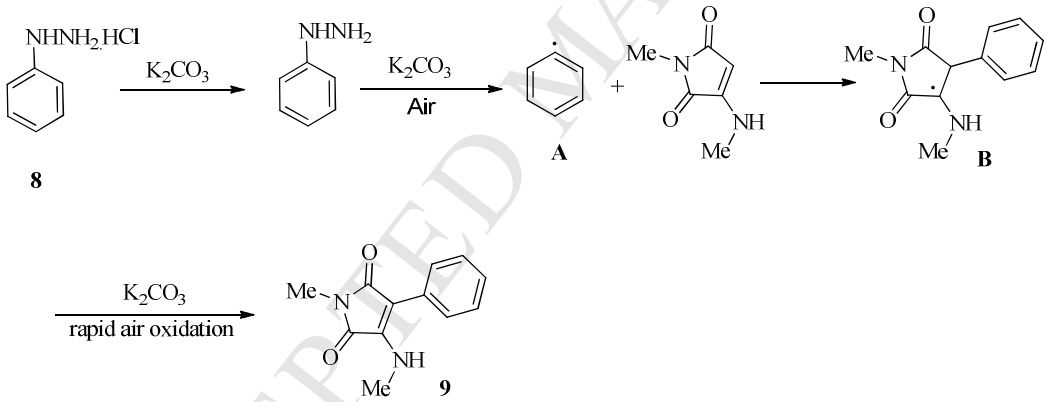


Figure 3: Crystal structure and unit cell packing of 1-Methyl-3-(methylamino)-4-phenyl-1*H*-pyrrole-2,5-dione (9a).

The arylation of 2-aminomaleimides have been proposed to be proceeding *via* aryl radicals generated *in situ* from arylhydrazine.hydrochloride in presence of K_2CO_3 under atmospheric conditions (Scheme 2).[11] The aryl radical adds to 2-aminomaleimide to give intermediate **B**, which on subsequent air oxidation gives 3-arylated-2-aminomaleimide **9**.



Scheme 2: Proposed pathway of arylation of substituted 2-aminomaleimide

The involvement of free radicals has been confirmed by reaction of 2-aminomaleimide (1.0 mmol) and phenylhydrazine hydrochlodide (1.2 mmol) in presence of TEMPO (2.0 mmol) under identical condition. We did not observe any reaction in presence of TEMPO.

Conclusion

In conclusion, we have reported a novel metal free methodology for thioarylation, selenoarylation and arylation of substituted 2-aminomaleimides by K_2CO_3 mediated aerobic oxidation in DMSO at room temperature. A variety of maleimide derivatives have been synthesized in good yields using mild reaction conditions.

EXPERIMENTAL

All the chemicals were commercial and purchased from Sigma-Aldrich or Merck and used as received. Thin layer chromatography (GF-254) was used to monitor reaction progress. Melting points were measured on Buchi M-560 melting point apparatus and are uncorrected. IR (neat) spectra were recorded on a SHIMADZU FTIR spectrophotometer and the values are expressed as ν max cm^{-1}. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Jeol JNM ECX-400P at 400 and 100 MHz respectively, using TMS as an internal standard. The chemical shift values are recorded on δ scale and the coupling constants (*J*) are in Hz. Mass spectral data were recorded on Agilent 6200 Q-TOf (ESI-HRMS) mass spectrometer.

General procedure for the thioarylation of 2-aminomaleimides (3a-3k)

A mixture of substituted 2-aminomaleimides (1) (1.0 mmol), thiophenol (2) (2.0 mmol) and K_2CO_3 (4 equiv.) in 2 mL of DMSO was placed in a 50 mL round bottomed flask mounted over a magnetic stirrer. The contents were stirred magnetically at room temperature and the progress of the reaction was monitored by TLC (eluent: ethyl acetate:petroleum ether, 20:80, v/v). After completion of the reaction (Table 2), the reaction was quenched by adding 20 mL of cold water. The reaction mixture was extracted with DCM (3x10 mL) and the combined extract was dried over anhyd. Na_2SO_4. The solvent was removed on a rotavapour and the crude product was purified by flash column chromatography on silica gel (230-400 mesh) with petroleum ether:ethyl acetate (95:5, v/v) as eluent to afford the pure products (3a-3j). The reaction of 2-marcaptoethanol was carried out in presence of 2-3 crystals of iodine under otherwise identical conditions and gave the product **3k**. All the products were characterized by IR, ^{1}H NMR, ^{13}C NMR and HRMS analysis.

General procedure for the selenoarylation of 2-aminomaleimides (5a-5b)

A mixture of substituted 2-aminomaleimides (1) (1.0 mmol), diarylselenides (4) (1.2 mmol) and K_2CO_3 (4 equiv.) in 2 mL of DMSO was placed in a 50 mL round bottomed flask mounted over a magnetic stirrer. The contents were stirred magnetically at room temperature and the progress of the reaction was monitored by TLC (eluent: ethyl acetate:petroleum ether, 20:80, v/v). After completion of the reaction (Table 3), reaction was quenched by addition of 20 mL of cold water.

The reaction mixture was extracted with DCM (3x10 mL) and the combined extract was dried over anhyd. Na_2SO_4. The solvent was removed on a rotavapour and the crude product was purified by flash column chromatography on silica gel (230-400 mesh) with petroleum ether:ethyl acetate (95:5, v/v) as eluent to afford the pure products (5). All the products were characterized by IR, ^{1}H NMR, ^{13}C NMR and HRMS analysis.

General procedure for the arylation of 2-aminomaleimides (9a-9f)

A mixture of substituted 2-aminomaleimides (1) (1.0 mmol), arylhydrazine hydrochloride (8) (1.2 mmol) and K_2CO_3 (4 equiv.) in 2 mL of DMSO was placed in a 50 mL round bottomed flask mounted over a magnetic stirrer. The reactants were stirred magnetically at room temperature and the progress of the reaction was monitored by TLC (eluent: ethyl acetate:petroleum ether, 20:80, v/v). After completion of the reaction (Table 4), reaction was quenched by adding 20 mL of cold water. The reaction mixture was extracted with DCM (3x10 mL) and the combined extract was dried over anhyd. Na_2SO_4. The solvent was removed on a rotavapour and the crude product was purified by flash column chromatography on silica gel (230-400 mesh) using petroleum ether:ethyl acetate (95:5, v/v) as eluent to afford the pure products (9). All the products were characterized by IR, ^{1}H NMR, ^{13}C NMR and HRMS analysis.

Spectral data

4-((4-Chlorophenyl)thio)-1-methyl-3-(methylamino)-1*H*-pyrrole-2,5-dione (3a)

Yellow solid; m.p.: 190-192 °C; IR (ν_{max} cm^{-1})(Neat): 3294, 1703, 1445, 1382, 1084, 984; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, J = 8.7 Hz, 2H, **ArH**), 7.15 (d, J = 8.7 Hz, 2H, **ArH**), 5.93 (s, 1H, **NH**), 3.32 (d, J = 5.5 Hz, 3H, NH**C**$\mathbf{H_3}$), 3.06 (s, 3H, N**C**$\mathbf{H_3}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.37, 165.83, 150.66, 138.38, 129.01, 126.19, 125.56, 30.41, 24.33; HRMS (ESI) calcd. for $C_{12}H_{11}ClN_2O_2S$ $[M + H]^+$: 283.0308; Found: $[M + H]^+$: 283.0303 and $[M + H + 2]^+$: 285.0277.

1-Methyl-3-(methylamino)-4-(phenylthio)-1*H*-pyrrole-2,5-dione (3b)

Yellow solid; m.p.: 161-163 °C; IR (ν_{max} cm^{-1})(Neat): 3300, 1703, 1614, 1445, 1383, 988, 743; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.06 (m, 5H, **ArH**), 6.01 (s, 1H, **NH**), 3.29 (s, 3H, NH**C**$\mathbf{H_3}$), 3.04 (s, 3H, N**C**$\mathbf{H_3}$); ^{13}C NMR (100 MHz, DMDO-d_6): δ 171.56, 165.72, 152.60, 139.23, 130.18, 129.51, 127.34, 30.29, 24.54; HRMS (ESI) calcd. for $C_{12}H_{12}N_2O_2S$ $[M + H]^+$: 249.0698; Found: $[M + H]^+$: 249.0709.

1-Methyl-3-(methylamino)-4-(4-tolylthio)-1*H*-pyrrole-2,5-dione (3c)

Yellow solid; m.p.: 180-182 °C; IR (ν_{max} cm^{-1})(Neat): 3238, 1736, 1649, 1240, 1008, 781; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.11 (d, J = 7.8 Hz, 2H, **ArH**), 7.04 (d, J = 8.2 Hz, 2H, **ArH**), 5.93 (s, 1H, **NH**), 3.30 (d, J = 5.5 Hz, 3H, NH**C**$\mathbf{H_3}$), 3.01 (s, 3H, N**C**$\mathbf{H_3}$), 2.26 (s, 3H, Ar**C**$\mathbf{H_3}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.33, 166.10, 150.30, 135.68, 129.82, 126.88, 30.50, 24.29, 20.88; HRMS (ESI) calcd. for $C_{13}H_{14}N_2O_2S$ $[M + H]^+$: 263.0854; Found: $[M + H]^+$: 263.0849.

1-Methyl-3-(methylamino)-4-(naphthalen-2-yl)thio)-1*H*-pyrrole-2,5-dione (3d)

Yellow solid; m.p.: 216-218 °C; IR (ν_{max} cm^{-1})(Neat): 3321, 1697, 1620, 1437, 984, 678; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77-7.69 (m, 3H, **ArH**), 7.58 (s, 1H, **ArH**), 7.50-7.31 (m, 3H, **ArH**), 5.98 (s, 1H, **NH**), 3.33 (d, J = 5.5 Hz, 3H, NH**C**$\mathbf{H_3}$), 3.08 (s, 3H, N**C**$\mathbf{H_3}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.51, 166.16, 150.90, 133.92, 131.75, 128.89, 127.85, 127.09, 126.73, 125.64, 124.88, 124.23, 30.62, 24.56; HRMS (ESI) calcd. for $C_{16}H_{14}N_2O_2S$ $[M + H]^+$: 299.0854; Found: $[M + H]^+$: 299.0872.

4-((3-Methoxyphenyl)thio)-1-methyl-3-(methylamino)-1*H*-pyrrole-2,5-dione (3e)

Yellow solid; m.p.: 141-143 °C; IR (ν_{max} cm^{-1})(Neat): 3316, 1622. 1582, 1246, 1096, 750; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (t, J = 8.0 Hz, 1H, **ArH**), 6.77-6.68 (m, 2H, **ArH**), 6.63 (dd, J = 8.2, 2.3 Hz, 1H, **ArH**), 6.20 (bs, 1H, **NH**), 3.73 (s, 3H, O**C**$\mathbf{H_3}$), 3.25 (d, J = 5.6 Hz, 3H, NH**C**$\mathbf{H_3}$), 3.01 (s, 3H, N**C**$\mathbf{H_3}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.60, 166.06, 160.15, 151.03, 140.17, 130.02, 118.46, 112.09, 110.86, 55.35, 30.54, 24.46; HRMS (ESI) calcd. for $C_{13}H_{14}N_2O_3S$ $[M + H]^+$: 279.0803; Found: $[M + H]^+$: 279.0803.

4-((4-Bromophenyl)thio)-1-methyl-3-(methylamino)-1*H*-pyrrole-2,5-dione (3f)

Yellow solid; m.p.: 186-188 °C; IR (ν_{max} cm^{-1})(Neat): 3296, 1701, 1612, 1383, 986; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, J = 8.7 Hz, 2H, **ArH**), 7.08 (d, J = 8.7 Hz, 2H, **ArH**), 5.98 (s, 1H, **NH**), 3.31 (d, J = 5.5 Hz, 3H, NH**CH$_3$**), 3.06 (s, 3H, N**CH$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.12, 165.81, 132.09, 127.93, 119.42, 30.50, 24.44; HRMS (ESI) calcd. for $C_{12}H_{11}BrN_2O_2S$ $[M + H]^+$: 326.9803; Found: $[M + H]^+$: 326.9809 and $[M + H + 2]^+$: 328.9789.

1-Benzyl-3-(benzylamino)-4-(phenylthio)-1*H*-pyrrole-2,5-dione (3g)

Yellow solid; m.p.: 133-134 °C; IR (ν_{max} cm^{-1})(Neat): 3316, 1707, 1622, 1431, 1074, 691; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.11 (m, 15H, **ArH**), 6.06 (s, 1H, **NH**), 4.90 (d, J = 6.0 Hz, 2H, NH**CH$_2$**Ar), 4.70 (s, 2H, N**CH$_2$**Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.84, 165.81, 149.24, 136.34, 129.22, 129.07, 128.76, 128.66, 128.34, 127.96, 126.70, 125.92, 47.43, 42.25; HRMS (ESI) calcd. for $C_{24}H_{20}N_2O_2S$ $[M + H]^+$: 401.1324; Found: $[M + H]^+$: 401.1322.

1-Benzyl-3-(benzylamino)-4-((4-chlorophenyl)thio)-1*H*-pyrrole-2,5-dione (3h)

Yellow solid; m.p.: 125-126 °C; IR (ν_{max} cm^{-1})(Neat): 3302, 1707, 1625,1059, 692; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.23 (m, 8H, **ArH**), 7.22-7.11 (m, 4H, **ArH**), 7.06 (d, J = 8.2 Hz, 2H, **ArH**), 6.25-6.07 (m, 1H, **ArH**), 4.92 (d, J = 6.0 Hz, 2H, NH**CH$_2$**Ar), 4.69 (s, 2H, N**CH$_2$**Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.71, 165.67, 149.30, 136.36, 136.25, 131.88, 129.27, 129.10, 128.79, 128.66, 128.35, 128.09, 128.00, 127.79, 47.40, 42.30; HRMS (ESI) calcd. for $C_{24}H_{19}ClN_2O_2S$ $[M + H]^+$: 435.0934; Found: $[M + H]^+$: 435.1021.

1-Phenyl-3-(phenylamino)-4-(phenylthio)-1*H*-pyrrole-2,5-dione (3i)

Yellow solid; m.p.: 130-132 °C; IR (ν_{max} cm^{-1})(Neat): 3321, 1697, 1628, 1439, 1385, 1065; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (s, 1H, **NH**), 7.47 (m, 4H, Ar**H**), 7.38-7.33 (m, 1H, Ar**H**), 7.25-7.16 (m, 3H, Ar**H**), 7.10-7.02 (m, 5H, Ar**H**), 6.94-6.90 (m, 2H, Ar**H**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.75, 165.96, 143.05, 135.05, 135.01, 131.83, 129.14, 128.83, 128.42, 127.78, 126.39, 126.09, 125.77, 124.16, 92.32; HRMS (ESI) calcd. for $C_{22}H_{16}N_2O_2S$ $[M + H]^+$: 373.1011; Found: $[M + H]^+$: 373.0981.

3-(Phenylthio)-1-(4-tolyl)-4-(4-tolylamino)-1*H*-pyrrole-2,5-dione (3j)

Yellow solid; m.p.: 162-164 °C; IR (ν_{max} cm^{-1})(Neat): 3030, 1705, 1618, 1491, 1389, 1088; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.27 (s, 1H, **NH**), 7.44-7.37 (m, 3H, Ar**H**), 7.26-7.18 (m, 2H, Ar**H**), 7.17-7.02 (m, 4H, Ar**H**), 7.00-6.92 (m, 2H, Ar**H**), 6.79 (m, 1H, Ar**H**), 2.26 (s, 3H, ArC**H$_3$**), 2.24 (s, 3H, Ar**CH$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.17, 166.13, 157.55, 143.98, 137.63, 136.68, 134.09, 132.64, 130.31, 129.44, 128.74, 127.51, 127.09, 125.74, 125.47, 123.48, 121.54, 121.10, 117.29, 20.02, 19.73; HRMS (ESI) calcd. for $C_{24}H_{21}N_2O_2S$ $[M + H]^+$: 401.1324; Found: $[M + H]^+$: 401.1327.

1-(4-chlorophenyl)-3-((4-chlorophenyl)amino)-4-((2-hydroxyethyl)thio)-1*H*-pyrrole-2,5-dione (3k)

Yellow solid; m.p.: 125-126 °C; IR (ν_{max} cm^{-1})(Neat): 3289, 1707, 1628, 1489, 1383, 826; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (s, 1H, **NH**), 7.39-7.28 (m, 6H, Ar**H**), 7.21-7.15 (m, 2H, ArH), 3.56 (t, J = 5.5 Hz, 2H, CH_2**CH$_2$**OH), 2.63-2.57 (t, J = 5.4 Hz, 2H, S**CH$_2$**CH_2), 1.96 (s, 1H, CH_2OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.06, 165.26, 143.78, 134.05, 133.49, 132.40, 129.95, 129.27, 128.91, 126.68, 125.58, 60.57, 38.66; HRMS (ESI) calcd. for $C_{18}H_{14}Cl_2N_2O_3S$ $[M + H]^+$: 409.0180; Found: $[M + H]^+$: 409.0193 and $[M + H + 2]^+$: 411.0166.

1-Methyl-3-(methylamino)-4-(phenylseleno)-1*H*-pyrrole-2,5-dione (5a)

Yellow solid; m.p.: 141-142 °C; IR (ν_{max} cm^{-1})(Neat): 3304, 1701, 1614, 1444, 984; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, J = 8.2 Hz, 2H, **ArH**), 7.27-7.13 (m, 3H, **ArH**), 5.87 (bs, 1H, **NH**), 3.31 (d, J = 5.5 Hz, 3H, NH**CH$_3$**), 3.04 (s, 3H, N**CH$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.79, 166.93, 150.91, 129.50, 129.43, 126.57, 30.65, 24.59; HRMS (ESI) calcd. for $C_{12}H_{12}N_2O_2Se$ $[M + H]^+$: 297.0142; Found: $[M + H]^+$: 297.0149.

1-Methyl-3-(methylamino)-4-(4-tolylseleno)-1*H*-pyrrole-2,5-dione (5b)

Yellow solid; m.p.: 152-154 °C; IR (ν_{max} cm^{-1})(Neat): 3312, 1767, 1703, 1618, 983; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, J = 8.1 Hz, 2H, Ar**H**), 7.03 (d, J = 8.0 Hz, 2H, Ar**H**), 5.86 (s, 1H, **NH**), 3.32 (d, J = 5.6 Hz, 3H, NH**CH$_3$**), 3.02 (s, 3H, N**CH$_3$**), 2.27 (s, 3H, Ar**CH$_3$**); ^{13}C NMR

(100 MHz, $CDCl_3$): δ 171.84, 166.73, 150.37, 136.66, 130.21, 130.13, 30.70, 24.54, 21.09; HRMS (ESI) calcd. for $C_{13}H_{14}N_2O_2Se$ $[M + H]^+$: 311.0299; Found: $[M + H]^+$: 311.0306.

1-Methyl-3-(methylamino)-4-phenyl-1*H*-pyrrole-2,5-dione (9a)

Yellow solid; m.p.: 145-146 °C; IR (ν_{max} cm^{-1})(Neat): 3352, 1697, 1634, 1445, 982, 654; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39-7.19 (m, 5H, **ArH**), 5.38 (s, 1H, **NH**), 2.99 (s, 3H, **NCH_3**), 2.75 (d, J = 5.5 Hz, 3H, NH**CH_3**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.39, 167.87, 143.01, 130.46, 129.90, 127.79, 127.19, 99.41, 31.68, 23.79; HRMS (ESI) calcd. for $C_{12}H_{12}N_2O_2$ $[M + H]^+$: 217.0977; Found: $[M + H]^+$: 217.0982.

4-(4-Chlorophenyl)-1-methyl-3-(methylamino)-1*H*-pyrrole-2,5-dione (9b)

Yellow solid; m.p.: 144-146 °C; IR (ν_{max} cm^{-1})(Neat): 3360, 1699, 1636, 1447, 1084, 980, 833; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33 (d, *J* = 8.7 Hz, 2H, **ArH**), 7.25 (d, *J* = 8.2 Hz, 2H, **ArH**), 5.49 (s, 1H, **NH**), 3.02 (s, 3H, N**CH_3**), 2.79 (d, *J* = 5.5 Hz, 3H, NH**CH_3**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.34, 167.72, 143.37, 133.27, 131.82, 128.19, 98.17, 31.90, 23.98; HRMS (ESI) calcd. for $C_{12}H_{11}N_2O_2Cl$ $[M + H]^+$: 251.0587; Found: $[M + H]^+$: 251.0594 and $[M + H + 2]^+$: 253.0568.

1-Methyl-3-(methylamino)-4-(4-tolyl)-1*H*-pyrrole-2,5-dione (9c)

Yellow solid; m.p.: 152-153 °C; IR (ν_{max} cm^{-1})(Neat): 3364, 1697, 1633, 1447, 980, 750; ^1H NMR (400 MHz, $CDCl_3$): δ 7.21 (m, 4H, **ArH**), 5.39 (d, *J* = 3.2 Hz, 1H, **NH**CH_3), 3.05 (s, 3H, N**CH_3**), 2.81 (d, *J* = 5.5 Hz, 3H, NH**CH_3**), 2.37 (s, 3H, Ar**CH_3**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.57, 168.01, 142.80, 137.01, 130.34, 128.55, 126.85, 99.54, 31.62, 23.78, 21.21; HRMS (ESI) calcd. for $C_{13}H_{14}N_2O_2$ $[M + H]^+$: 231.1134; Found: $[M + H]^+$: 231.1823.

4-(4-Bromophenyl)-1-methyl-3-(methylamino)-1*H*-pyrrole-2,5-dione (9d)

Yellow solid; m.p.: 151-152 °C; IR (ν_{max} cm^{-1})(Neat): 3362, 1695, 1636, 1449, 986, 831, 501; ^1H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.2 Hz, 2H, **ArH**), 7.23 (d, *J* = 8.2 Hz, 2H, **ArH**), 5.49 (s, 1H, **NH**), 3.06 (s, 3H N**CH_3**), 2.84 (d, *J* = 5.5 Hz, 3H, NH**CH_3**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.20, 167.70, 143.28, 132.12, 131.16, 129.00, 98.30, 121.48, 31.94, 24.01; HRMS

(ESI) calcd. for $C_{12}H_{11}N_2O_2Br$ $[M + H]^+$: 295.0082; Found: $[M + H]^+$: 295.0088 and $[M + H + 2]^+$: 297.0069.

4-(4-Methoxyphenyl)-1-methyl-3-(methylamino)-1*H*-pyrrole-2,5-dione (9e)

Yellow solid; m.p.: 138-140 °C; IR (ν_{max} cm^{-1})(Neat): 3360, 1703, 1656, 1451, 987; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, J = 8.7 Hz, 2H, ArH), 6.90 (d, J = 8.7 Hz, 2H, **ArH**), 5.30 (d, J = 3.7 Hz, 1H, **NH**), 3.81 (s, 3H, ArO**C**$\mathbf{H_3}$), 3.01 (s, 3H, N**C**$\mathbf{H_3}$), 2.79 (d, J = 5.5 Hz, 3H, NH**C**$\mathbf{H_3}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.88, 168.20, 158.97, 142.76, 131.76, 122.21, 113.51, 99.49, 55.36, 31.68, 23.91; HRMS (ESI) calcd. for $C_{13}H_{14}N_2O_3$ $[M + H]^+$: 247.1083; Found: $[M + H]^+$: 247.1080.

4-(1-Methyl-4-(methylamino)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)benzonitrile (9f)

Yellow solid; m.p.: 184-186 °C; IR (ν_{max} cm^{-1})(Neat): 3325, 2222, 1705, 1655, 1441, 982, 847; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, J = 8.2 Hz, 2H, **ArH**), 7.43 (d, J = 8.2 Hz, 2H, **ArH**), 5.64 (s, 1H, **NH**), 3.04 (s, 3H, N**C**$\mathbf{H_3}$), 2.83 (d, J = 5.5 Hz, 3H, NH**C**$\mathbf{H_3}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.62, 167.19, 144.05, 135.17, 131.69, 130.89, 118.85, 110.55, 97.60, 32.33, 24.16; HRMS (ESI) calcd. for $C_{13}H_{11}N_3O_2$ $[M + H]^+$: 242.0930; Found: $[M + H]^+$: 242.0927.

Conflicts of interest

"There are no conflicts to declare".

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Highlights

- Transition metal free thioarylation, selenoarylation and arylation of 2-aminomaleimide has been reported.
- We develop a novel K_2CO_3/DMSO reagent for thioarylation, selenoarylation for different substrates.
- This methodology is provides general, green and efficient methods for thioarylation.
- A novel method for synthesis of polyfunctionalized maleimides.
- thioarylation, selenoarylation and arylation of 2-aminomaleimide has been reported at room temperature in high yields.