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Substituent effects on the regioselectivity of maleamic acid formation and hydrogen chloride addition to N-aryl maleimides

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Itaconic anhydride reacts with aryl amines to give a substituent controlled equilibrium mixture of regioisomeric (Z)-2-methyl- and (Z)-3-methyl-4-oxo-4-(arylamino)but-2-enoic acids. Electron-donating groups favor nucleophilic attack on C-5 carbonyl, while the presence of electron-withdrawing groups enhances the bias for attack on C-2 carbonyl. The treatment of (Z)-2-methyl- and (Z)-3-methyl-4-oxo-4-(arylamino)but-2-enoic acids with $SOCl_2$-Et_3N in THF provided the corresponding maleimides in high yields while under the same conditions the maleic anhydride aryl amine addition products gave predominately the corresponding 3-chloro-1-arylpyrrolidine-2,5-diones and maleimides in substituent dependent ratio.

Key Words: Cyclic anhydrides, maleimides, chlorosuccinimides, LFERs, substituent effect

Introduction

A number of methods for the preparation of imides have been developed and the main strategy used is the dehydration of the intermediate amidocarboxylic acid with acetic anhydride.[1,2] *N*-Arylmaleimides have been prepared in 2 steps via a reaction of aniline with maleic anhydride in ethyl ether to produce an intermediate amide, which is then cyclized to the imide by refluxing its solution in toluene and dimethyl sulfoxide in the presence of a catalytic amount of concentrated sulfuric acid.[3,4] However, attempts to exploit the known procedures in maleimide synthesis[2] in some cases were reported to be disappointing in terms of both yield and reproducibility.[5] N-Arylmaleamic acids were reported to convert to N-aryl 3-chlorosuccinimides in moderate to good yields when dissolved in $SOCl_2$ at room temperature.[6] An intramolecular chloride ion migration is considered for the formation of the corresponding 3-chlorosuccinimides.[6c] The dehydrohalogenation of 3-chlorosuccinimides in the presence of Et_3N to give the corresponding maleimides was also reported.[6b]

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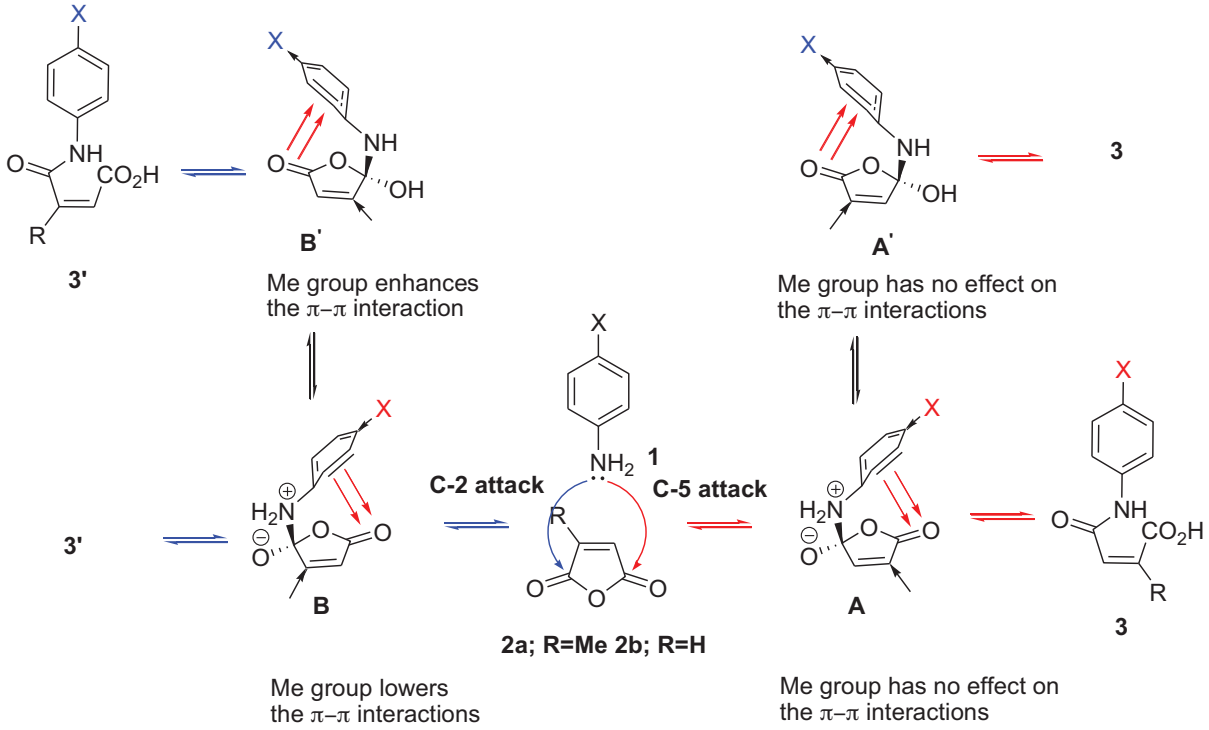
The reaction of tert-butyl 2-aminobenzylcarbamate with methylmaleic anhydride was reported to give 2 regioisomers, namely (Z)-2-methyl- as major and (Z)-3-methyl-4-oxo-4-(arylamino)but-2-enoic acids as minor in 85/15 ratio respectively.[7a] The anilic acids prepared have been converted to the corresponding esters by using diazomethane. The base catalyzed cyclizations of the latter furnish the corresponding N-aryl imides, which are converted to tricyclic and tetracyclic 1,3-diaza-heterocycles with potential anti-cancer activity upon treatment with TFA.[7a] The synthesis of (±)-piliformic[7b] and (±)-*erythro*-roccellic acids[7c] are examples of N-arylmaleimide use in the synthesis of natural products.



Scheme 1. Probable mechanism for the substituent controlled regioisomers **3/3'** ratio.

As a continuation of our interest in the substituent effect on the diastereoselectivity of cycloaddition reactions we needed a series of substituted N-aryl maleimides. During the search for an optimal method for the synthesis of the latter we found that substituents control the transamidation equilibrium of regioisomeric (Z)-2-methyl- **3** and (Z)-3-methyl-4-oxo-4-(arylamino)but-2-enoic acids **3'**, which are products from the ring-opening reaction of itaconic anhydride with aryl amines (Scheme 1). A plausible mechanism for the substituent dependent regiochemistry of the above reaction is discussed (Scheme 1).

Results and discussion

Substituted anilines **1** were reacted with maleic anhydrides **2** in THF heating at reflux temperature to give the corresponding maleamic acids **3** and **3'** (Scheme 1). In the case of **2a** the reaction mixtures were investigated with ^{1}H-NMR and the ratio of **3** to **3'** was determined (Table 1).

Table 1. Effect of substituents on the formation of (Z)-4-oxo-4-(arylamino)but-2-enoic acids and their cyclizations in the presence of $SOCl_2$-Et_3N.

1-5	X	**R**	**3** [a]	**3'**	$\log K_{3/3'}$	**4**[a]	**5**	$\log(K_{4/5})$
a	**H**	Me	82.4[b]	17.6	0.67	100	0	
b	**Me**	Me	91.1	8.9	1.01	100	0	
c	**MeO**[c]	Me	95.1	4.9	1.29	100	0	
d	**NO_2**	Me	50.2	49.8	0.00	100	0	
e	**Cl**	Me	80.2	19.8	0.61	100	0	
f	**Br**	Me	83.4	16.6	0.69	100	0	
g	**H**	H	50	50	0	21.9	78.1	–0.55
h	**Me**	H	50	50	0	18	82	–0.66
i	**MeO**	H	50	50	0	20.6	79.4	–0.59
j	**NO_2**	H	50	50	0	38.3	61.7	–0.21
k	**Cl**	H	50	50	0	25.4	74.6	–0.47
l	**Br**	H	50	50	0	25.9	74.1	–0.46

[a] The values are averages of 3 experiments and were determined by ^{1}H-NMR; standard deviations for the **3/3'** and **4/5** ratios are within the range 0.01-0.07. [b] The isolated **3** were heated in THF at reflux temperature for 24 h to give the corresponding equilibrium mixtures of **3** and **3'**. In the case of **3d** the corresponding amine (22%) and 3-methylfuran-2,5-dione (9%) were also detected in the reaction mixture. [c] The reaction of 3-methoxyaniline and **2a** gave **3** and **3'** in 70/30 ratio. Antranilic acid reacted to give 52/48 ratio for **3/3'** as expected for an electron-withdrawing group. Electron-donating SH group in the case of 2-aminobenzenethiol led to 2-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-2-yl)propanoic acids, which implies that SH favors C-5 attack to give the corresponding maleamic acid, which cyclizes to give the latter.

(Z)-2-Methyl-4-oxo-4-(arylamino)but-2-enoic acids **3** were isolated and purified by recrystallization from THF. The regio- and stereochemistry of compounds **3** and **3'** were confirmed by NOESY1D experiments (Figure 1). The irradiation of the methyl's singlet at 1.96 ppm enhances the singlet of C3-H by 1.5%, while the irradiation of the C3-H at 6.08 ppm leads to enhancements of the methyl and amide protons' singlets. The irradiation of the amide proton's singlet leads also to enhancement of the C3-H proton signal. The irradiation of the singlet at 5.87 ppm of compound **3'd** enhances the methyl's singlet at 2.05 ppm. These experiments clearly prove the assigned regio- and stereochemistry of compounds **3** and **3'**.

The plot of the regioisomers ratio ($\log K_{3/3'}$) versus the substituent constants σ and σ^- revealed that the regioselectivity of the reaction in THF at reflux temperature is controlled by the substituents on the aniline derivatives. The correlations with σ and σ^- constants have ρ = –1.08 and r^2 = 0.93, and ρ = –0.74 and r^2 = 0.88 respectively. It was surprising that σ^+ constants derived for electron-deficient intermediates like carbocations provided the correlation $\log(K_{3/3'})_X$ = -0.82σ^+ + $\log(K_{3/3'})_{X=H}$ (Figure 2).

Electron-donating groups favor the attack on C-5 carbonyl while the presence of electron-withdrawing groups enhances the bias for attack on the carbonyl that is closer to the C-3 methyl group (C-2 carbonyl).

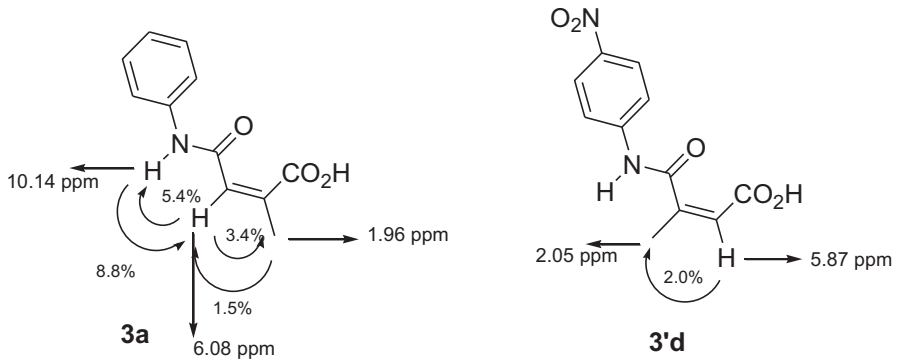


Figure 1. Selected NOESY1D experiments for compounds **3a** and **3'd**.

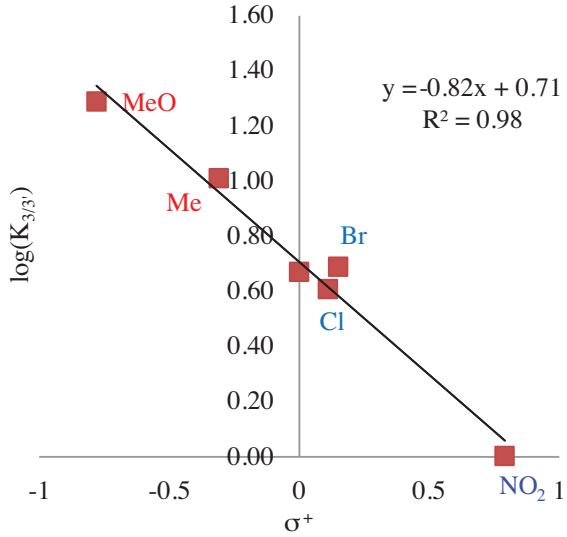
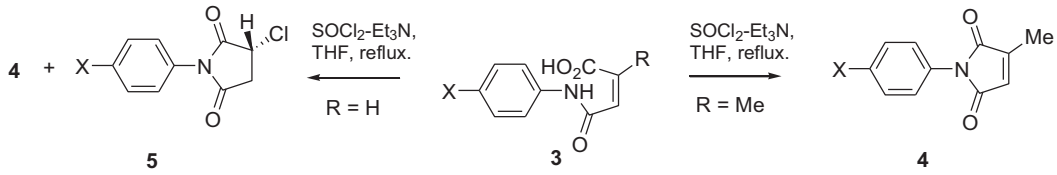


Figure 2. Effect of substituents on the regioselectivity of ring opening of 3-methylmaleic anhydride.

The above discussed correlation of $\log(K_{3/3'})$ implies that the substituents in the rate limiting steps leading to **3** and **3'** are interacting with both positively or uncharged centers, intermediates **A**, **B** and **A'**, **B'** in Scheme 1. The nucleophilic attack on C-5 and C-2 will produce **A** and **B**, respectively. The correlation implies that electron-donating groups stabilize intermediates **A** and **B**, pushing electrons to the carbon bearing the ammonium nitrogen. We assume that $\pi - \pi$ stacking between the N-aromatic ring and the lactone carbonyl may play an important role. In the cases of electron-donating substituents, intermediates **A** are better stabilized than **B** due to the unfavorable effect of the electron-donating methyl at C-3. Thus, in the cases of electron-donating substituents, compounds **3** probably form through ring-opening and proton migration of **A**. Electron-withdrawing substituents destabilize **A** and **B** and shift the equilibria to **A'** and **B'**. The $\pi - \pi$ interactions in this case we assume to be between the same groups discussed above but the direction of charge transfer is reversed. Thus the C-3 methyl in **B'** now is favoring stacking, thus leading to **3'**, while it has no effect on the stability of **A'**.

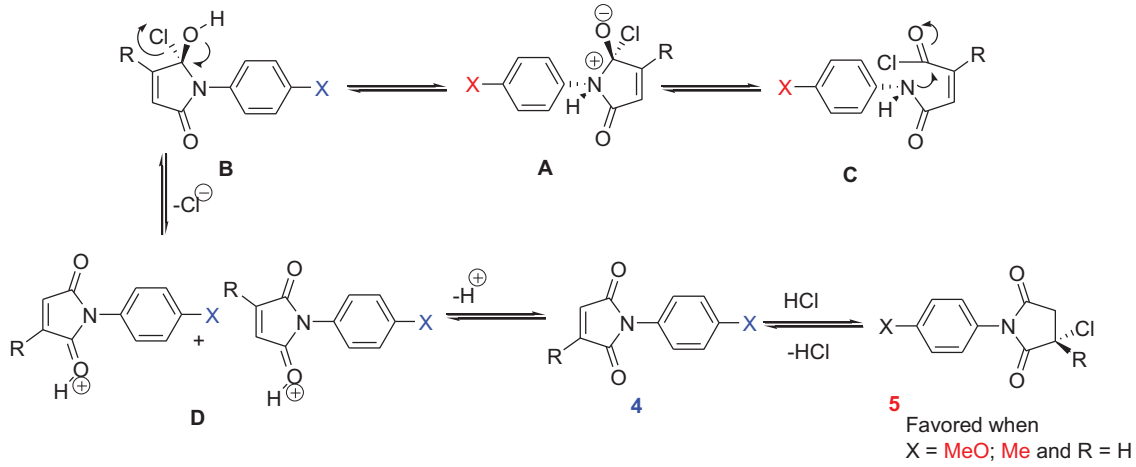
Compounds **3** and **3'** were heated in THF at reflux temperature with equimolar amounts of Et_3N and $SOCl_2$ until the maleamic acid was fully consumed. In the cases of maleamic acids **3-3'/a-f** the only product

from the cyclization was the corresponding maleimide **4**, while under the same conditions compounds **3g-l** (R = H) converted mainly to succinimides **5** and maleimides **4** in substituent dependent ratios (Scheme 2, Table 1).



Scheme 2. $SOCl_2$-Et_3N induced cyclization of N-arylmaleamic acids to **4** and **5**.

A probable mechanism for the formation of compounds **4** and **5** (when R = H) through initially formed acid chloride **C** is depicted below. The intramolecular cyclization of the latter can lead to intermediate **A** (Scheme 3), which probably is in equilibrium with **B**.



Scheme 3. Probable mechanism for the formation of compounds **4** and **5**.

The elimination of HCl in the cases of less basic aniline derivatives (e.g., 4-nitroaniline) is favored to give the corresponding maleimides **4**. However, in the cases of aniline derivatives **3** with electron-donating substituents the formation of 3-chlorosuccinimides **5** is predominating (e.g., 4-methoxyaniline). If we assume that compounds **5** arise from the electrophilic addition of HCl to **4** then **4a-f** can be expected to give **5a-f** more easily due to formation of a more stable tertiary carbocation. However, it was not the case that the only products formed were the corresponding maleimides **4a-f**. HCl(g) was passed through the THF solutions of **4f** and **4l** and the mixtures left overnight at room temperature. It was surprising that the methyl substituted **4f** remained unchanged while **4l** was converted to **5l** in quantitative yield. It seems that the formation of compounds **5g-l** under the conditions discussed somewhat deviates from the mechanism of electrophilic addition to alkene. The presence of an electron-donating alkyl group probably stabilizes the intermediates of type **D** (Scheme 3), which are less prone to undergo addition of chloride ion to the olefinic carbon than their hydrogen substituted analogs. However, the effect of the substituents on the aniline ring in the case of C-3 unsubstituted **4g-l** is just the reverse. The presence of electron-donating groups favor the HCl addition and thus **5** predominates in

the mixture, while electron-withdrawing groups (e.g. -NO_2) enhance relatively the amount of corresponding **4**. The plot of $\log(K_{4/5})$ versus the σ^- constants[10] (Table 1 and Figure 3) provided the equation $\log(K_{4/5})_X = 0.28\sigma^- + \log(K_{4/5})_{X=H}$, which describes the effect of substituents on the electrophilic addition reactions of in situ formed maleimides **4g-l**.[11]

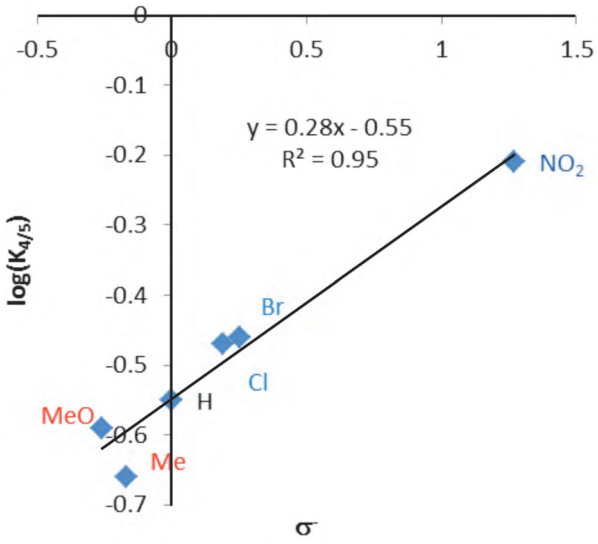


Figure 3. Effect of substituents on the hydrogen chloride addition to N-aryl maleimides.

The correlation with σ provided ρ constant 0.39 ($r^2 = 0.93$). No satisfactory correlation with σ^+ constants was observed.

Conclusion

For the first time we report on substituent control on the interconversion of (Z)-2-methyl- and (Z)-3-methyl-4-oxo-4-(arylamino)but-2-enoic acids **3** and **3'**. (Z)-2- or 3-methyl-4-oxo-4-(arylamino)but-2-enoic acids convert quantitatively to N-arylmaleimides upon treatment with $SOCl_2$-Et_3N in THF upon heating at reflux temperature, while their C-3(2) unsubstituted analogs convert mainly to 3-chlorosuccinimides **5** under the same conditions. Plausible mechanisms for the regioselectivity of maleamic acid formations as well as their cyclizations under the discussed reaction conditions were proposed.

Experimental

The solvents and reagents were Aldrich or Merck quality and were used without additional purification. Melting points were taken on an Electrothermal Digital melting point apparatus. Infrared spectra were recorded on a Thermo-Nicolet 6700 FTIR. 1D and 2D NMR experiments were performed on a Varian Mercury Plus 400 MHz spectrometer. Elemental analyses were performed on a EuroEA 3000 CHNS analyzer. Attempts to record the MS spectra of compounds **5g-l** with a GC-MS spectrometer revealed their thermal instability at 250 °C

injection temperature. The retention times of the peaks in the chromatograms and the corresponding mass spectra were identical with those of the corresponding **4g-l**.

Synthesis of (Z)-2-methyl-4-oxo-4-(arylamino)but-2-enoic acid 3a-f. General procedure: To a solution of 3-methylmaleic anhydride (20 mmol, 2.2872 g) in THF (60 mL) was added aniline derivative (20 mmol) and the mixture heated at reflux for 2 h. The solvent was partly evaporated and the mixture left to crystallize at room temperature. The formed crystals were collected by filtration and dried under vacuum.

(Z)-2-methyl-4-oxo-4-(phenylamino)but-2-enoic acid 3a. Yield, 3.283 g, 80%. White crystals, mp 175-176 °C. Lit[2] mp 172 °C. IR (KBr) ν_{OH} 3449, ν_{NH} 3287, $\nu_{C=O}$ 1709, $\nu_{C=C}$ 1631 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.96 (3H, s), 6.08 (1H, s), 7.03 (1H, t, J = 7.0 Hz), 7.28 (2H, t, J = 7.6 Hz), 7.59 (2H, d, J = 8.8 Hz), 10.14 (1H, s), 12.9 (1H, brs). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 21.0; 119.6; 123.6; 123.9; 129.2; 139.4; 143.1; 163.1; 170.7. Anal calcd for $C_{11}H_{11}NO_3$ (205.21) C, 64.38; H, 5.40; N, 6.83; Found C, 64.50; H, 5.25; N, 6.90.

(Z)-4-(p-toluidino)-2-methyl-4-oxobut-2-enoic acid 3b. Yield, 3.771 g, 86%. Yellowish crystals, mp 179-180 °C. IR (KBr) ν_{OH} 3477, ν_{NH} 3289, $\nu_{C=O}$ 1700, $\nu_{C=C}$ 1632 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.96 (3H, s), 2.23 (3H, s), 6.06 (1H, s), 7.09 (2H, d, J = 8.0 Hz) 7.47 (2H, d, J = 8.0 Hz), 10.07 (1H, s), 12.9 (1H, s). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 20.9, 21.0; 119.6; 123.6; 129.6; 132.9, 136.8, 143.0; 162.9; 170.6. Anal calcd for $C_{12}H_{13}NO_3$ (219.24) C, 65.74; H, 5.98; N, 6.39; Found C, 66.00; H, 6.04; N, 6.59.

(Z)-4-(4-methoxyphenylamino)-2-methyl-4-oxobut-2-enoic acid 3c. Yield, 4.328 g, 92%. Green powder, mp 181-182 °C. IR (KBr) ν_{OH} 3500, ν_{NH} 3279, $\nu_{C=O}$ 1690, $\nu_{C=C}$ 1627 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.96 (3H, s), 3.70 (3H, s), 6.06 (1H, s), 6.87 (2H, d, J = 7.6 Hz) 7.51 (2H, d, J = 7.6 Hz), 10.06 (1H, s), 13.0 (1H, s). 13C-NMR (100 MHz, DMSO-d_6): δ 21.1; 55.6; 114.3; 121.2; 123.7; 132.4; 142.8; 155.8; 162.7; 170.5. Anal calcd for $C_{12}H_{13}NO_4$ (235.24) C, 61.27; H, 5.57; N, 5.95; Found C, 61.13; H, 5.60; N, 6.00.

(Z)-2-methyl-4-(4-nitrophenylamino)-4-oxobut-2-enoic acid 3d.[12] Yield, 1.5 g, 30%. Yellow needles, mp 166-167 °C. IR (KBr) ν_{OH} 3473 cm^{-1}, ν_{NH} 3279, $\nu_{C=O}$ 1702, $\nu_{C=C}$ 1633 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.98 (3H, s), 6.11 (1H, s), 7.83 (2H, d, J = 9.2 Hz) 8.2 (2H, d, J = 9.2 Hz), 10.71 (1H, s), 12.9 (1H, s). 13C-NMR (100 MHz, DMSO-d_6): δ 20.8; 119.3; 123.2; 125.5; 142.7; 144.2; 145.7; 163.9; 170.5. Anal calcd for $C_{11}H_{10}N_2O_5$ (250.21) C, 52.80; H, 4.03; N, 11.20; Found C, 53.00; H, 3.91; N, 11.30.

(Z)-4-(4-chlorophenylamino)-2-methyl-4-oxobut-2-enoic acid 3e. Yield 3.834 g, 80%. Cream powder, mp 188-189 °C. IR(KBr) ν_{OH} 3464, ν_{NH} 3280, $\nu_{C=O}$ 1707, $\nu_{C=C}$ 1631 cm^{-1}; ^{1}H-NMR(400 MHz, DMSO) : δ 1.96 (3 H, s), 6.06 (1H, s), 7.34 (2H, d, J = 8.8 Hz), 7.62 (2H, d, J = 8.8 Hz), 10.26 (1H, s), 12.86 (1H, s). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 20.9; 121.2; 123.4; 127.4; 129.1; 138.4; 143.3; 163.2; 170.6. Anal calcd for $C_{11}H_{10}ClNO_3$ (239.65) C, 55.13; H, 4.21; N, 5.84; Found C, 55.30; H, 3.97; N, 6.01.

(Z)-4-(4-bromophenylamino)-2-methyl-4-oxobut-2-enoic acid 3f. Yield 4.546 g, 80%. Yellow powder, mp 185-186 °C. IR (KBr) ν_{OH} 3456, ν_{NH} 3282, $\nu_{C=O}$ 1710, $\nu_{C=C}$ 1634 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO): δ 1.96 (3 H, s), 6.06 (1H, s), 7.47 (2H, d, J = 9.2 Hz), 7.57 (2H, d, J = 9.2 Hz), 10.26 (1H, s), 12.86 (1H, s). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 20.9; 115.4; 121.5; 123.4; 132.0; 138.8; 143.3; 163.2; 170.6. Anal calcd for $C_{11}H_{10}BrNO_3$ (284.11) C, 46.50; H, 3.55; N, 4.93; Found C, 46.55; H, 3.38; N, 5.10.

Synthesis of N-aryl maleimides 4a-f. General procedure: To a solution of maleic anhydride **2a** (20 mmol, 2.2872 g) in THF (60 mL) was added aniline derivative (20 mmol) and the reaction mixture stirred

for 2 h. Triethylamine (20 mmol, 2.8 mL) and $SOCl_2$ (24 mmol, 1.76 mL) were added successively and the reaction mixture stirred at reflux for 6 h. The solvent was evaporated and the mixture poured into water (80 mL) and extracted with chloroform (3 × 15 mL). The combined extracts were dried over anhydrous Na_2SO_4. The organic solvent was evaporated and the residue dissolved in ethanol-ether (1:2) and left to crystallize in a refrigerator.

3-Methyl-1-phenyl-1*H*-pyrrole-2,5-dione 4a. Yield 2.471 g, 66%. Brown powder, mp 93-94 °C. IR (KBr) $\nu_{C=O}$ 1709 cm^{-1}; $\nu_{C=C}$ 1653 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.17 (3H, d, J = 2.0 Hz), 6.48 (1H, q, J = 2.0 Hz), 7.35 (3H, t, J = 7.2 Hz), 7.46 (2H, t, J = 7.2 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 11.2; 125.9; 127.5; 127.7; 129.1; 131.6; 145.8; 169.6; 170.6. Anal calcd for $C_{11}H_9NO_2$ (187.19) C, 70.58; H, 4.85; N, 7.48; Found C, 70.75; H, 4.73; N, 7.70.

3-Methyl-1-p-tolyl-1*H*-pyrrole-2,5-dione 4b. Yield 2.696 g, 67%. Brown powder, mp 112-113 °C. IR (KBr) $\nu_{C=O}$ 1701 cm^{-1}; $\nu_{C=C}$ 1638 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.16 (3H, d, J = 2.0 Hz), 2.38 (3H, s), 6.46 (1H, q, J = 2.0 Hz), 7.2 (2H, d, J = 8.4 Hz), 7.26 (2H, d, J = 8.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 11.2; 21.2; 125.9; 127.4; 128.9; 129.7; 137.8; 145.7; 169.8; 170.8. Anal calcd for $C_{12}H_{11}NO_2$ (201.22) C, 71.63; H, 5.51; N, 6.96; Found C, 71.70; H, 5.65; N, 7.17.

1-(4-Methoxyphenyl)-3-methyl-1*H*-pyrrole-2,5-dione 4c. Yield 3.345 g, 77%. Brown powder, mp 115-116 °C. IR (KBr) $\nu_{C=O}$ 1708 cm^{-1}; $\nu_{C=C}$ 1641 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.16 (3H, d, J = 2.0 Hz), 3.82 (3H, s), 6.46 (1H, q, J = 2.0 Hz), 6.97 (2H, d, J = 8.8 Hz), 7.23 (2H, d, J = 8.8 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 11.2; 55.5; 114.4; 124.2; 127.4; 127.5; 145.7; 159.0; 169.9; 170.9. Anal calcd for $C_{12}H_{11}NO_3$ (217.22) C, 66.35; H, 5.10; N, 6.45; Found C, 66.50; H, 5.14; N, 6.55.

3-Methyl-1-(4-nitrophenyl)-1*H*-pyrrole-2,5-dione 4d. Yield 3.111 g, 67%. Brownish plates, mp 154-155 °C. IR (KBr) $\nu_{C=O}$ 1721 cm^{-1}; $\nu_{C=C}$ 1642 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.22 (3H, d, J = 2.0 Hz), 6.57 (1H, q, J = 2.0 Hz), 7.69 (2H, d, J = 9.6 Hz), 8.32 (2H, d, J = 9.6 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 11.3; 124.4; 125.2; 127.9; 137.5; 145.9; 146.4; 168.5; 169.7. Anal calcd for $C_{11}H_8N_2O_4$ (232.19) C, 56.90; H, 3.47; N, 12.06; Found C, 56.88; H, 3.48; N, 12.20.

1-(4-Chlorophenyl)-3-methyl-1*H*-pyrrole-2,5-dione 4e. Yield 3.236 g, 73%. Brownish plates, mp 114-115 °C. IR (KBr) $\nu_{C=O}$ 1710 cm^{-1}; $\nu_{C=C}$ 1638 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.17 (3H, d, J = 1.6 Hz), 6.49 (1H, q, J = 1.6 Hz), 7.32 (2H, d, J = 8.8 Hz), 7.42 (2H, d, J = 8.8 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 11.2; 126.9; 127.6; 129.2; 130.2; 133.3; 146.0; 169.2; 170.3. Anal calcd for $C_{11}H_8ClNO_2$ (221.64) C, 59.61; H, 3.64; N, 6.32; Found C, 59.70; H, 3.75; N, 6.50.

1-(4-Bromophenyl)-3-methyl-1*H*-pyrrole-2,5-dione 4f. Yield 3.725 g, 70%. Brownish plates, mp 113-114 °C. IR (KBr) $\nu_{C=O}$ 1711 cm^{-1}; $\nu_{C=C}$ 1642 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.18 (3H, d, J = 2.0 Hz), 6.49 (1H, q, J = 2.0 Hz), 7.26 (2H, d, J = 9.2 Hz), 7.58 (2H, d, J = 9.2 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 11.2; 121.3; 127.2; 127.6; 130.7; 132.2; 146.0; 169.1; 170.2. Anal calcd for $C_{11}H_8BrNO_2$ (266.09) C, 49.65; H 3.03; N, 5.26; Found C, 49.80; H, 3.35; N, 5.37.

Synthesis of 3-chloro-1-arylsuccinimides 5. General procedure: To a solution of maleic anhydride **2b** (5 mmol, 0.49 g) in THF (15 mL) was added aniline derivative (5 mmol) and the reaction mixture stirred for 2 h. Triethylamine (5 mmol, 0.7 mL) and $SOCl_2$ (6 mmol, 0.44 mL) were added successively and the reaction mixture stirred at reflux for 6 h. The solvent was evaporated and the mixture poured into crushed ice

(20 g). The formed amorphous solid was filtered and dried in a vacuum oven. Pure samples were obtained by crystallization from THF-ether (1:2).

3-Chloro-1-phenylsuccinimide 5g. Yield 0.755 g, 72%. Brownish plates, mp 114-116, lit[6a] mp 115 °C. IR (KBr) $\nu_{C=O}$ 1722 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.09 (1H, dd, J = 18.8; 4 Hz), 3.48 (1H, dd, J = 18.8; 9.2 Hz), 4.79 (1H, dd, J = 9.2; 4.4 Hz), 7.31 (2H, d, J = 7.2 Hz), 7.41-7.51 (3H, m). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 39.4; 48.9; 125.32; 126.2; 129.2; 129.4; 171.9; 172.0. Anal calcd for $C_{10}H_8ClNO_2$ (209.63) C, 57.30; H, 3.85; N, 6.68; Found C, 57.45; H, 3.95; N, 6.80.

3-Chloro-1-p-tolylsuccinimide 5h. Yield 0.850 g, 76%. Yellow powder, mp 157-158, lit[6b] mp 157-158 °C. IR (KBr) $\nu_{C=O}$ 1720 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.39 (3H, s), 3.07 (1H, dd, J = 18.8; 4.4 Hz), 3.46 (1H, dd, J = 18.8; 8.8 Hz), 4.77 (1H, dd, J = 8.8; 4.4 Hz), 7.18 (2H, d, J = 8.4 Hz), 7.29 (2H, d, J = 8.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.3; 39.4; 48.9; 126.0; 128.5; 130.0; 139.4; 172.1; 172.2. Anal calcd for $C_{11}H_{10}ClNO_2$ (223.66) C, 59.07; H, 4.51; N, 6.26; Found C, 59.17; H, 4.50; N, 6.46.

3-Chloro-1-(4-methoxyphenyl)succinimide 5i. Yield 0.911 g, 76%. Brown powder, mp 145-146, lit[8] mp 144-145.5 °C. IR (KBr) $\nu_{C=O}$ 1712 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.07 (1H, dd, J = 18.8; 4.0 Hz), 3.46 (1H, dd, J = 18.8; 8.4 Hz), 3.83 (3H, s), 4.77 (1H, dd, J = 8.4; 4.0 Hz), 6.99 (2H, d, J = 8.8 Hz), 7.22 (2H, d, J = 8.8 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 39.3; 48.9; 55.5; 114.6; 123.7; 127.5; 159.9; 172.2; 172.3. Anal calcd for $C_{11}H_{10}ClNO_3$ (239.66) C, 55.13; H, 4.21; N, 5.84; Found C, 54.95; H, 4.19; N, 6.01.

3-Chloro-1-(4-nitrophenyl)succinimide 5j. Yield 0.611 g, 48%. Brownish powder, mp 167-170, lit[6b] mp 173-174 °C. IR (KBr) $\nu_{C=O}$ 1722 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.16 (1H, dd, J = 19.2; 4.4 Hz), 3.50 (1H, dd, J = 19.2; 8.4 Hz), 4.84 (1H, dd, J = 8.4; 4.4 Hz), 7.63 (2H, d, J = 9.2 Hz), 8.37 (2H, d, J = 9.2 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 39.4; 48.7; 124.6; 126.8; 134.6; 136.5; 171.1; 171.2. Anal calcd for $C_{10}H_7ClN_2O_4$ (254.63) C, 47.17; H, 2.77; N, 11.00; Found C, 47.30; H, 2.78; N, 11.15.

3-Chloro-1-(4-chlorophenyl)succinimide 5k. Yield 0.659 g, 54%. Cream powder, mp 151-152, Lit[6b] mp 153-154 °C. IR (KBr) $\nu_{C=O}$ 1722 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.10 (1H, dd, J = 19.2; 4.4 Hz), 3.49 (1H, dd, J = 19.2; 8.8 Hz), 4.78 (1H, dd, J = 8.8; 4.4 Hz) 7.29 (2H, d, J = 9.2 Hz), 7.47 (2H, d, J = 9.2 Hz). 13C-NMR (100 MHz, $CDCl_3$): δ 39.3; 48.8; 127.5; 129.6; 135.0; 171.1 (2 C). Anal calcd for $C_{10}H_7Cl_2NO_2$ (244.07) C, 49.21; H, 2.89; N, 5.74; Found C, 49.10; H, 2.90; N, 6.00.

1-(4-Bromophenyl)-3-chlorosuccinimide 5l. Yield 0.779 g, 54%. Cream powder, mp 162-163 °C. IR (KBr) $\nu_{C=O}$ 1720 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.09 (1H, dd, J = 18.8; 4.4 Hz), 3.48 (1H, dd, J = 18.8; 8.8 Hz), 4.78 (1H, dd, J = 8.8; 4.4 Hz) 7.23 (2H, d, J = 8.4 Hz), 7.63 (2H, d, J = 8.4 Hz). 13C-NMR (100 MHz, $CDCl_3$): δ 39.4; 48.8; 123.1; 127.7; 130.1; 132.5; 171.6 (2 C). Anal calcd for $C_{10}H_7BrClNO_2$ (288.53) C, 41.63; H, 2.45; N, 4.85; Found C, 41.42; H, 2.50; N, 5.05.

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11. **Maleimides 4g-l.** The crude mixtures from the cyclization of maleamic acids in the presence of triethylamine (5 mmol, 0.7 mL) and $SOCl_2$ (6 mmol, 0.44 mL) were treated with additional amounts of triethylamine (4.1 mmol, 0.57 mL) for 0.5 h at room temperature. The mixture was poured into crushed ice (20 g) and the formed solid was filtered and dissolved in ethanol or ethanol-ether (1:2) and left to crystallize in a refrigerator. The crystalline product was filtered and dried under vacuum. The identity of the products was proved by spectral means and comparison with authentic samples. **4g**; Yield 71%, mp 87-88, lit[6b] mp 89-90 °C. **4h**; Yield 73%, mp 147-148, lit[6b] mp 145-146 °C. **4i**; Yield 90%, mp 150-151, lit[8] mp 148-148.5 °C. **4j**; Yield 91%, mp 167-168, lit[6b] mp 168-170 °C. **4k**; Yield 63%, mp 116-117, lit[6b] mp 114-115 °C. **4l**; Yield 90%, mp 126-127, lit[9] mp 123-124 °C.
12. **(Z)-2-methyl-4-(4-nitrophenylamino)-4-oxobut-2-enoic acid 3′ d**. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.05 (3H, s), 5.87 (1H, s), 7.83 (2H, d, J = 9.2 Hz) 8.2 (2H, d, J = 9.2 Hz), 10.74 (1H, s), 12.69 (1H, s). The spectrum is elicited from a mixture of **3d** and **3'd** containing 41% **3'd**.