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Rearrangements of tetrahydroimidazo[1,5-*b*]isoxazole-2,3-dicarboxylates to pyrrolo[1,2-*e*]imidazol-6-ols, precursors of 2,5-dihydro-1*H*-pyrrole derivatives

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ABSTRACT

Isoxazolines **2** from the cycloaddition of imidazoline 3-oxides **1** with DMAD rearrange in the presence of methoxide to give *cis*-3-methoxy-7-(methoxycarbonyl)-2,7a-diaryl-5-oxo-2,3,5,7a-tetrahydro-1*H*-pyrrolo[1,2-*e*]imidazol-6-olates **3** with 100% de. The acidic hydrolysis of **3** led to kinetically controlled formation of methyl 1-formyl-4-hydroxy-5-oxo-2-phenyl-2-((arylamino)methyl)-2,5-dihydro-1*H*-pyrrole-3-carboxylates **6a**–**e**. The intramolecular transformylations of the latter to the corresponding (*E*)- and (*Z*)-methyl 4-hydroxy-2-((*N*-(aryl)formamido)methyl)-5-oxo-2-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylates **7a**–**e** were shown to be substituent dependent (correlate with σ) and characterized by Hammett type equations. The effect of temperature was investigated and the ρ constants determined for the same reaction series at 50, 60 and 70 °C. The amide diastereomeric ratio [(*E*)-**7**]/[(*Z*)-**7**] is substituent dependent and can be described by the equation $\log[(E)]/[(Z)]_X=-\rho\sigma_I+\log[(E)]/[(Z)]_{X=H}$.

1. Introduction

The synthetic utility of the 1,3-dipolar cycloaddition reaction is evident from the number and the scope of targets that can be prepared by this chemistry. The nitrones are the most useful through their ability to generate nitrogen- and oxygen-based functionalities from the cycloaddition reactions.[1] The cycloadducts of di- and triarylimidazolin-3-oxides[2] with variety of dipolarophiles[3] are bicyclic compounds with potentially interesting biological activities. On the other hand, they are source of new heterocyclic compounds via interesting ring-opening reactions.[4] Previously, we reported the synthesis of stable adducts of 3-imidazolin-3-oxides with dimethyl acetylenedicarboxylate (DMAD)[3d,e] and alkyl 3-phenylpropiolates.[3f] Thermally- and base-induced ring-opening reactions of these adducts were demonstrated.

There is still a large interest in 4-isoxazolines[1a,5,6] due to their biological activities[7a] and as a source of interesting rearrangements.[7b,c]

2. Results and discussion

Recently, we have reported the reaction of acyclic nitrones[8] with DMAD in benzene at room temperature to produce 4-isoxazolines in good yields. These latter were shown to undergo substituent dependent rearrangement to the corresponding oxazolines, which fragment to an aldehyde and extremely reactive iminocarbene.[9] We have also reported the treatment of 4-isoxazolines with methoxide in methanol at room temperature to produce highly functionalized diastereomeric mixtures of 1-(methoxy(aryl)methyl)-4-(methoxycarbonyl)-2-oxo-5-aryl-2,5-dihydro-1*H*-pyrrol-3-ols,[9] which can be further elaborated to give some biologically active pyrrole[10] analogues of (−)-codonopsinine and (−)-codonopsine alkaloids.[11] The latter are attractive for both synthetic and medicinal chemists due to the challenging penta-substituted pyrrolidine nucleus, and their varied biological activities as antibiotics and as antihypertensive agents without any effects on the central nervous system.[12]

As part of an ongoing program in our laboratory for the synthesis of NHC based catalysts useful in C–C coupling reactions such as Heck, Suzuki, etc. we aimed to prepare imidazolinium salts **4** (Scheme 1) and treat them with bases to asses their ability to give NHCs **5**.

The treatment of imidazolin-3-oxides[13] **1** with DMAD will produce compounds **2**, heating the latter at reflux in methanol in the presence of methoxide would give enolates **3** as we have recently reported for acyclic nitrone DMAD adducts. The treatment of

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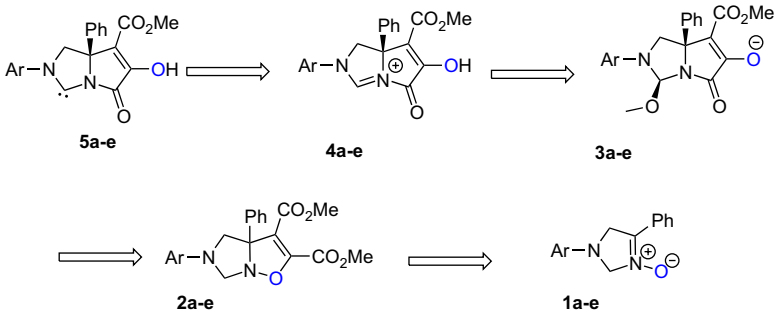


Scheme 1. Retrosynthetic analysis of NHCs **5**.

enolates **3** with acids was expected to produce imidazolinium salts **4**, which upon basification would provide NHCs **5**.

Here we report on the methoxide-induced diastereoselective rearrangement of isoxazolines **2a–e** (Schemes 1 and 2) into 3-methoxy-7-(methoxycarbonyl)-2,7a-diaryl-5-oxo-2,3,5,7a-tetrahydro-1*H*-pyrrolo[1,2-*e*]imidazol-6-olates **3a–e** and their conversion to the corresponding methyl 1-formyl-4-hydroxy-5-oxo-2-phenyl-2-((arylamino)methyl)-2,5-dihydro-1*H*-pyrrole-3-carboxylates **6a–e**. The effect of substituents on the transformylation of **6a–e** to the corresponding amides (*E*)- and (*Z*)-methyl 4-hydroxy-2-((*N*-(aryl)formamido)methyl)-5-oxo-2-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylates **7a–e** as well as the effect of substituents on the (*E*)- and (*Z*)-**7** ratio is reported.

2.1. Synthesis and structural elucidation of compounds 3a–e

Heating isoxazolines **2a–e** in methanol at reflux in the presence of a three fold excess of sodium methoxide produced the corresponding *cis* enolates **3a–e** with 100% de. The treatment of *cis*-dimethyl 3a,5,6-triaryl-3a,4,5,6-tetrahydroimidazo[1,5-*b*]isoxazole-2,3-dicarboxylates with methoxide produced the corresponding mixture of Michael adducts dimethyl 2-methoxy-3a,5,6-triaryl-hexahydroimidazo[1,5-*b*]isoxazole-2,3-dicarboxylates.[3e] Enolates **3** have carbonyl stretching frequencies at 1727 and 1679 cm^{-1}. Characteristic AB system parts in the ^1H NMR spectra of the compounds in DMSO-d_6 at δ 3.08 (1H, d, J=9.4 Hz) and 4.70 ppm (1H, d, J=9.4 Hz) are assigned to C1–H_2. The one proton singlet at 5.57 ppm corresponds to the C3–H proton. The three proton singlets at 3.12 and 3.41 ppm are assigned to the ether and ester methoxy groups, respectively. All other peaks are in agreement with the proposed structures. Characteristic chemical shifts assignments based on 1D and 2D NMR experiments for compound **3c** are given in Figure 1.

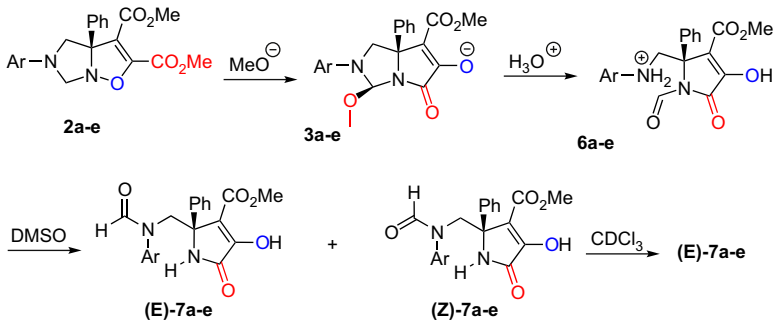
NOESY1D experiments revealed that the MeO group at C3 is on the same side as the aromatic ring at C7a. The energy minimized model of **3c** and some characteristic NOE correlations are given in Figure 2. The irradiation of the methoxy group led to enhancements of the signals of C3–H and C1–Ha by 0.5 and 0.6%, respectively. C1–Ha was irradiated and the signal for the *o*-protons of the C7a-aromatic ring and C1–Hb were enhanced by 10 and 9%, respectively. Irradiation of the *o*-protons of the C7a–Ph enhanced the signal of C3–OMe by 1.4%. Thus we concluded that the methoxy group at C3 and the phenyl at C7a are cis oriented.

2.2. Probable mechanism for the rearrangement of isoxazolines 2 to pyrroloimidazoles 3

A methoxide-induced intramolecular elimination of **2** gives resonance stabilized imine enolates **A** and **B** (Scheme 3). This, or most probably its protonated form **C**, reacts with methoxide to give the diastereomer **D**, the cyclization of which produces enolate **3**. The preferred cis product formation can be rationalized by assuming that the addition of the methoxide to the C=N bond from the side where the phenyl group is located (path a) is accompanied by synchronous protonation from the opposite side, thus the transition state leading to **D** should be much more stable than the one leading to the trans product **D′** (path b).

2.3. Synthesis and structural elucidation of compounds 6

The reaction of compounds **3** with CF_3CO_2H led to the formation of a white solid upon pouring the reaction mixtures in ice water.[14] The elemental analyses and spectral data revealed that the compounds are the corresponding **6a–e** hydrates instead of the expected **4a–e**. The compounds have broad bands corresponding to ν_{OH} at ca. 3470 and a broad highly structured band characteristic for ammonium salts at 2955–2492 cm^{-1} in their IR



Scheme 2. **1–7a**, Ar=Ph; **1–7b**, Ar=4-MeC_6H_4; **1–7c**, Ar=4-MeOC_6H_4; **1–7d**, Ar=4-ClC_6H_4; **1–7e**, Ar=4-BrC_6H_4.

spectra. $\nu_{C=O}$ at 1760, 1710, 1691 and $\nu_{C=C}$ at 1646 cm^{-1} are in agreement with the proposed structure. The characteristic ^1H and ^{13}C NMR assignments based on gCOSY, gHMQC and gHMBC experiments are given for **6c** in Figure 1. The signals for the enolic protons and the aromatic amine NH are seen in the cases of **6d**,**e** while in the case of **6a**–**c** they are seen under one broad singlet together with the water resonances at ca. 3.70 ppm. However when the spectra are repeated with addition of an equimolar amount of Et_3N an ABX spectral pattern for the $NHCH_2$ appeared with the following characteristics: ca. 4.20 ppm (1H, dd, J=13.2 Hz, 6.4 Hz), 4.33 ppm (1H, dd, J=13.2 Hz, 5.2 Hz), 4.84 ppm (1H, t, J=6.4 Hz, 5.2 Hz). The triplet of NH at ca. 4.84 ppm disappeared upon treatment with D_2O.

Compound **6c** was heated in methanol at reflux in the presence of 2 equiv of methoxide. The solvent was evaporated and the residue was triturated with ether to give 4-(methoxycarbonyl)-5-((4-methoxyphenylamino)methyl)-2-oxo-5-phenyl-2,5-dihydro-1*H*-pyrrol-3-olate. The ^1H NMR spectrum of the crude mixture indicated that the main compound is the corresponding deformylation product, which have characteristic ABX pattern 3.44 (1H, dd, J_{AB}=12.0 Hz, J_{Ax}=4.0 Hz), 3.97 (1H, dd, J_{AB}=12.0 Hz, J_{Bx}=7.6 Hz), 4.49 (1H, dd, J_{Bx}=7.6 Hz, J_{Ax}=4.0 Hz). The D_2O exchange experiments revealed that the protons at 4.49 and 8.76 ppm corresponding to the ArN*H* and the pyrrolidin-5-one N*H*, respectively are readily exchangeable. ^{13}C NMR data also revealed the absence of the carbon signal corresponding to N–CHO. It was surprising that the mixture contained **3c** (ca. 7%), which implies that under these reaction conditions the deformylation process is accompanied by the competing cyclization to **4**, which then undergo nucleophilic addition of methoxide.

The probable mechanism for the formation of **4** and their hydrolyzes to **6** is shown in Scheme 4.

The treatment of enolates **3** with acids led to the protonation of the enolate oxygen as well as demethoxylation at C3 to give compounds **4**. The hydrolysis of the latter through **4′** and **4″** produces protonated **6**. The most characteristic peak for compounds **6** in DMSO-d_6, the formyl hydrogen at ca. 8.91 ppm, gradually disappears while singlets at ca. 8.10, 8.23, 9.07, 9.32 and 11.11 ppm appear. The latter four singlets disappear upon treatment with D_2O. NMR analyses of the formed two products revealed that they are the corresponding amides[15] (*E*)- and (*Z*)-**7**. Characteristic assignments for the (*E*)- and (*Z*)-**7c** and NOE based correlations are given in Figure 3. Irradiation of the signal at 8.19 ppm led to the enhancement of the N–Ar ortho proton signal while the irradiation of the singlet at 8.16 ppm enhanced the signal of one of the N–CH_2 as well as the signal of the pyrrolinone NH. These data were used to assign (*E*)- geometry for the first and (*Z*)- for the second diastereomer.

It is clear that the hydrolyzes of compounds **4** are chemoselective, kinetically controlled processes. This in fact is an unexpected case of *N*-acyliminium salt hydrolysis since the products of such hydrolyzes lead to the corresponding amide and the carbonyl derivative.

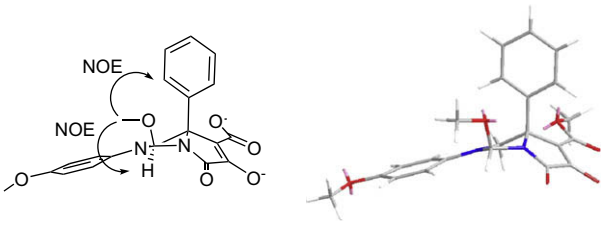


Figure 2. Characteristic NOE correlations shown on the energy minimized molecular model of *cis*-enolate **3c**.

2.4. Substituent effect on the transformylation of 6 to 7

To elucidate the effect of substituents on the transformylation of **6** to (*E*)- and (*Z*)-**7** and on the product ratios we performed a series of experiments for **6a**–**e** each 3.75×10^{-2} M in DMSO-d_6 at 20 °C and followed the reactions by ^1H NMR spectroscopy after a week. The relative amounts of the diastereomers and the starting **6** were measured by integration of the corresponding formyl hydrogen peaks in their ^1H NMR spectra. The concentrations (%) determined after a week and the corresponding log *K* are given in Table 1. The data clearly reveal that the nature of the substituent on the *N*-aromatic ring determines the ratio of the products. Electron-donating groups accelerate while electron-withdrawing groups decelerate the reactions. The reaction susceptibility constants of (*E*)- and (*Z*)-**7** are too close to each other.

The log of both ratios [(*E*)-**7**]/[**6**] (K_E) and [(*Z*)-**7**]/[**6**] (K_Z) correlate with the Hammett σ constants (Fig. 4). The correlation of log *K*, *K* defined as [(*E*)-**7**]+[(*Z*)-**7**]/[**6**], with the same constants produced equation $\log(K)_X=-6.38\sigma+\log(K)_H$. The value of the reaction constant clearly implies that there is a high charge separation in the rate limiting step of the transformylation reaction. Attempts to correlate the (*E*)/(*Z*) ratios with substituent constants did not produce an acceptable linearity.

2.5. Probable mechanism for the transformylation of 6 to 7

The probable mechanism for the formation of (*E*)- and (*Z*)-**7** is depicted in Scheme 5. As the Hammett correlations imply, the transformylation reaction rate limiting step should be the nucleophilic attack of the amine nitrogen to the *N*-formyl group. The attack to the upward orientated carbonyl will produce imidazolidine **A** while the downward orientated will produce the other diastereomer **A′**. Proton migration from the ammonium nitrogen to the pyrrolinone carbonyl will produce intermediates **B** and **B′**. The

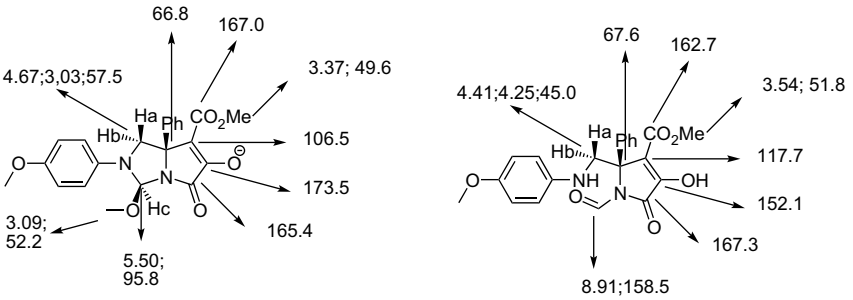
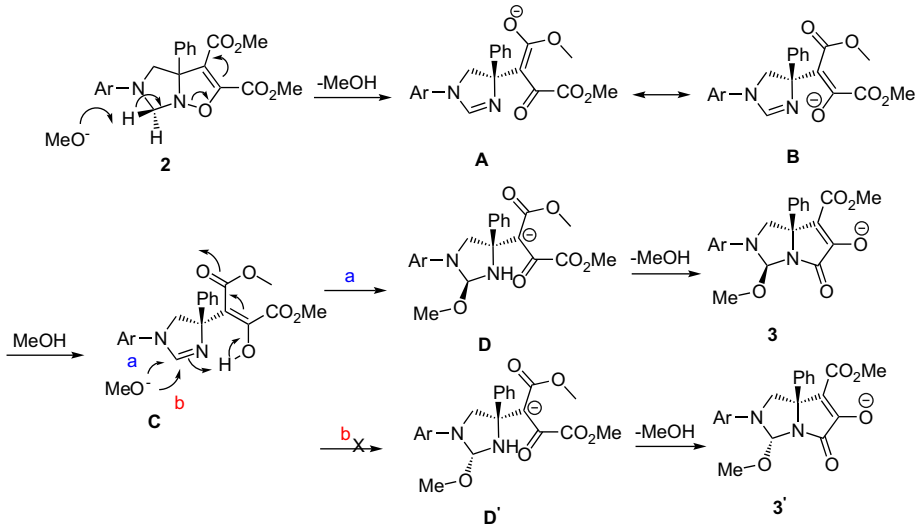


Figure 1. Comparison of the characteristic NMR data of **3c** and **6c** in DMSO-d_6.



Scheme 3. Probable mechanism for the rearrangement of isoxazolines **2** into **3**.

deprotonation and tautomerization of the latter will give the corresponding (*E*)- and (*Z*)-**7**.

2.6. Temperature effect on the transformylation of 6 to 7

To elucidate the temperature effect on the susceptibility of transformylation reaction of **6** to **7** we have determined the ρ constants at 50, 60 and 70 °C. The reaction series equilibrated for 8 days in DMSO-d_6 at 20 °C then were heated at 50 °C for 1 h. The contents of the corresponding (*E*)-, (*Z*)-**7** and **6** were determined and the log K_E, log K_Z and log K plotted versus the Hammett σ constants. The same was repeated for the reaction series at 60 and 70 °C. The plots were linear in all cases (Table 2, Fig. 5). The *E*/*Z* ratios remained nearly constant at all reaction temperatures. It was observed that the increase of the temperature decreased the absolute values of the reaction constants.

The heating of the same reaction series again at 50 °C for 14 h revealed that the reaction is not reversible but the values obtained again are in linear correlation with the Hammett σ constants (Table 3, Fig. 6).

The comparison of the ρ constants at 20–70 °C clearly indicates that they decrease as the temperature is increased. The comparison of the reaction constants ρ at 50 °C for 1 h and 14 h revealed that its absolute value is also decreasing as the reaction time is increased.

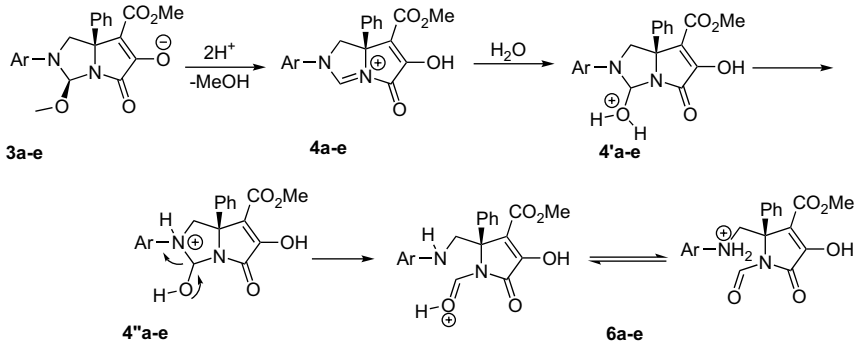
2.7. Solvent effect on the (*E*)-, (*Z*)-7 equilibria

The extraction of the products with $CHCl_3$ from the reactions of **6** in DMSO-d_6 produced yellowish oils, which solidify on drying under vacuum. The spectra of the latter compounds in $CDCl_3$ (5.6×10^{-3} M) revealed that they are (*E*)-**7a–e** confirmed by NOESY1D experiments.[18] The spectra of the same compounds dissolved in DMSO-d_6 (5.6×10^{-3} M) revealed that they easily convert to the corresponding amide isomers (*E*)- and (*Z*)-**7**. The isomer ratios measured at 25 °C were in linear correlation with σ_I constants with a $\rho=-0.24$ (Table 4 and Fig. 7). This implies that the *N*-aromatic ring in compounds **7** is not coplanar with the amide functional group thus it cannot exert its full electronic effect (otherwise the correlations would be better with σ or σ^+ constants).

The geometry of the stereoisomer (*E*)-**7** is suitable for the formation of intramolecular hydrogen bond between the carbonyl oxygen and the pyrroline NH moiety (see Fig. 3). This is probably the main reason for the predomination of the latter in polar solvents in the cases where substituents with $-\sigma_I$ are present on the *N*-aromatic ring.

3. Conclusions

Thus we disclose for the first time a new diastereoselective rearrangement of isoxazolines **2** in the presence of a base to give 3-methoxy-7-(methoxycarbonyl)-2,7a-diaryl-5-oxo-2,3,5,7a-tetrahydro-1*H*-pyrrolo[1,2-*e*]imidazol-6-olates **3**. Compounds **3** were demonstrated to be useful precursors in the synthesis of pyrrole derivatives as 1-formyl-4-hydroxy-5-oxo-2-phenyl-2-((arylamino)methyl)-2,5-dihydro-1*H*-pyrrole-3-carboxylates **6a–e** or their transformylated analogues. Compounds **7** preferred (*E*)-configuration in relatively less polar solvents as $CDCl_3$ while in more polar solvents as DMSO-d_6 they exist as an equilibrium mixture.



Scheme 4. Ring opening of compounds **4** to methyl 2-arylaminomethyl-1-formyl-4-hydroxy-5-oxo-2-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylates **6**.

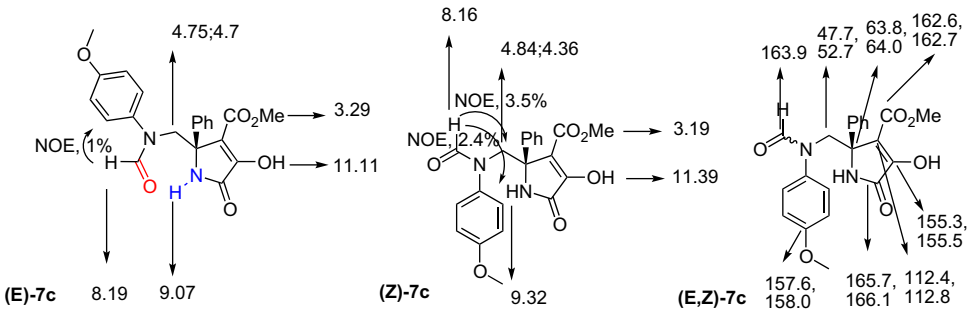


Figure 3. Characteristic assignments for pyrroles (*E*)- and (*Z*)-**7c**. The enolic hydrogens chemical shifts are from the ^{1}H NMR of **7b**.

Although the species **4** were not isolated as stable products this does not restrict the possibility for their in situ formation from **6** or **7** in acidic anhydrous media. The investigations in this respect are underway. For the first time the conversion of **6** to **7** was characterized by a Hammett equation $\log(K)_x=\rho\sigma+\log(K)_H$. The ratios of amide isomers in equilibrium are controlled by the inductive effect of the substituents on the *N*-aromatic ring.

4. Experimental

4.1. General

The solvents and the reagents used in the syntheses of compounds **1**–**3**,**6**–**7** were Merck (MeOH, $CHCl_3$, petroleum ether 40–60 °C, EtOH, benzene and the aromatic amines), Aldrich (Formaldehyde, DMAD, CF_3CO_2H) or Fluka (Phenacyl bromide and $(NH_2OH)_2H_2SO_4$) quality.

Melting points were recorded 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. The compounds prepared were dried in a vacuum oven at room temperature. Nitrones **1a**–**f** were prepared according to the previously reported methods.[2] The elemental analyses were performed on a EuroEA 3000 CHNS analyzer.

4.2. Synthesis of 4-phenyl-1-aryl-2,5-dihydro-1*H*-imidazole 3-oxides 1a–e

4.2.1. General procedure

To a solution of aniline derivative (40 mmol) in ethanol (80 mL) phenacyl bromide oxime (20 mmol, 4.28 g) was added and the mixture stirred at room temperature for 25 min. Formaldehyde (40 mmol, 3.2 mL, 37%) was added to the reaction mixture and stirred for further 3 h. The precipitated product was filtered and recrystallized from ethanol. In the cases of *p*-chloro- and bromoanilines a second product precipitates together with the imidazoline 3-oxide. The latter were separated by column chromatography and characterized to be (1,3-bis(4-aryl)imidazolidin-4-yl)(phenyl)methanones **1′d**,**e** (Scheme 6). The probable mechanism for their formation is discussed below.

Table 1
Linear free energy relationships in the transformylation of **6** to (*E*)-**7** and (*Z*)-**7** at 20 °C[17]

Ar	*E*-**7**[a]	*Z*-**7**[a]	**6**[a]	log K_E	log K_Z	log K[b]	σ
Ph	28.5	23	48.5	−0.23	−0.32	1.13	0
p-MeC_6H_4	45	33.5	22	0.31	0.18	1.84	−0.14
p-$MeOC_6H_4$	51.5	45.5	3	1.24	1.18	2.89	−0.28
p-ClC_6H_4	6	5.5	88.5	−1.17	−1.21	−0.43	0.24
p-BrC_6H_4	4.5	4.5	91	−1.31	−1.31	−0.65	0.26

[a] Content of the compound (%) after a week at 20 °C.
[b] The ratios were defined as follows K_E=[(*E*)-**7**]/[**6**], K_Z=[(*Z*)-**7**]/[**6**], K=[(*E*)-**7**][(*Z*)-**7**]/[**6**].

4.2.2. 1,4-Diphenyl-2,5-dihydro-1H-imidazole 3-oxide **1a**

Yield 1.90 g, 40%. Colourless powder, mp 206–207.5 °C; lit[2b] mp 186–187 °C. IR (KBr) $\nu_{C=N-O}$ 1587, $\nu_{C=N-O}$ 1229 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.81 (2H, t, J=4.0 Hz), 5.31 (2H, t, J=4.0 Hz), 6.71 (2H, d, J=8.0 Hz), 7.78 (1H, t, J=7.6 Hz), 7.27 (2H, t, J=8.0 Hz), 7.51–7.53 (3H, m), 8.37–8.40 (2H, m). ^{13}C NMR (100 MHz, DMSO-d_6): δ 53.1 (C5), 78.1 (C2), 112.5 (N–Ar-*o*), 118.2 (N–Ar-*p*), 127.0 (C4–Ph-*o*), 127.8 (C4), 129.0 (C4–Ph-*m*), 129.7 (N–Ar-*m*), 131.0 (C4–Ph-*p*), 136.2 (C4–Ph-*ipso*), 145.1 (N–Ar-*ipso*).

Anal. Calcd for $C_{15}H_{14}N_2O$ (238.28) C, 75.61; H, 5.92; N, 11.76. Found C, 75.55; H, 5.93; N, 11.80.

4.2.3. 4-Phenyl-1-p-tolyl-2,5-dihydro-1H-imidazole 3-oxide **1b**

Yield 2.27 g, 45%. Colourless crystals, mp 223–224 °C; lit[2b] mp 223–224 °C. IR (KBr) $\nu_{C=N-O}$ 1581, $\nu_{C=N-O}$ 1236 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.21 (3H, s), 4.77 (2H, t, J=4.0 Hz), 5.27 (2H, t, J=4.0 Hz), 6.62 (2H, d, J=8.0 Hz), 7.02 (2H, d, J=8.4 Hz), 7.50–7.53 (3H, m), 8.36–8.38 (2H, m). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.5 (Me), 53.3 (C5), 78.4 (C2), 112.7 (N–Ar-*o*), 126.9 (N–Ar-*p*), 127.0 (C4–Ph-*o*), 127.8 (C4), 129.0 (C4–Ph-*m*), 130.1 (N–Ar-*m*), 131.0 (C4–Ph-*p*), 136.3 (C4–Ph-*ipso*), 143.1 (N–Ar-*ipso*).

Anal. Calcd for $C_{16}H_{16}N_2O$ (252.31) C, 76.16; H, 6.39; N, 11.10. Found C, 75.94; H, 6.36; N, 11.36.

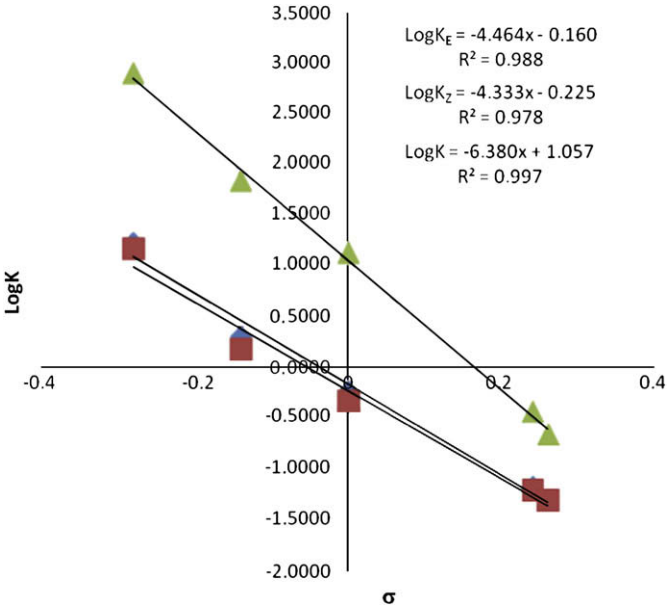
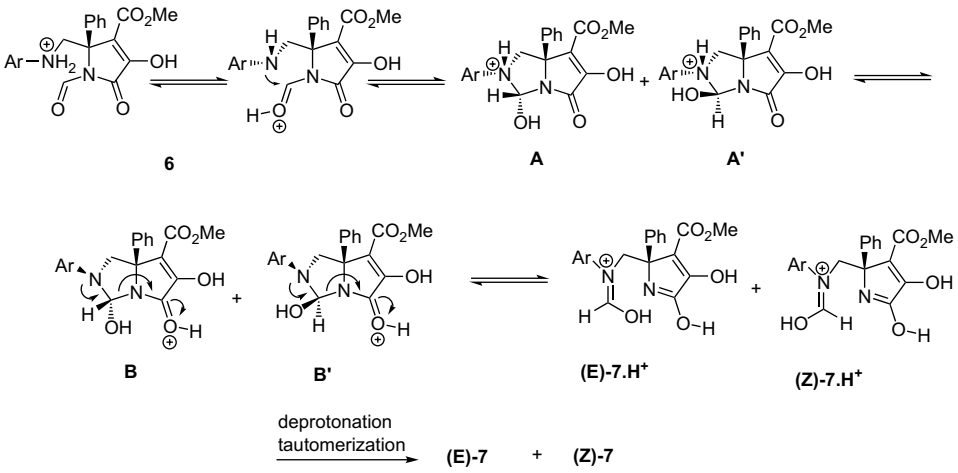


Figure 4. Plot of log K_E, log K_Z and log K versus σ.



Scheme 5. Probable mechanism for the transformylation of methyl 2-arylaminomethyl-1-formyl-4-hydroxy-5-oxo-2-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylates **6a–e**.

4.2.4. 1-(4-Methoxyphenyl)-4-phenyl-2,5-dihydro-1H-imidazole 3-oxide ***1c***

Yield 2.41 g, 45%. Colourless crystals, mp 189–190 °C; lit[2b] mp 189–190 °C. IR (KBr) $\nu_{C=N-O}$ 1588, $\nu_{C=N-O}$ 1225 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.68 (3H, s), 4.75 (2H, t, J=4.0 Hz), 5.25 (2H, t, J=4.0 Hz), 6.68 (2H, d, J=9.2 Hz), 6.89 (2H, d, J=8.8 Hz), 7.49–7.53 (3H, m), 8.36–8.38 (2H, m). ^{13}C NMR (100 MHz, DMSO-d_6): δ 53.7 (C5), 55.8 (MeO), 78.8 (C2), 113.7 (N–Ar), 115.3 (N–Ar), 126.9 (C4–Ph), 127.8 (C4), 129.0 (C4–Ph), 130.9 (C4–Ph), 136.3 (C4–Ph-*ipso*), 139.7 (N–Ar-*ipso*), 152.6 (N–Ar-*p*).

Anal. Calcd for $C_{16}H_{16}N_2O_2$ (268.31) C, 71.62; H, 6.01; N, 10.44. Found C, 71.78; H, 5.87; N, 10.06.

4.2.5. 1-(4-Chlorophenyl)-4-phenyl-2,5-dihydro-1H-imidazole 3-oxide ***1d***

Yield 0.54 g, 10%. Colourless crystals, mp 231–232 °C; IR (KBr) $\nu_{C=N-O}$ 1595, $\nu_{C=N-O}$ 1235 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 4.81 (2H, t, J=4.0 Hz), 5.31 (2H, t, J=4.0 Hz), 6.72 (2H, d, J=9.2 Hz), 7.31 (2H, d, J=8.8 Hz), 7.51–7.54 (3H, m), 8.36–8.38 (2H, m). ^{13}C NMR (100 MHz, DMSO-d_6): δ 53.3 (C5), 78.0 (C2), 114.1 (N–Ar-*o*), 126.0 (N–Ar-*p*), 126.9 (C4–Ph), 127.7 (C4), 129.1 (C4–Ph), 129.4 (N–Ar-*m*), 131.0 (C4–Ph), 136.1 (C4–Ph-*ipso*), 143.9 (N-Ar-*ipso*).

Anal. Calcd for $C_{15}H_{13}ClN_2O$ (272.73) C, 66.06; H, 4.80; N, 10.27. Found C, 65.64; H, 4.71; N, 9.88.

4.2.6. 1-(4-Bromophenyl)-4-phenyl-2,5-dihydro-1H-imidazole 3-oxide ***1e***

Yield 1.14 g, 16%. Colourless crystals from ethanol, mp 236–237 °C; IR (KBr) $\nu_{C=N-O}$ 1598, $\nu_{C=N-O}$ 1245 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 4.80 (2H, t, J=4.0 Hz), 5.31 (2H, t, J=4.0 Hz), 6.67 (2H, d, J=9.2 Hz), 7.42 (2H, d, J=8.8 Hz), 7.51–7.53 (3H, m), 8.36–8.38 (2H, m). ^{13}C NMR (100 MHz, DMSO-d_6): δ 53.2 (C5), 77.9 (C2), 109.5 (N–Ar-*p*), 114.6 (N–Ar-*o*), 126.9 (C4–Ph), 127.7 (C4), 129.1 (C4–Ph), 131.0 (C4–Ph), 132.2 (N–Ar-*m*), 136.1 (C4Ph-*ipso*), 144.2 (N–Ar-*ipso*).

Anal. Calcd for $C_{15}H_{13}BrN_2O$ (317.18) C, 56.80; H, 4.13; N, 8.83. Found C, 56.45; H, 4.18; N, 8.81.

4.3. Spectral data for (1,3-bis(4-aryl)imidazolidin-4-yl)(phenyl)methanones 1′d,e

4.3.1. (1,3-Bis(4-chlorophenyl)imidazolidin-4-yl)(phenyl)methanone ***1′d***

Yield 0.397 g, 5%. Mp 175–176 °C. IR (KBr) $\nu_{C=O}$, 1693 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.69 (1H, dd, J=10.0, 1.6 Hz), 3.94 (1H, dd, J=10.0, 8.4 Hz), 4.70 (1H, d, J=3.6 Hz), 4.88 (1H, d, J=3.6 Hz), 6.03 (1H, dd, J=8.4, 1.6 Hz), 6.63 (2H, d, J=8.8 Hz), 6.73 (2H, d, J=8.8 Hz), 7.21 (2H, d, J=8.0 Hz), 7.22 (2H, d, J=8.8 Hz), 7.59 (2H, t, J=7.2 Hz), 7.72 (1H, t, J=7.2 Hz), 8.09 (2H, d, J=7.8 Hz). ^{13}C NMR (100 MHz,

Table 2
Linear free energy relationships in the transformylation of **6** to (*E*)-**7** and (*Z*)-**7** in DMSO-d_6 at different temperatures

Ar	*E*-**7**[a]	*Z*-**7**[a]	**6**[a]	log K_E	log K_Z	log K[b]	(*E*)/(*Z*)
50 °C-1 h	Content (%)						
Ph	34	27	39	−0.06	−0.16	1.37	1.24
p-MeC_6H_4	50	37	13	0.59	0.45	2.15	1.34
p-$MeOC_6H_4$	54	46					1.13
p-ClC_6H_4	8	8	84	−1.02	−1.02	−0.12	1.09
p-BrC_6H_4	7	7	86	−1.09	−1.09	−0.24	1.00
60 °C-1 h	Content (%)						
Ph	36	29	35	0.012	−0.08	1.48	1.26
p-MeC_6H_4	51	40	9	0.75	0.65	2.36	1.35
p-$MeOC_6H_4$	54	46					1.18
p-ClC_6H_4	11	11	78	−0.85	−0.85	0.19	1.00
p-BrC_6H_4	8	8	84	−1.02	−1.02	−0.12	1.00
70 °C-1 h	Content (%)						
Ph	42	34	24	0.24	0.15	1.77	1.24
p-MeC_6H_4	52	41	7	0.87	0.77	2.48	1.28
p-$MeOC_6H_4$	52	48					1.15
p-ClC_6H_4	14	15	71	−0.71	−0.66	0.47	1.00
p-BrC_6H_4	14	14	72	−0.71	−0.71	0.44	1.00

[a] Content of the compound (%) after 1 h heating at the corresponding temperature.
[b] The ratios defined as in the legend of Table 1.

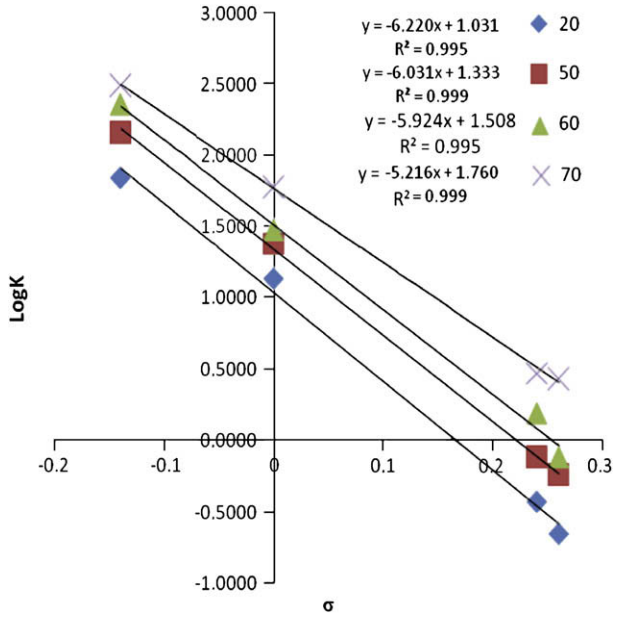


Figure 5. Plot of log K versus σ at different temperatures.

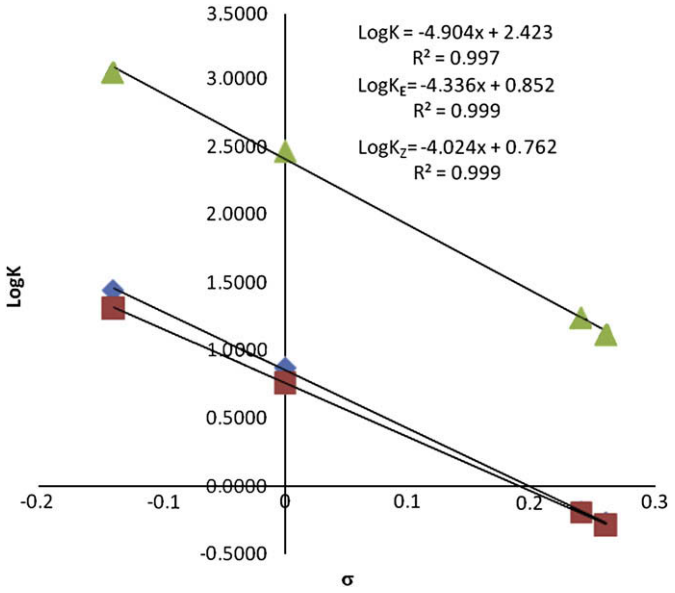


Figure 6. Plot of log K, log K_E and log K_Z versus σ for the reaction series after 14 h at 50 °C.

DMSO-d_6): δ 50.5 (C5), 61.4 (C4), 66.6 (C2), 114.3, 114.6 (N1–Ar-*o* and N3–Ar-*o*), 121.3, 121.6 (N1–Ar-*p* and N3–Ar-*p*), 129.0 (Bz-*o*), 129.1, 129.2 (N1–Ar-*m* and N3–Ar-*m*), 129.5 (Bz-*m*), 134.5 (2C; Bz-*p* and Bz-*ipso*), 144.1 (N1–Ar-*ipso*), 145.0 (N3–Ar-*ipso*), 198.0 (C=O).

Anal. Calcd for $C_{22}H_{18}Cl_2N_2O$ (397.3) C, 66.51; H, 4.57; N, 7.05. Found C, 66.61; H, 4.48; N, 7.14.

4.3.2. (1,3-Bis(4-bromophenyl)imidazolidin-4-yl)(phenyl) methanone ***1′e***

Yield 0.778 g, 8%. Mp 174–175 °C. IR (KBr) $\nu_{C=O}$ 1685 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.69 (1H, dd, J=10 Hz, 1.2 Hz), 3.94 (1H, t, J=9.2 Hz), 4.69 (1H, d, J=3.6 Hz), 4.86 (1H, d, J=3.6 Hz), 6.03 (1H, d, J=9.2, 1.2 Hz), 6.59 (2H, d, J=9.2 Hz), 6.68 (2H, d, J=9.2 Hz), 7.32 (2H, d, J=9.2 Hz), 7.33 (2H, d, J=9.2 Hz), 7.59 (2H, t, J=8.0 Hz), 7.72 (1H, t, J=7.2 Hz), 8.09 (2H, d, J=7.2 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 50.4 (C5), 61.3 (C4), 66.5 (C2), 108.8, 109.2 (N1–Ar-*p* and N3–Ar-*p*), 114.9, 115.1 (N1–Ar-*o* and N3–Ar-*o*), 129.0 (Bz-*o*), 129.6 (Bz-*m*), 132.0, 132.1 (N1–Ar-*m* and N3–Ar-*m*), 134.5 (Bz-*p*), 134.6 (Bz-*ipso*), 144.5, 145.3 (N1–Ar-*ipso* and N3–Ar-*ipso*), 198.0 (C=O).

Anal. Calcd for $C_{22}H_{18}Br_2N_2O$ (486.2) C, 54.35; H, 3.73; N, 5.76. Found C, 54.55; H, 3.93; N, 6.00.

4.4. Synthesis of 2,5-dihydro-1*H*-imidazole 3-oxide DMAD adducts 2a–e

4.4.1. General procedure

The adducts were prepared according to the procedure, which we have recently reported.[3d–e] The ratio of the starting nitrone DMAD was 1:1.5 instead of 1:4 as was before. To a solution of **1** (2 mmol) in benzene (13 mL) DMAD (3 mmol, 0.431 g, 99%) was added and the reaction mixture heated at reflux for 3 h; **2a**,**e** are new compounds and the spectral and elemental analyses results are given below. The other adducts are previously reported nevertheless we report their ^{1}H and ^{13}C NMR spectra recorded in DMSO-d_6. The previous reports included mainly their ^{1}H NMR spectra in $CDCl_3$. The conversions were monitored by ^{1}H NMR and were quantitative. The yields reported are based on the isolated crystals after crystallizations from ethanol.

4.4.2. Dimethyl 3a,5-diphenyl-3a,4,5,6-tetrahydroimidazo[1,5-b]isoxazole-2,3-dicarboxylate ***2a***

Yield 0.684 g, 90%. Yellow crystals, mp 138.5–139.5 °C. IR (KBr) $\nu_{C=O}$ 1754, 1712; $\nu_{C=C}$ 1657 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.42 (1H, d, J=10.4 Hz), 3.57 (3H, s), 3.82 (3H, s), 4.19 (1H, d, J=11.2 Hz), 4.56 (1H, d, J=10.4 Hz), 5.25 (1H, d, J=11.2 Hz), 6.83 (1H, t, J=7.2 Hz), 6.92 (2H, d, J=8.0 Hz), 7.24 (2H, t, J=8.0 Hz), 7.33 (1H, t, J=7.2 Hz), 7.40 (2H, t, J=7.2 Hz), 7.52 (2H, d, J=7.2 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 52.4, 54.0, 56.6, 75.9, 82.5, 110.4, 115.9, 119.9, 127.3, 128.5, 128.8, 129.6, 141.1, 146.6, 152.5, 159.3, 162.2.

Anal. Calcd for $C_{21}H_{20}N_2O_5$ (380.39) C, 66.31; H, 5.30; N, 7.36. Found C, 66.26; H, 5.36; N, 7.26.

4.4.3. Dimethyl 3a-phenyl-5-p-tolyl-3a,4,5,6-tetrahydro imidazo[1,5-b]isoxazole-2,3-dicarboxylate ***2b***

Yield 0.733 g, 93%. Colourless crystals, mp 139–140 °C, lit[3d–e] mp 134.8 °C. IR (KBr) $\nu_{C=O}$ 1754, 1711; $\nu_{C=C}$ 1658 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.20 (3H, s), 3.36 (1H, d, J=10.4 Hz), 3.57

Table 3
Linear free energy relationships in the transformylation of **6** to (*E*)-**7** and (*Z*)-**7** in DMSO-d_6 after 14 h at 50 °C

Ar	*E*-**7**[a]	*Z*-**7**[a]	**6**[a]	log K_E	log K_Z	log K[b]	(*E*)/(*Z*)
50 °C-14 h	Content (%)						
Ph	52	41	7	0.87	0.77	2.48	1.27
p-MeC_6H_4	56	42	2	1.45	1.32	3.07	1.33
p-MeOC_6H_4	54	46	0				1.17
p-ClC_6H_4	28	28	44	−0.20	−0.20	1.25	1
p-BrC_6H_4	26	25	49	−0.28	−0.29	1.12	1.04

[a] Content of the compound (%) after 14 h heating at 50 °C.
[b] The ratios defined as in the legend of Tables 1 and 2.

Table 4
Substituent dependence of [(*E*)-**7**]/[(*Z*)-**7**] in DMSO-d_6 at 25 °C

Ar	*E*-**7**	*Z*-**7**	[(*E*)-**7**]/[(*Z*)-**7**][a]	log[(*E*)-**7**]/[(*Z*)-**7**]	σ_I
Ph	56.5	43.5	1.30	0.11	0
p-MeC_6H_4	57.6	42.4	1.36	0.13	−0.05
p-MeOC_6H_4	53.7	46.3	1.16	0.06	0.27
p-ClC_6H_4	50.5	49.5	1.02	0.01	0.46
p-BrC_6H_4	50.4	49.6	1.02	0.01	0.44

[a] The values are averages of three measurements for each mixture, STDEV are ca. 0.01.

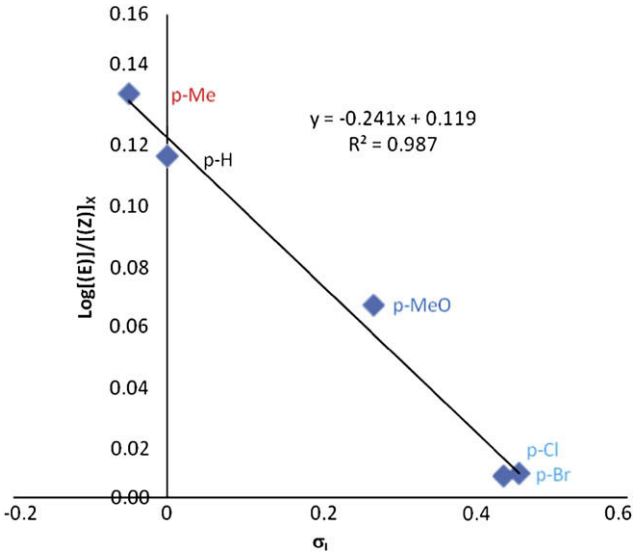


Figure 7. Plot of $\log[(E)]/[(Z)]_x$ versus σ_I at 25 °C.

(3H, s), 3.82 (3H, s), 4.11 (1H, d, *J*=11.6 Hz), 4.53 (1H, d, *J*=10.4 Hz), 5.19 (1H, d, *J*=11.6 Hz), 6.82 (2H, d, *J*=8.4 Hz), 7.05 (2H, d, *J*=8.4 Hz), 7.32 (1H, t, *J*=7.6 Hz), 7.40 (2H, t, *J*=7.6 Hz), 7.52 (2H, d, *J*=7.6 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.6, 52.4, 54.0, 57.0, 76.3, 82.5, 110.5, 116.1, 127.3, 128.5, 128.7, 128.8, 130.0, 141.2, 144.4, 152.5, 159.3, 162.2.

Anal. Calcd for $C_{22}H_{22}N_2O_5$ (394.42) C, 66.99; H, 5.62; N, 7.10. Found C, 66.98; H, 5.60; N, 7.22.

4.4.4. Dimethyl 5-(4-methoxyphenyl)-3a-phenyl-3a,4,5,6-tetra hydroimidazo[1,5-b]isoxazole-2,3-dicarboxylate ***2c***

Yield 0.681 g, 83%. Colourless crystals, mp 118–119 °C, lit[3d–e] mp 116 °C. IR (KBr) $\nu_{C=O}$ 1753, 1711; $\nu_{C=C}$ 1656 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.30 (1H, d, *J*=10.4 Hz), 3.37 (3H, s), 3.68 (3H, s), 3.83 (3H, s), 4.06 (1H, d, *J*=11.6 Hz), 4.49 (1H, d, *J*=10.4 Hz), 5.17 (1H, d, *J*=11.6 Hz), 6.83 (2H, d, *J*=9.6 Hz), 6.89 (2H, d, *J*=9.6 Hz), 7.32 (1H, t, *J*=7.2 Hz), 7.40 (2H, t, *J*=7.2 Hz), 7.51 (2H, d, *J*=7.2 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 52.3 (C3–CO_2*Me*), 54.0 (C2–CO_2*Me*), 55.7 (MeO), 57.5 (C4), 76.9 (C6), 82.6 (C3a), 110.4 (C3), 115.0 (N–Ar-*o*), 117.4 (N–Ar-*m*), 127.3 (C3a–Ph), 128.4 (C3a–Ph), 128.8 (C3a–Ph), 140.5 (C3a–Ph-*ipso*), 141.2 (N–Ar-*ipso*), 152.5 (N–Ar-*p*), 153.6 (C2), 159.3 (C3–*C*O$_2$Me), 162.2 (C2–*C*O$_2$Me).

Anal. Calcd for $C_{22}H_{22}N_2O_6$ (410.42) C, 64.38; H, 5.40; N, 6.83. Found C, 64.53; H, 5.53; N, 6.90.

4.4.5. Dimethyl 5-(4-chlorophenyl)-3a-phenyl-3a,4,5,6-tetra hydroimidazo[1,5-b]isoxazole-2,3-dicarboxylate ***2d***

Yield 0.704 g, 85%. Colourless crystals, mp 134–135 °C, lit[3d–e] mp 135.5 °C. IR (KBr) $\nu_{C=O}$ 1754, 1721; $\nu_{C=C}$ 1659 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.45 (1H, d, *J*=10.4 Hz), 3.57 (3H, s), 3.82 (3H, s), 4.22 (1H, d, *J*=11.6 Hz), 4.55 (1H, d, *J*=10.4 Hz), 5.25 (1H, d, *J*=11.6 Hz), 6.94 (2H, d, *J*=8.8 Hz), 7.26 (2H, d, *J*=8.8 Hz), 7.33 (1H, t, *J*=7.2 Hz), 7.40 (2H, t, *J*=6.8 Hz), 7.52 (2H, d, *J*=9.2 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 52.3, 54.0, 57.5, 76.9, 82.6, 110.4, 115.0, 117.4, 127.3, 128.4, 128.8, 140.5, 141.2, 152.5, 153.6, 159.3, 162.2.

Anal. Calcd for $C_{21}H_{19}ClN_2O_5$ (414.84) C, 60.80; H, 4.62; N, 6.75. Found C, 61.2; H, 4.62; N, 6.76.

4.4.6. Dimethyl 5-(4-bromophenyl)-3a-phenyl-3a,4,5,6-tetra hydroimidazo[1,5-b]isoxazole-2,3-dicarboxylate ***2e***

Yield 0.817 g, 89%. Colourless crystals, mp 149–150 °C. IR (KBr) $\nu_{C=O}$ 1754, 1711; $\nu_{C=C}$ 1658 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.45 (1H, d, *J*=10.8 Hz), 3.57 (3H, s), 3.82 (3H, s), 4.21 (1H, d, *J*=11.6 Hz), 4.55 (1H, d, *J*=10.8 Hz), 5.41 (1H, d, *J*=11.6 Hz), 6.90 (2H, d, *J*=8.8 Hz), 7.31–7.42 (5H, m), 7.51 (2H, d, *J*=7.6 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 52.4, 54.1, 56.5, 76.6, 82.5, 110.4, 111.2, 118.0, 127.3, 128.6, 128.8, 132.1, 140.9, 145.9, 152.4, 159.2, 162.1.

Anal. Calcd for $C_{21}H_{19}BrN_2O_5$ (459.30) C, 54.92; H, 4.17; N, 6.10. Found C, 55.33; H, 4.15; N, 6.15.

4.5. Synthesis of 3-methoxy-7-(methoxycarbonyl)-2,7a-diaryl-5-oxo-2,3,5,7a-tetrahydro-1*H*-pyrrolo[1,2-*e*]imidazol-6-olates 3a–e

4.5.1. General procedure

To a solution of sodium methoxide in methanol (5 mL, 1.5 mmol Na, 0.035 g) at reflux, 3a,4,5,6-tetrahydroimidazo[1,5-*b*]isoxazole-2,3-dicarboxylate **2** (0.5 mmol) was added and the mixture stirred for an hour, except **1a** where the reaction time is 3 h. The white precipitate was filtered and dried under vacuum.

4.5.2. (cis)-3-Methoxy-7-(methoxycarbonyl)-5-oxo-2,7a-diphenyl-2,3,5,7a-tetrahydro-1H-pyrrolo[1,2-e]imidazol-6-olate ***3a***

Yield 0.125 g, 62%. White powder, mp 282–283 °C. IR (KBr) $\nu_{C=O}$ 1727, 1676 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.10 (1H, d, *J*=9.6 Hz), 3.12 (3H, s), 3.38 (3H, s), 4.72 (1H, d, *J*=9.6 Hz), 5.59 (1H, s), 6.74–6.78 (3H, m), 7.13 (1H, t, *J*=7.2 Hz), 7.19–7.24 (4H, m), 7.50 (2H, d, *J*=7.6 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 49.5, 52.3, 57.1, 66.8, 95.1, 106.4, 110.0, 113.4, 118.9, 126.6, 127.7, 129.5, 143.9, 145.8, 165.3, 166.8, 173.4.

Anal. Calcd for $C_{21}H_{19}N_2NaO_5$ (402.38) C, 62.68; H, 4.76; N, 6.96. Found C, 62.55; H, 4.70; N, 6.85.

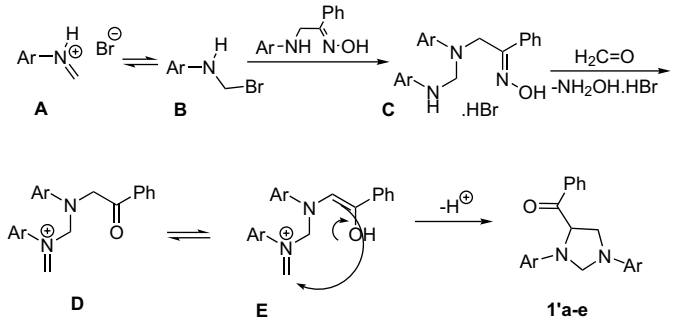
4.5.3. (cis)-3-Methoxy-7-(methoxycarbonyl)-5-oxo-7a-phenyl-2-p-tolyl-2,3,5,7a-tetrahydro-1H-pyrrolo[1,2-e]imidazol-6-olate ***3b***

Yield 0.164 g, 79%. White powder, mp 287–289 °C. IR (KBr) $\nu_{C=O}$ 1727, 1676 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.18 (3H, s), 3.05 (1H, d, *J*=9.6 Hz), 3.10 (3H, s), 3.38 (3H, s), 4.69 (1H, d, *J*=9.6 Hz), 5.34 (1H, s), 6.66 (2H, d, *J*=8.0 Hz), 7.02 (2H, d, *J*=8.0 Hz), 7.13 (1H, t, *J*=7.2 Hz), 7.22 (2H, t, *J*=7.2 Hz), 7.50 (2H, d, *J*=7.2 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.5, 49.5, 52.2, 63.5, 66.8, 95.4, 106.5, 113.4, 126.6, 127.5, 127.7, 129.9, 143.7, 144.0, 152.4, 165.4, 165.6, 173.5.

Anal. Calcd for $C_{22}H_{21}N_2O_5Na$ (416.41) C, 63.46; H, 5.08; N, 6.72. Found C, 63.40; H, 5.06; N, 7.00.

4.5.4. (cis)-3-Methoxy-7-(methoxycarbonyl)-2-(4-methoxy phenyl)-5-oxo-7a-phenyl-2,3,5,7a-tetrahydro-1H-pyrrolo [1,2-e]imidazol-6-olate ***3c***

Yield 0.166 g, 77%. White powder, mp 287–288 °C. IR (KBr) $\nu_{C=O}$ 1727, 1676 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.03 (1H, d, *J*=9.2 Hz), 3.09 (3H, s), 3.37 (3H, s), 3.66 (3H, s), 4.67 (1H, d, *J*=9.2 Hz), 5.50 (1H, s), 6.72 (2H, d, *J*=9.2 Hz), 6.82 (2H, d, *J*=9.2 Hz), 7.13 (1H, t, *J*=7.2 Hz), 7.22 (2H, t, *J*=7.6 Hz), 7.50 (2H, d, *J*=7.2 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 49.6 (7-CO_2*Me*), 52.2 (C3–O*Me*), 55.7 (N–Ar–O*Me*), 57.5 (N*C*H$_2$), 66.8 (C7a), 95.8 (C3), 106.5 (C7), 114.5



Scheme 6. Probable mechanism for the formation of compounds **1′a–e**.

(N–Ar), 115.0 (N–Ar), 126.6 (C7a–Ph), 126.7 (C7a–Ph), 127.7 (C7a–Ph), 140.2 (C7a–Ph-*ipso*), 143.8 (N–Ar-*ipso*), 152.9 (N–Ar-*p*), 165.4 (NCO), 167.0 (C7–*C*O$_2$Me), 173.5 (C6).

Anal. Calcd for $C_{22}H_{21}N_2O_6Na$ (432.41) C, 61.11; H, 4.89; N, 6.48. Found C, 60.95; H, 4.64; N, 6.74.

4.5.5. (cis)-2-(4-Chlorophenyl)-3-methoxy-7-(methoxycarbonyl)-5-oxo-7a-phenyl-2,3,5,7a-tetrahydro-1H-pyrrolo[1,2-e]imidazol-6-olate **3d**

Yield 0.146 g, 67%. White powder, mp 286–287 °C. IR (KBr) $\nu_{C=O}$ 1727, 1676 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.11 (1H, d, J=9.2 Hz), 3.11 (3H, s), 3.38 (3H, s), 4.72 (1H, d, J=9.2 Hz), 5.60 (1H, s), 6.77 (2H, d, J=9.2 Hz), 7.13 (1H, t, J=7.6 Hz), 7.20–7.24 (4H, m), 7.49 (2H, d, J=7.2 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 49.5, 52.4, 57.2, 66.8, 94.9, 106.4, 115.1, 118.5, 122.6, 126.6, 127.7, 129.2, 143.8, 144.6, 165.3, 166.7, 173.4.

Anal. Calcd for $C_{21}H_{18}ClN_2NaO_5$ (436.83) C, 57.74; H, 4.15; N, 6.41. Found C, 57.60; H, 4.10; N, 6.37.

4.5.6. (cis)-2-(4-Bromophenyl)-3-methoxy-7-(methoxycarbonyl)-5-oxo-7a-phenyl-2,3,5,7a-tetrahydro-1H-pyrrolo[1,2-e]imidazol-6-olate **3e**

Yield 0.168 g, 70%. White powder, mp 295–296 °C. IR (KBr) $\nu_{C=O}$ 1727, 1676 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.10 (1H, d, J=9.6 Hz), 3.11 (3H, s), 3.37 (3H, s), 4.71 (1H, d, J=9.6 Hz), 5.59 (1H, s), 6.72 (2H, d, J=9.2 Hz), 7.13 (1H, t, J=7.2 Hz), 7.22 (2H, t, J=7.6 Hz), 7.34 (2H, d, J=9.2 Hz), 7.49 (2H, d, J=7.2 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 49.6, 52.4, 57.2, 66.8, 94.8, 106.4, 110.3, 115.6, 126.6 (C7a–Ph, 2C), 127.7, 132.0, 143.8, 145.0, 165.3, 166.7, 173.4.

Anal. Calcd for $C_{21}H_{18}BrN_2NaO_5$ (481.28) C, 52.41; H, 3.77; N, 5.82. Found C, 52.37; H, 3.65; N, 5.86.

4.6. Synthesis of 1-formyl-4-hydroxy-5-oxo-2-phenyl-2-((arylamino)methyl)-2,5-dihydro-1*H*-pyrrole-3-carboxylate trifloroacetates 6a–e

4.6.1. General procedure

Compound **3** (0.15 mmol) was dissolved in CF_3CO_2H (0.5 mL) and stirred for 5 min. The solution was dropped into ice water (2.5 mL). The white solid precipitated was filtered and dried under vacuum.

4.6.2. Methyl 1-formyl-4-hydroxy-5-oxo-2-phenyl-2-((phenyl amino)methyl)-2,5-dihydro-1H-pyrrole-3-carboxylate **6a**

Yield 0.038 g, 51%. White powder, mp 94–95 °C. IR (KBr) ν_{OH} 3466; ν^{+}_{NH2} 2955–2492 medium, broad highly structured band; $\nu_{C=O}$ 1762, 1710, 1692, 1653 cm^{-1}. ^{1}H NMR (400 MHz, 6.25×10^{-3} M DMSO-d_6): δ 3.54 (3H, s), 3.96 (5H, br s), 4.30 (1H, d, J=13.6 Hz), 4.48 (1H, d, J=13.6 Hz), 6.48 (1H, t, J=7.6 Hz), 6.53 (2H, d, J=7.6 Hz), 7.00 (2H, t, J=7.6 Hz), 7.24 (1H, t, J=7.2 Hz), 7.30 (2H, t, J=7.6 Hz), 7.36 (2H, d, J=7.6 Hz), 8.91 (1H, s). ^{13}C NMR (100 MHz, 3.75×10^{-2} M DMSO-d_6): 43.8 (N–CH_2), 51.8 (CO_2*Me*), 67.6 (C2), 112.9 (N–Ar-*o*), 115.7 (q, J^1_{CF}=288.3 Hz), 116.5 (N–Ar-*p*), 117.6 (C3), 126.5 (C2–Ph-*o*), 128.0 (C2–Ph-*p*), 128.6 (C2–Ph-*m*), 129.3 (N–Ar-*m*), 138.0 (C2–Ph-*ipso*), 149.4 (N–Ar-*ipso*), 152.2 (C4), 158.8 (q, J^2_{CF}=37.4 Hz), 158.9 (N–CHO), 162.8 (C3–*C*O$_2$Me), 167.3 (C5).

Anal. Calcd for **6a**·$CF_3CO_2H\cdot H_2O$ $C_{22}H_{21}F_3N_2O_8$ (498.41) C, 53.02; H, 4.25; N, 5.62. Found C, 52.66; H, 3.99; N, 5.58.

4.6.3. Methyl 2-((p-toluidino)methyl)-1-formyl-4-hydroxy-5-oxo-2-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate **6b**

Yield 0.055 g, 72%. White powder, mp 112–113 °C. IR (KBr) ν_{OH} 3460; ν^{+}_{NH2} 2955–2492 medium, broad highly structured band; $\nu_{C=O}$ 1759, 1712, 1691; $\nu_{C=C}$ 1652 cm^{-1}. ^{1}H NMR (400 MHz, 6×10^{-3} M DMSO-d_6): δ 2.10 (3H, s), 3.54 (3H, s), 3.71 (5H, br s), 4.27 (1H, d, J=13.6 Hz), 4.43 (1H, d, J=13.6 Hz), 6.44 (2H, d, J=8.8 Hz), 6.82 (2H, d, J=8.8 Hz), 7.24 (1H, t, J=6.8 Hz), 7.30 (2H, t, J=7.2 Hz), 7.35 (2H, d, J=7.2 Hz), 8.91 (1H, s). ^{13}C NMR (100 MHz, 3.75×10^{-2} M DMSO-d_6): δ 20.5 (N–Ar–*Me*), 44.1 (N–CH_2), 51.7 (CO_2*Me*), 67.6 (C2), 113.0 (N–Ar-*o*), 115.8 (q, J^1_{CF}=288.1 Hz), 117.6 (C3), 124.9 (N–Ar-*p*), 126.5 (C2–Ph-*o*), 128.0 (C2–Ph-*p*), 128.6 (C2–Ph-*m*), 129.7 (N–Ar-*m*), 138.0 (C2–Ph-*ipso*), 147.0 (N–Ar-*ipso*), 152.1 (C4), 158.8 (q, J^2_{CF}=37.4 Hz), 158.8 (N–CHO), 162.8 (C3–CO_2Me), 167.3 (C5).

Anal. Calcd for **6b**·$CF_3CO_2H\cdot H_2O$, $C_{23}H_{23}F_3N_2O_8$: (512.43) C, 53.91; H, 4.52; N, 5.47. Found C, 53.95; H, 4.42; N, 5.38.

4.6.4. Methyl 1-formyl-4-hydroxy-2-((4-methoxyphenylamino) methyl)-5-oxo-2-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate **6c**

Yield 0.067 g, 85%. White powder, mp 110–111 °C. IR (KBr) ν_{OH} 3472; ν^{+}_{NH2} 2955–2492 medium, broad highly structured band; $\nu_{C=O}$ 1760, 1710, 1691; $\nu_{C=C}$ 1646 cm^{-1}. ^{1}H NMR (400 MHz, 6×10^{-3} M DMSO-d_6 solution): δ 3.54 (3H, s), 3.61 (3H, s), 3.78 (5H, br s), 4.26 (1H, d, J=13.6 Hz), 4.41 (1H, d, J=13.6 Hz), 6.51 (2H, d, J=8.8 Hz), 6.65 (2H, d, J=8.8 Hz), 7.24 (1H, t, J=6.8 Hz), 7.30 (2H, t, J=7.2 Hz), 7.34 (2H, d, J=7.2 Hz), 8.91 (1H, s). ^{13}C NMR (100 MHz, 3.75×10^{-2} M DMSO-d_6): δ 45.0 (N–CH_2), 51.8 (CO_2*Me*), 55.7 (N–Ar–OMe), 67.6 (C2), 114.5 (N–Ar-*o*), 114.9 (N–Ar-*m*), 115.7 (q, J^1_{CF}=289.1 Hz), 117.7 (C3), 126.5 (C2–Ph-*o*), 128.0 (C2–Ph-*p*), 128.6 (C2–Ph-*m*), 138.0 (C2–Ph-*ipso*), 143.0 (N–Ar-*ipso*), 151.5 (N–Ar-*p*), 152.1 (C4), 158.8 (q, J^2_{CF}=37.4 Hz), 158.9 (N–CHO), 162.7 (C3–*C*O$_2$Me), 167.3 (C5).

Anal. Calcd for **6c**·$CF_3CO_2H\cdot H_2O$, $C_{23}H_{23}F_3N_2O_9$ (528.43) C, 52.28; H, 4.39; N, 5.30. Found C, 52.06; H, 4.25; N, 5.25.

4.6.5. Methyl 2-((4-chlorophenylamino)methyl)-1-formyl-4-hydroxy-5-oxo-2-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate **6d**

Yield 0.051 g, 63%. White powder, mp 101–102 °C. IR (KBr) ν_{OH} 3452; ν^{+}_{NH2} 2955–2492 medium, broad highly structured band; $\nu_{C=O}$ 1768, 1710, 1691; $\nu_{C=C}$ 1652 cm^{-1}. ^{1}H NMR (400 MHz, 6×10^{-3} M DMSO-d_6): δ 3.54 (3H, s), 3.80 (3H, br s), 4.29 (1H, d, J=13.6 Hz), 4.47 (1H, d, J=13.6 Hz), 5.87 (1H, br s), 6.53 (2H, d, J=8.8 Hz), 7.03 (2H, d, J=8.8 Hz), 7.24 (1H, t, J=6.8 Hz), 7.30 (2H, t, J=7.2 Hz), 7.36 (2H, d, J=7.2 Hz), 8.91 (1H, s), 11.86 (1H, br s). ^{13}C NMR (100 MHz, 3.75×10^{-2} M DMSO-d_6): δ 43.7 (N–CH_2), 51.8 (CO_2*Me*), 67.5 (C2), 114.1 (N–Ar-*o*), 115.8 (q, J^1_{CF}=288.1 Hz), 117.4 (C3), 119.6 (N–Ar-*p*), 126.5 (C2–Ph-*o*), 128.1 (C2–Ph-*p*), 128.6 (C2–Ph-*m*), 129.0 (N–Ar-*m*), 137.9 (C2–Ph-*ipso*), 148.3 (N–Ar-*ipso*), 152.2 (C4), 158.8 (q, J^2_{CF}=37.4 Hz), 158.9 (N–CHO), 162.8 (C3–CO_2Me), 167.2 (C5).

Anal. Calcd for **6d**·$CF_3CO_2H\cdot H_2O$, $C_{22}H_{20}ClF_3N_2O_8$ (532.85) C, 49.59; H, 3.78; N, 5.26. Found C, 50.00; H, 3.77; N, 5.43.

4.6.6. Methyl 2-((4-bromophenylamino)methyl)-1-formyl-4-hydroxy-5-oxo-2-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate **6e**

Yield 0.052 g, 74%. White powder, mp 96–97 °C. IR (KBr) ν_{OH} 3460; ν^{+}_{NH2} 2955–2492 medium, broad highly structured band; $\nu_{C=O}$ 1767, 1712, 1691; $\nu_{C=C}$ 1652 cm^{-1}. ^{1}H NMR (400 MHz, 6×10^{-3} M DMSO-d_6): δ 3.54 (3H, s), 3.65 (3H, br s), 4.29 (1H, d, J=13.6 Hz), 4.47 (1H, d, J=13.6 Hz), 5.91 (1H, br s), 6.49 (2H, d, J=8.8 Hz), 7.14 (2H, d, J=8.8 Hz), 7.24 (1H, t, J=6.8 Hz), 7.30 (2H, t, J=7.2 Hz), 7.35 (2H, d, J=7.2 Hz), 8.91 (1H, s), 11.84 (1H, br s). ^{13}C NMR (100 MHz, 3.75×10^{-2} M DMSO-d_6): δ 43.6 (N–CH_2), 51.8 (CO_2*Me*), 67.5 (C2), 107.0 (N–Ar-*p*), 114.7 (N–Ar-*o*), 115.8 (q, J^1_{CF}=288.1 Hz), 117.4 (C3), 126.5 (C2–Ph-*o*), 128.1 (C2–Ph-*p*), 128.6 (C2–Ph-*m*), 131.8 (N–Ar-*m*), 137.9 (C2–Ph-*ipso*), 148.6 (N–Ar-*ipso*), 152.2 (C4), 158.8 (q, J^2_{CF}=37.4 Hz), 158.9 (N–CHO), 162.8 (C3–CO_2Me), 167.2 (C5).

Anal. Calcd for **6e**·$CF_3CO_2H\cdot H_2O$, $C_{22}H_{20}BrF_3N_2O_8$ (577.3) C, 45.77; H, 3.49; N, 4.85. Found C, 45.46; H, 3.40; N, 4.94.

4.7. Synthesis of methyl 4-hydroxy-5-oxo-2-phenyl-2-((*N*-arylformamido)methyl)-2,5-dihydro-1*H*-pyrrole-3-carboxylates 7a–e

4.7.1. General procedure A

Solutions (DMSO-d_6, 0.8 mL) of compounds **6** (0.03 mmol) in NMR tubes were heated at 80 °C on a water bath for 5, 2.5, 1, 14, 14 h for **6a**–**e**, respectively. The reaction mixtures were poured into ice water (5 mL) and extracted with $CHCl_3$ (2×5 mL). The combined extracts were washed with water (2×10 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and the organic solvent evaporated under vacuum. The residue was dried under vacuum and triturated with ether.

4.7.2. (E)-Methyl 4-hydroxy-5-oxo-2-phenyl-2-((N-phenyl formamido)methyl)-2,5-dihydro-1H-pyrrole-3-carboxylate **7a**

Yield 0.0092 g, 91%. Yellow powder, mp 189–190 °C. IR (KBr) ν_{OH} 3423; ν_{NH} 3199; $\nu_{C=O}$ 1723, 1694, 1674; $\nu_{C=C}$ 1625 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.51 (3H, s), 4.70 (1H, d, J=13.6 Hz), 5.00 (1H, d, J=13.6 Hz), 6.53 (1H, s, D_2O exch.), 7.04 (2H, d, J=8.8 Hz), 7.25–7.40 (8H, m), 8.34 (1H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ 47.9 (N–CH_2), 51.8 (CO_2*Me*), 64.6 (C7a), 114.3 (C3), 124.6 (N–Ar), 125.9 (C7a–Ph), 127.2 (N–Ar), 128.5 (C7a–Ph), 128.5 (N–Ar), 129.7 (N–Ar), 137.4 (C7a–Ph-*ipso*), 140.8 (N–Ar-*ipso*), 158.1 (C4), 164.1 (C3–CO_2Me), 164.3 (N–CHO), 165.0 (C5).

Anal. Calcd for $C_{20}H_{18}N_2O_5$ (366.37) C, 65.57; H, 4.95; N, 7.65. Found C, 65.30; H, 4.90; N, 7.55.

4.7.3. (E)-Methyl 4-hydroxy-5-oxo-2-phenyl-2-((N-p-tolylform amido)methyl)-2,5-dihydro-1H-pyrrole-3-carboxylate **7b**

Yield 0.011 g, 97%. Yellowish powder, mp 176–177 °C. IR (KBr) ν_{OH} 3447; ν_{NH} 3180; $\nu_{C=O}$ 1719, 1699, 1672; $\nu_{C=C}$ 1632 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.34 (3H, s), 3.52 (3H, s), 4.66 (1H, d, J=14.0 Hz), 4.97 (1H, d, J=14.0 Hz), 6.49 (1H, s, D_2O exch.), 6.91 (2H, d, J=8.0 Hz), 7.17 (2H, d, J=8.0 Hz), 7.31–7.40 (5H, m), 8.29 (1H, s), 8.94 (1H, br s, D_2O exch.). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9 (N–Ar*Me*), 48.0 (N–CH_2), 51.7 (CO_2*Me*), 64.5 (C7a), 114.5 (C3), 124.6 (N–Ar), 125.9 (C7a–Ph), 128.6 (N–Ar), 128.8 (C7a–Ph), 130.2 (Ar), 137.4 (N–Ar-*ipso*), 137.5 (C7a–Ph-*ipso*), 138.2 (N–Ar-*ipso*), 158.1 (C4), 164.1 (C3–CO_2Me), 164.3 (N–CHO), 165.0 (C5).

Anal. Calcd for $C_{21}H_{20}N_2O_5$ (380.39) C, 66.31; H, 5.30; N, 7.36. Found C, 66.45; H, 5.18; N, 7.18.

4.7.4. (E)-Methyl 4-hydroxy-2-((N-(4-methoxyphenyl)formamido) methyl)-5-oxo-2-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylates **7c**

Yield 0.012 g, 99%. Yellowish powder, mp 124–125 °C. IR (KBr) ν_{OH} 3447; ν_{NH} 3214; $\nu_{C=O}$ 1718, 1699, 1663 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.54 (3H, s, CO_2Me), 3.81 (3H, s, OMe), 4.61 (1H, d, J=14.4 Hz, C1–Ha), 4.96 (1H, d, J=14.4 Hz, C1–Ha), 6.57 (1H, s, OH), 6.88 (2H, d, J=9.2 Hz), 6.95 (2H, d, J=9.2 Hz), 7.30–7.39 (5H, m), 8.26 (1H, s, C3–H), 9 (1H, br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 48.4 (N–CH_2), 51.8 (CO_2*Me*), 55.6 (N–Ar–O*Me*), 64.6 (C7a), 114.6 (N–Ar-*o*), 115.5 (N–Ar-*m*), 115.5 (C3), 125.9 (C7a–Ph), 126.3 (C7a–Ph), 128.8 (C7a–Ph), 132.6 (N–Ar-*ipso*), 137.5 (C7a–Ph-*ipso*), 158.1 (N–Ar-*p*), 158.6 (C4), 164.1 (C3–CO_2Me), 164.3 (N–CHO), 165.0 (C5).

Anal. Calcd for $C_{21}H_{20}N_2O_6$ (396.39) C, 63.63; H, 5.09; N, 7.07. Found C, 63.55; H, 4.98; N, 7.26.

4.7.5. Procedure B

A solution of **6** (0.20 mmol) in methanol (5 mL) and H_2O (2.5 mL) was refluxed for 15 min. The solvent was evaporated under vacuum and the residue dissolved in chloroform (15 mL). The organic phase was washed with water (2×15 mL), separated, dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated under vacuum to give yellow oil, which solidifies on standing in a vacuum oven.

Compound **7c**; yield 0.072 g, 91%. The spectral characteristics of the product were identical with those of obtained according to procedure A.

4.7.6. Procedure C

A solution of **6** (0.25 mmol) in acetonitrile (2.5 mL) was heated at reflux for 4 h. The solvent was evaporated under vacuum and the residue treated with ether. The formed yellow powder was filtered and dried.

4.7.7. (E,Z)-Methyl 4-hydroxy-2-((N-(4-methoxyphenyl) formamido)methyl)-5-oxo-2-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylates (E,Z)-**7c**

The following NMR data are for the (*E*,*Z*)-mixture formed in DMSO-d_6 at 20 °C after 7 days.

^1H NMR (400 MHz, DMSO-d_6): δ 3.19 (3H, s, CO_2Me), 3.29 (3H, s, CO_2Me), 3.72 (3H, s, OMe), 3.73 (3H, s, OMe), 4.36 (1H, d, J=14.8 Hz), 4.7 (1H, d, J=13.6 Hz), 4.75 (1H, d, J=13.6 Hz), 4.84 (1H, d, J=14.8 Hz), 6.82–6.99 (8H, m), 7.22–7.35 (10H, m), 8.16 (1H, s, N–CHO), 8.19 (1H, s, N–CHO), 9.07 (1H, s, –NH–CO–), 9.32 (1H, s, –NH–CO–). ^{13}C NMR (100 MHz, DMSO-d_6): δ 47.7 (N–CH_2), 50.8, 50.9 (CO_2Me), 52.7 (N–CH_2), 55.7, 55.8 (N–Ar–O*Me*), 63.8, 64.0 (C2), 112.4, 112.8 (C–3), 113.8, 114.6 (N–Ar-*o*), 115.7 (q, J^1_{CF}=286.8 Hz), 126.5, 126.7, 127.9, 128.1, 128.5, 128.7 (C5–Ph), 132.4, 134.6 (N–Ar-*ipso*), 139.8, 140.0 (C2–Ph-*ipso*), 155.3, 155.5 (C4), 157.6, 158.0 (N–Ar-*p*), 158.8 (q, J^2_{CF}=38.2 Hz), 162.6, 162.8 (C3–CO_2Me), 163.9 (N–CHO), 165.7, 166.1 (C5).

4.7.8. (E)-Methyl 4-hydroxy-2-((N-(4-chlorophenyl)formamido) methyl)-5-oxo-2-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylates **7d**

Yield 0.011 g, 92%. White powder, mp 174–175 °C. IR (KBr) ν_{OH} 3423; ν_{NH} 3246; $\nu_{C=O}$ 1716, 1694, 1674; $\nu_{C=C}$ 1634 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.56 (3H, s), 4.68 (1H, d, J=14.0 Hz), 4.96 (1H, d, J=14.0 Hz), 6.54 (1H, s, D_2O exch.), 6.98 (2H, d, J=8.8 Hz), 7.32–7.37 (7H, m), 8.30 (1H, s), 8.94 (1H, br s, D_2O exch.). ^{13}C NMR (100 MHz, $CDCl_3$): δ 48.0 (N–CH_2), 51.9 (CO_2*Me*), 64.6 (C7a), 114.3 (C3), 125.8 (C7a–Ph), 125.9 (C7a–Ph), 128.7 (N–Ar), 128.9 (C7a–Ph), 129.8 (N–Ar), 133.1 (N–Ar), 137.2 (C7a–Ph-*ipso*), 139.4 (N–Ar-*ipso*), 157.8 (C4), 163.7 (C3–CO_2Me), 164.2 (N–CHO), 164.6 (C5).

Anal. Calcd for $C_{20}H_{17}ClN_2O_5$ (400.81) C, 59.93; H, 4.28; N, 6.99. Found C, 59.99; H, 4.38; N, 6.85.

4.7.9. (E)-Methyl 2-((N-(4-bromophenyl)formamido)methyl)-4-hydroxy-5-oxo-2-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate **7e**

Yield 0.012 g, 91%. Yellow powder, mp 174–175 °C. IR (KBr) ν_{OH} 3423; ν_{NH} 3246; $\nu_{C=O}$ 1716, 1694, 1674; $\nu_{C=C}$ 1634 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.56 (3H, s), 4.68 (1H, d, J=13.6 Hz), 4.96 (1H, d, J=13.6 Hz), 6.57 (1H, s, D_2O exch.), 6.92 (2H, d, J=8.8 Hz), 7.32–7.39 (5H, m), 7.51 (2H, d, J=8.8 Hz), 8.30 (1H, s), 8.94 (1H, br s, D_2O exch.). ^{13}C NMR (100 MHz, $CDCl_3$): δ 48.0 (N–CH_2), 51.9 (CO_2*Me*), 64.6 (C7a), 114.3 (C3), 120.8 (N–Ar), 125.9 (C7a–Ph), 126.2 (C7a–Ph), 128.7 (N–Ar), 128.8 (C7a–Ph), 132.8 (N–Ar), 137.2 (C7a–Ph-*ipso*), 139.9 (N–Ar-*ipso*), 157.7 (C4), 163.6 (C3–CO_2Me), 164.4 (N–CHO), 164.7 (C5).

Anal. Calcd for $C_{20}H_{17}BrN_2O_5$ (445.26) C, 53.95; H, 3.85; N, 6.29. Found C, 53.85; H, 3.90; N, 6.32.

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References and notes

1. (a) Black, D. St. C.; Crozier, R. F.; Davis, V. C. *Synthesis* **1975**, 205–221; (b) Padwa, A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 123–180; (c) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10–23; (d) Dell, C. P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3873–3905; (e) Martin, J. N.; Jones, R. C. F. Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products. In *Nitrones. The Chemistry of Heterocyclic Compounds*; United Kingdom: Chichester, 2002; Vol. 59, pp 1–81.
2. (a) Coşkun, N.; Sümengen, D. *Synth. Commun.* **1993**, *23*, 1699–1706; (b) Coşkun, N.; Asutay, O. *Chim. Acta Turc.* **1997**, *25*, 69–72; (c) Coşkun, N.; Asutay, O. *Chim. Acta Turc.* **1999**, *27*, 17–23.
3. (a) Coşkun, N. *Tetrahedron Lett.* **1997**, *38*, 2299–2302; (b) Coşkun, N. *Tetrahedron* **1997**, *53*, 13873–13882; (c) Coşkun, N.; Ay, M. *Heterocycles* **1998**, *48*, 537–544; (d) Coşkun, N.; Tat, F. T.; Güven, Ö. Ö.; Ülkü, D.; Arıcı, C. *Tetrahedron Lett.* **2000**, *41*, 5407–5409; (e) Coşkun, N.; Tat, F. T.; Güven, Ö. Ö *Tetrahedron* **2001**, *57*, 3413–3417; (f) Coşkun, N.; Yılmaz, B. *Synth. Commun.* **2004**, *34*, 1617–1623; (g) Coşkun, N.; Tat, F. T.; Güven, Ö. Ö *Tetrahedron: Asymmetry* **2001**, *12*, 1463–1467; (h) Coşkun, N.; Tunçman, S. *Tetrahedron* **2006**, *62*, 1345–1350.
4. (a) Coşkun, N. *Turk. J. Chem.* **2001**, *25*, 267–272; (b) Coşkun, N.; Tat, F. T. *Phosphorus Sulfur* **2003**, *178*, 881–886; (c) Coşkun, N.; Tat, F. T. *Turk. J. Chem.* **2004**, *28*, 1–7.
5. Freeman, J. P. *Chem. Rev.* **1983**, *83*, 241–261.
6. Jones, R. C. F.; Martin, J. N.; Smith, P.; Gelbrich, T.; Light, M. E.; Hursthouse, M. B. *Chem. Commun.* **2000**, 1949–1950.
7. (a) Habeeb, A. G.; Rao, N. P.; Knaus, E. E. *J. Med. Chem.* **2001**, *44*, 2921–2927; (b) Ishikawa, T.; Kudoh, T.; Yoshida, J.; Yasuhara, A.; Manabe, S.; Saito, S. *Org. Lett.* **2002**, *4*, 1907–1910; (c) Chiacchio, U.; Rescifina, A.; Chiacchio, M. A.; Romeo, G.; Romeo, R. *J. Org. Chem.* **2003**, *68*, 3718–3720.
8. Coşkun, N.; Parlar, A. *Synth. Commun.* **2005**, *35*, 2445–2451.
9. Coşkun, N.; Öztürk, A. *Tetrahedron* **2006**, *62*, 12057–12063.
10. (a) Mesnard, F.; Girard, S.; Fliniaux, O.; Bhogal, R. K.; Gillet, F.; Lebreton, J.; Fliniaux, M. A.; Robins, R. J. *Plant Sci.* **2001**, *161*, 1011–1018; (b) Sunagawa, M.; Matsumura, H.; Inoue, T.; Fukasawa, M.; Kato, M. *J. Antibiot.* **1990**, *43*, 519–532; (c) Iso, Y.; Irie, T.; Nishino, Y.; Motokawa, K.; Nishitani, Y. *J. Antibiot.* **1996**, *49*, 199–209; (d) Imamura, H.; Shimizu, A.; Sato, H.; Sugimoto, Y.; Sakuraba, S.; Nakajima, S.; Abe, S.; Miura, K.; Nishimura, I.; Yamada, K.; Morishima, H. *Tetrahedron* **2000**, *56*, 7705–7713.
11. (a) Matkhalikova, S. F.; Malikov, V. M.; Yunusov, S. Y. *Khim. Prir. Soedin.* **1969**, *5*, 606–607; (b) Matkhalikova, S. F.; Malikov, V. M.; Yunusov, S. Y. *Khim. Prir. Soedin.* **1969**, *5*, 30–32.
12. Chandrasekhar, S.; Jagadeshwar, V.; Prakash, S. J. *Tetrahedron Lett.* **2005**, *46*, 3127–3129.
13. Nitrones **1a–f** were prepared according to the previously reported methods.[2] In the cases of *p*-chloro- and bromoanilines the corresponding (1,3-bis(4-aryl)-imidazolidin-4-yl)(phenyl)methanones **1′d,e** were isolated. The probable mechanism for their formation is discussed below. (Scheme 6): the methylenimminium salt **A** probably in equilibrium with *N*-bromomethylenaniline **B** reacts with anilinoacetophenone oxime to give intermediate **C**. The latter underwent condensation with formaldehyde and hydrolyze to imminium salts **D** and **E** the intramolecular Mannich reaction of which produce compounds **1′a–e**.
14. Attempts to isolate compounds **4** according to a procedure involving their formation in ether solution failed. The products in the filtrate after separation of ether insoluble CF_3CO_2Na were shown to be identical with those prepared according to the main procedure.
15. The amide[16] group is one of the most important functional groups in chemistry. Its planarity and relatively high barrier to rotation about the C–N bond are important factors in determining the conformations of peptides and related compounds.
16. (a) Stewart, W. E.; Siddall, T. H., III. *Chem. Rev.* **1970**, *70*, 517–551; (b) Wiberg, K. B.; Brenemant, C. M. *J. Am. Chem. Soc.* **1992**, *114*, 831–840.
17. Solutions (DMSO-d_6, 0.8 mL) of compounds **6** (0.03 mmol) in NMR tubes were heated at 80 °C on a water bath and the reaction times determined by ^{1}H NMR spectroscopy as 5, 2.5, 1, 14, 14 h for **6a–e**, respectively. As expected the logarithms of the average rates of the reactions are in linear correlation with the Hammett σ constants, $\rho=-2.09$ and $R^2=0.99$.
18. The NOESY1D experiments in $CDCl_3$ solution confirmed the stereochemistry of the (*E*)-**7**. Irradiation of the singlet at 8.26 led to the enhancement of the N–Ar ortho protons (0.8%), while the irradiation of N–Ar ortho protons enhanced the C3–H by 2.26%. The same irradiation enhanced also the C1–Ha (upward) by 2. 31% C1–Hb by 1%. The irradiation of the latter proton signal enhanced the N–Ar ortho protons signal, C1–Hb (downward) and the C7a–Ph ortho protons by 5.48, 19.8 and 4.26%, respectively. The irradiation of C1–Hb enhanced the signals of C1–Ha, N–Ar ortho and C7a–Ph ortho by 17, 4.65 and 2.93%, respectively.