New Synthetic Approach for the Preparation of Imidazole N^3-Oxide

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Abstract: A new synthetic procedure of 1-alkyl(aryl)-1*H*-4-methylimidazole N^3-oxide derivatives by cyclocondensation of α-amineoximes and orthoesters was studied. Low yields in the cyclization process were the result of predominant *Z*-stereoisomer around the oxime moiety of α-amineoxime reactants. Different attempts to improve these yields were assayed, mild conditions being those that produce the best results. Also, the special acidity of hydrogen-2 in the imidazole N^3-oxide system was studied in solution by NMR spectroscopy. This property provides a convenient intermediate to access 2-substituted analogues.

Keywords: imidazole *N*-oxide, cyclization, H-2 acidity

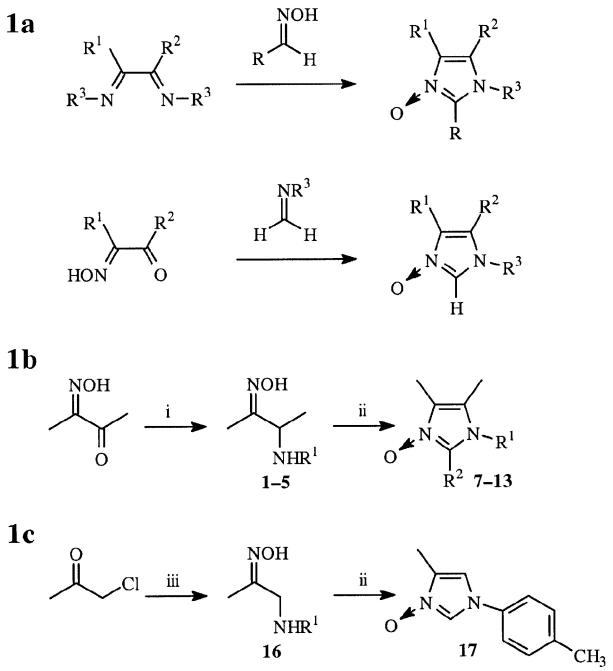
The synthesis and chemical reactivity of 1*H*-imidazole N^3-oxide have been little studied.[1–4] Interesting synthetic procedures were previously described. However, pharmacological aspects related with derivatives of this heterocyclic system were poorly reported.[4] To our knowledge, we were the first group that studied 1*H*-imidazole N^3-oxide derivatives as anti-parasitic agents.[5]

The synthetic routes described until now[1,2] for the preparation of 1*H*-imidazole N^3-oxide derivatives involucrate electrophile-nucleophile and nucleophile-electrophile synthons. The electrophile-nucleophile synthons described included 1,2-diimines that contribute with the final N-1, C-4 and C-5 heterocycle atoms, and α-oximineketones that contribute with the final N-3, C-4, and C-5 heterocycle atoms. Besides, the nucleophile-electrophile synthons described were oximes that contribute with the final C-2 and N-3 heterocycle atoms, and hexahydro-1,3,5-triazines or formaldimines that contribute with the final N-1 and C-2 heterocycle atoms (Scheme 1a). According to Lettau et al. the desired products were obtained in low yields due to the low stability of this kind of heterocycles.[2a,b]

In this work the synthesis of 1-alkyl(aryl)-1*H*-4-methylimidazole N^3-oxide derivatives involving a *bis*-nucleophile synthon (α-amineoximes that contribute with the final N-1, N-3, C-4 and C-5 atoms of the heterocyclic skeleton) and an electrophile synthon (orthoesters that contribute with the C-2 portion) is reported. These synthetic routes from diacetyl monooxime or α-chloroacetone are depicted in Schemes 1b and 1c, respectively.

α-Amineoximes were obtained by reductive amination of diacetyl monooxime[6] (**1**–**5**) or by nucleophilic substitution of α-chloroacetone with amines followed by oxime formation with hydroxylamine (**16**). The first procedure leads to the desired compounds in discrete yields (Table 1) without reaction in the case of the weak nucleophile *p*-nitroaniline (**6**). The substitution procedure proceeded with adequate yield only with *p*-toluidine (Table 1). In the other cases polyalkylated products were obtained (**14**, **15**).

Cyclization of α-amineoximes was initially carried out with orthoester as solvent in the presence of catalytic amounts of *p*-TsOH[6] (Method A). However, yields did not overpass 30% (Table 1) and the reactions were not complete (α-amineoximes were chromatographically observed after 48 h of reflux, longer time of reaction produced decomposition of the product). During the cy-



Scheme 1 (i) $R^1NH_2/ZnCl_2/NaCNBH_3/MeOH/r.t.$ (R^1: see Table 1); (ii) $R^2C(OR^3)_3$ (R^2 = H, CH_3; R^3 = CH_3, CH_2CH_3)/H^+; (iii) 1) $R^1NH_2/Na_2CO_3/KI/$ acetone/reflux; 2) $NH_2OH/NaOAc/MeOH/r.t.$

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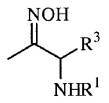
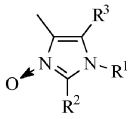
Table 1 α-Amineoxime Intermediates and Imidazole N^3-Oxide Developed by Method A





Compound	R^1	R^3	Yield (%)[a,b]	Compound	R^1	R^2	R^3	Yield (%)[a,c]
1	*n*-butyl	CH_3	24	**7**	CH_2CH_2Ph	H	CH_3	6
2	CH_2CH_2Ph	CH_3	48	**8**	CH_2CH_2Ph	CH_3	CH_3	27
3	CH_2-furyl	CH_3	46	**9**	CH_2-furyl	H	CH_3	NR
4	Ph-*p*-OCH_3	CH_3	32	**10**	CH_2-furyl	CH_3	CH_3	21
5	Ph-*p*-CH_3	CH_3	38	**11**	Ph-*p*-OCH_3	H	CH_3	10
6	Ph-*p*-NO_2	CH_3	NR[d]	**12**	Ph-*p*-CH_3	H	CH_3	8
14	CH_2CH_2Ph	H	NP[e]	**13**	Ph-*p*-CH_3	CH_3	CH_3	10
15	CH_2-furyl	H	NP	**17**	Ph-*p*-CH_3	H	H	15
16	Ph-*p*-CH_3	H	58					

[a] Chromatographically isolated products.
[b] Complete reactions.
[c] Incomplete reactions.
[d] NR: No reaction was observed.
[e] NP: No desired products but only polyalkylated products were obtained.

clization of **1** with methyl orthoformate a dimeric product was obtained that was characterized by NMR-HETCOR experiments. Two molecules of **1** were interconnected through the aminic nitrogen of one molecule and the oximic carbon of the other, the free *N*-aminic and *O*-oximic sites were blocked with orthoester units.

The imidazole N^3-oxide formation (**7**, **8**, **10**–**13** and **17**) was confirmed by spectroscopy. Clearly, the ^{13}C NMR, NMR-HETCOR experiments, i.e. HMQC, HMBC, and MS permit to endorse the presence of the heterocycle. ^{13}C NMR spectra showed the signal that corresponds to C-2 of the imidazole N^3-oxide. The presence of the *N*-oxide moiety easily became evident from spectroscopic data;[7] the N^3-oxide shifts moved to higher fields with respect to the imidazole C-2 signals [$d_{C\text{-}2}$ (imidazole) ca. 136 ppm, in these derivatives $d_{C\text{-}2}$ (2-non-substituted imidazole N^3-oxide) ca. 129–135 ppm and $d_{C\text{-}2}$ (2-CH_3 imidazole N^3-oxide) ca. 143–144 ppm]. The HMQC experiments permitted an unequivocal assignment for C-2 in the 2-non-substituted imidazole N^3-oxide. HMBC experiments allowed to confirm that the cyclization process took place. Figure 1 shows the corresponding HMBC experiments for derivatives **8** and **11**. For derivative **11** it is possible to observe that H-2 correlates, in the HMBC experiment, with C-4 and C-5 of the imidazole ring (Figure 1a). In the case of derivative **8** it is possible to observe correlation between C-2 and C-5 of the imidazole ring with methylenic hydrogens of the N^1-lateral chain (Figure 1b). The fragmentation patterns found in the mass spectrum corroborated the spectroscopy results described above. Alternatively, derivative **12** was also obtained by a procedure described by Alcázar et al.[1] and it was compared with the product obtained by our method for which chromatographic and spectroscopic results were identical.

The cyclization reactions evolved with improved yields in the synthesis of 2-methyl derivatives, when ethyl orthoacetate was used as solvent for the reaction (compare derivatives **7** with **8**, **9** with **10**, and **12** with **13**). These results could indicate that the reflux temperature has an influence on the product yield. This fact together with the non-completed reaction observation and with previous reports[3] conducted us to propose that the stereoisomeric form of the oxime in the α-amineoxime reactants was not adequate for the cyclization, since only the *E*-isomer is the spatial form that produced the desired heterocycle.

In order to study the proportion of the isomeric forms of the α-amineoxime in solution, we used ^1H NMR and ^{13}C NMR spectroscopy at room temperature.[8] As shown in the examples in Table 2, the oxime reactants exist in solution predominantly as *Z*-isomers, the non-reactive form. In all cases, the proportions of *E*-isomers were in agreement with the cyclization product yields. Therefore, this fact could be the main reason for the low yields during the cyclization process.

In order to improve these yields some experimental modifications were carried out. First, we studied the use of microwaves as the cyclization energy.[9] In this sense, different experimental conditions were assayed for the synthesis of derivative **11** (Table 3). The heterocycle was generated only without any solid support, but in lower

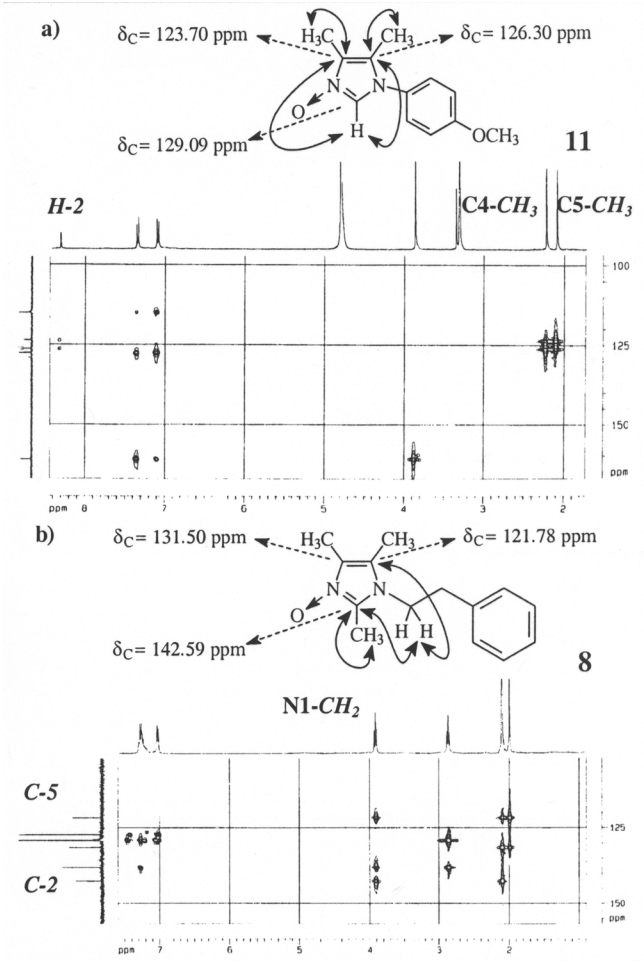
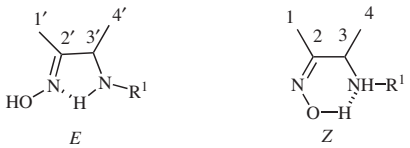


Figure 1 HMBC experiments of compounds **8** and **11**

Table 2 Selected α-Amineoximes and Signals Used for the Isomeric Study



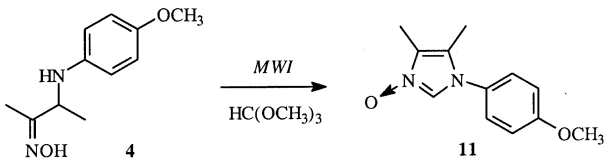
E *Z*

Compound	Proportion *E*:*Z*	Chemical shifts (ppm)
1	5:95	$\delta_{H\text{-}3'} = 3.94$, $\delta_{H\text{-}3} = 3.38$
2	11:89	$\delta_{H\text{-}3'} = 4.20$, $\delta_{H\text{-}3} = 3.45$[a]
4	16:84	$\delta_{H\text{-}3'} = 4.90$, $\delta_{H\text{-}3} = 4.07$
5	18:82	$\delta_{H\text{-}3'} = 4.94$, $\delta_{H\text{-}3} = 4.13$[b]

[a] $\delta_{C\text{-}3'} = 51.17$, $\delta_{C\text{-}3} = 57.34$.
[b] $\delta_{C\text{-}3'} = 45.99$, $\delta_{C\text{-}3} = 53.41$

yield than by using Method A (Table 1). Under these conditions a main product, **18**, was formed (Scheme 2). Compound **18** could be seen as the result of a fragmentation process of the cyclization intermediate mediated by microwaves. The structure of compound **18** has been determined by NMR spectroscopy. In addition, suitable crystals were obtained for X-ray diffraction studies. Figure 2 displays the ORTEP draw[10a] showing the labeling of the non-H atoms and their displacement ellipsoids at 30% probability level.

Table 3 Microwave Irradiation Processes

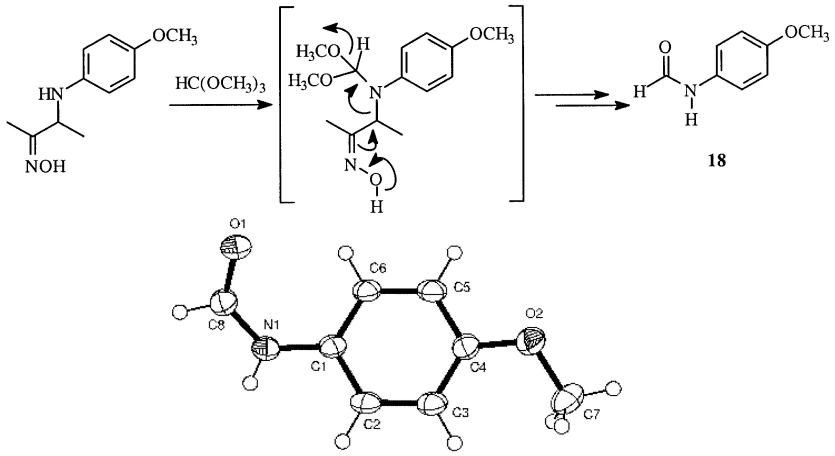


Entry[a]	Catalyst	Period of irradiation [s][b]	Total time [min]	Yield [%][c] **11/18**
1	SiO_2	30 (first 4 min) and 60 (last 10 min)	14	NP[d]
2	*p*-TsOH + SiO_2	60	14	NP
3	K10[e]	60	14	NP
4	*p*-TsOH + Al_2O_3[f]	60	14	NP
5	*p*-TsOH	180	15	4[g]/90

[a] Reagents: **4** (50 mg) and $HC(OCH_3)_3$ (0.5 mL).
[b] The reaction mixture was irradiated over the period of time indicated, each period was separated by 1–2 min of absence of irradiation.
[c] Isolated yield after chromatographic purification.
[d] NP: formation of imidazole N^3-oxide was not chromatographically observed.
[e] Montmorillonite K10.
[f] Neutral aluminum oxide.
[g] Entry 5 was repeated for the preparation of derivative **12** with 5% of yield.

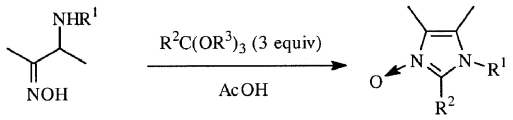
In an other attempt to increase the cyclization yields the use of acetic acid as *Z*/*E* isomerization promoting agent was employed. Our initial approach consisted in the use of AcOH as the reaction solvent at reflux temperature. Under these conditions the desired products were generated (Table 4). However, the number of secondary products was increased, generating very complex reaction mixtures. Mild conditions (room temperature) permitted to obtain the 1-alkyl(aryl)-1*H*-4-methylimidazole N^3-oxide derivatives in best yields (Method B, Table 4).

During the characterization of 2-non-substituted 1*H*-imidazole N^3-oxide (**7**, **11**, **12**, and **17**) by ^{1}H NMR spectroscopy an interesting phenomenon was observed. The H-2 signal appeared as a broad singlet and its chemical shift seemed to be highly dependent of the solvent. As it was already reported for *N*-protonated or *N*-alkylated imidazole and thiazole these facts indicate that H-2 presents an unusual acidity.[11] Furthermore, it was described recently that this property could be used in the 2-functionalization of azoles by reacting them with an adequate electrophile, via azolium ylide[11] (as hypothesized in Scheme 3 for our system).



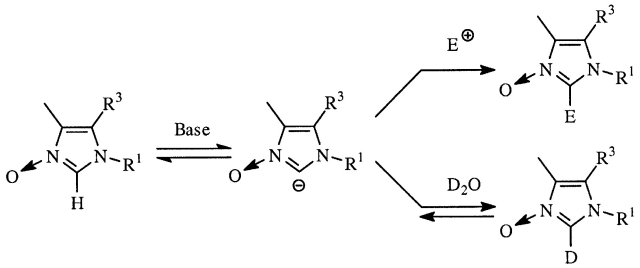
Scheme 2 Microwave formation and ORTEP diagram of **18**

Table 4 Cyclization in Acetic Acid as Solvent



Compound	R^1	R^2	Conditions	Time	Yield [%][a]
			Method A		6
7	CH_2CH_2Ph	H	Reflux	20 h	5
			r.t.[b]	7 d[c]	89
			Method A		27
8	CH_2CH_2Ph	CH_3	Reflux	20 h	10
			r.t.[b]	7 d[c]	40
			Method A		8
12	Ph-*p*-CH_3	H	r.t.[b]	20 d[c]	30
			Method A		10
13	Ph-*p*-CH_3	CH_3	r.t.[b]	20 d[c]	35

[a] Chromatographically isolated products.
[b] Method B.
[c] Incomplete reactions.



Scheme 3 Acidity of H-2 of 1-alkyl(aryl)-1*H*-4-methylimidazole N^3-oxide

We also present herein the first approach to study the H-2 deprotonation conditions for 2-non-substituted imidazole N^3-oxides. The process was studied by ^{1}H NMR spectroscopy using isotopic H/D exchange[12] at C-2 of the imidazolium species at different pHs. We evaluated the variation on H-2 integration by the action of different agents and at different times at room temperature (see Table 5 for studies on derivative **12**).

Clearly it was possible to observe that the H-2 on 2-non-substituted imidazole N^3-oxides was slightly exchangeable in acidic and neutral aqueous solution at room temperature and exposure during 24 h. If the solution was slightly basic the H/D exchange increased (Table 5, compare entries 1–3). Increasing the amount of base lead to an increase of the exchange rate , when the time of exposure was longer (Table 5, compare entries 4 and 5). However, if one mole of NaOD per mole of compound **12** was used the H/D exchange was completed within 5 min at room temperature (Table 5, entry 6).

Table 5 Selected Experiments on H/D Exchange at H-2 of 2-Non-Substituted Imidazole N^3-Oxides

	Conditions[a]		
Entry	Reagent/Volume [mL]	Time	H/D exchange [%]
1	DCl (1 M, pH = 1.0)/ 0.1	24 h	10
2	D_2O/0.1	24 h	20
3	K_2CO_3 (0.05 M)[b]/0.1[c]	24 h	35
4	K_2CO_3 (0.15 M)[b]/0.1[d]	30 min	80
5	NaOD (0.25 M)[b]/0.1[e]	5 min	15
6	NaOD (0.50 M)[b]/0.1[f]	5 min	>98

[a] Derivative **12** in acetone-d_6, standard concentrations were 10 mg/0.5 mL.
[b] Solution prepared with D_2O.
[c] Corresponding to 0.1 mole of K_2CO_3 per mole of **12**.
[d] Corresponding to 0.3 mole of K_2CO_3 per mole of **12**.
[e] Corresponding to 0.5 mole of NaOD per mole of **12**.
[f] Corresponding to 1.0 mole of NaOD per mole of **12**.

A new synthetic approach of 1-alkyl(aryl)-1*H*-imidazole N^3-oxide derivatives involving α-amineoximes as nucleophilic synthons and orthoesters as electrophiles was studied. The heterocycle was obtained in acetic acid at room temperature. The H-2 acidity of 2-non-substituted 1*H*-imidazole N^3-oxide derivatives was studied using H/D exchange.

^{1}H NMR, ^{13}C NMR spectra and HETCOR experiments were recorded on a BRUKER DPX-400 (400 MHz) spectrometer using the solvent indicated. Standard concentration of the samples was 20 mg/mL. Chemical shifts are reported in ppm (δ) relative to TMS as an internal standard. MS (EI) were recorded with a GC-MS SHIMADZU QP 1100 EX spectrometer operating at 70 eV. IR spectra were recorded with a SHIMADZU DR-8031 spectrometer as KBr pellets. Melting points were determined using a Leitz Microscope Heating Stage Model 350 apparatus and are uncorrected. Elemental analyses were obtained from vacuum-dried samples (over phosphorous pentoxide at 3–4 mm Hg, 24 h at r.t.) and performed on a Fisons EA 1108 CHNS-O analyzer, and were within ±0.4% of theoretical values. TLC analyses were carried out on aluminum sheets silica gel 60 F_{254}. Column chromatography was performed on silica gel 60 (Merck, 60–230 mesh) with typically 30–50 g of stationary phase per gram substance.

Synthesis of α-Aminooximes 1–5; General Procedure

A mixture of butane-2,3-dione oxime (1.00 g, 9.9 mmol), the corresponding amine (14.9 mmol), catalytic amounts of $ZnCl_2$, MeOH (10 mL) and molecular sieves (4 Å) was stirred at r.t. for 24 h. $NaCNBH_3$ (0.62 g, 9.9 mmol) was added and the mixture was stirred at r.t. for 48 h (complete consumption of carbonyl compound). The solvent was removed in vacuo. The residue was dissolved in EtOAc (30 mL) and washed with an aq soln of sat. $NaHCO_3$ (3 × 10 mL). The organic layer was dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by column chromatography (petroleum ether–EtOAc, 1:1).

3-(Butylamino)butan-2-one Oxime (1)

Colorless oil.

^{1}H NMR ($CDCl_3$): δ = 0.92 (t, 3 H, *J* = 7.2 Hz, CH_2CH_3 both isomers), 1.22 (d, 3 H, *J* = 6.7 Hz, 4-H both isomers), 1.35 (m, 2 H, CH_2CH_2 both isomers), 1.46 (m, 2 H, CH_2CH_2 both isomers), 1.85 (s, 3 H, 1-H both isomers), 2.50 (m, 2 H, $HNCH_2$ both isomers), 3.38 (q, 1 H, *J* = 6.7 Hz, 3-H *Z*-isomer), 3.94 (q, 1 H, *J* = 6.9 Hz, 3-H *E*-isomer), 7.20 (br s, 2 H, NH, OH both isomers).

^{13}C NMR ($CDCl_3$): δ (*Z*-isomer) = 9.21, 14.34, 19.80, 20.83, 32.70, 47.62, 57.60, 161.37.

3-[(2-Phenylethyl)amino]butan-2-one Oxime (2)

Yellow oil.

^{1}H NMR ($CDCl_3$): δ = 1.20 (d, 3 H, *J* = 6.7Hz, 4-H *E*), 1.22 (d, 3 H, *J* = 6.7Hz, 4-H *Z*), 1.76 (s, 3 H, 1-H *E*), 1.78 (s, 3 H, 1-H *Z*), 2.80 (m, 4 H, $HNCH_2CH_2Ph$, both isomers), 3.45 (q, 1 H, *J* = 6.7Hz, 3-H *Z*), 4.20 (q, 1 H, *J* = 6.7Hz, 3-H *E*), 5.40 (br s, 1 H, NH both isomers), 6.40 (br s, 1 H, OH both isomers), 7.22 (m, 3 H, Ph both isomers), 7.28 (m, 2 H, Ph both isomers).

^{13}C NMR ($CDCl_3$): δ (both isomers) = 9.27, 16.14, 18.00, 19.61, 36.47, 48.90, 49.39, 51.17, 57.34, 126.67, 128.84, 129.12, 140.26, 160.14, 160.35.

MS (EI, 70 eV): *m*/*z* (%) = 206 ($M^{+\cdot}$, 2), 189 ($M^{+\cdot}$ – 17, 1), 132 (10), 115 (28), 91 (9), 56 (100).

3-[(2-Furfuryl)amino]butan-2-one Oxime (3)

Yellow oil.

^{1}H NMR ($CDCl_3$): δ = 1.21 (d, 3 H, *J* = 6.8 Hz, 4-H both isomers), 1.84 (s, 3 H, 1-H both isomers), 3.43 (q, 1 H, *J* = 6.8Hz, 3-H *Z*), 3.68 (dd, 1 H, J_1 = 14.5 Hz J_2 = 2.5 Hz, $HNCH_2$ both isomers), 3.73 (dd, 1 H, J_1 = 14.5 Hz J_2 = 2.4 Hz, $HNCH_2$ both isomers), 4.12 (q, 1 H, *J* = 7.1Hz, 3-H *E*), 5.74 (br s, 2 H, OH, NH both isomers), 6.17 (m, 1 H, furyl both isomers), 6.29 (m, 1 H, furyl both isomers), 7.34 (m, 1 H, furyl both isomers).

MS (EI, 70 eV): *m*/*z* (%) = 182 ($M^{+\cdot}$, 1), 165 ($M^{+\cdot}$ – 17, 21), 96 (33), 115 (28), 81 (100).

3-[(*p*-Methoxyphenyl)amino]butan-2-one Oxime (4)

Yellow oil.

^{1}H NMR ($CDCl_3$): δ = 1.37 (d, 3 H, *J* = 6.8 Hz, 4-H *E*), 1.38 (d, 3 H, *J* = 6.8 Hz, 4-H *Z*), 1.74 (s, 3 H, 1-H *E*), 1.84 (s, 3 H, 1-H *Z*), 3.75 (s, 3 H, OCH_3 both isomers), 4.07 (q, 1 H, *J* = 6.8 Hz, 3-H *Z*), 4.90 (q, 1 H, *J* = 6.8 Hz, 3-H *E*), 6.68 (m, 2 H, Ph both isomers), 6.77 (m, 2 H, Ph both isomers), 9.92 (br s, 1 H, NH both isomers), 10.88 (br s, 1 H, OH both isomers).

MS (EI, 70 eV): *m*/*z* (%) = 208 ($M^{+\cdot}$, 4), 192 ($M^{+\cdot}$ – 17, 1), 107 (100), 101 (20).

3-[(*p*-Methylphenyl)amino]butan-2-one Oxime (5)

Yellow oil.

^{1}H NMR ($CDCl_3$): δ = 1.38 (d, 3 H, *J* = 6.8 Hz, 4-H *E*), 1.39 (d, 3 H, *J* = 6.8 Hz, 4-H *Z*), 1.76 (s, 3 H, 1-H *E*), 1.86 (s, 3 H, 1-H *Z*), 2.25 (s, 3 H, $PhCH_3$ both isomers), 3.65 (br s, 1 H, NH both isomers), 4.13 (q, 1 H, *J* = 6.8 Hz, 3-H *Z*), 4.94 (q, 1 H, *J* = 6.8 Hz, 3-H *E*), 6.58 (d, 2 H, *J* = 8.2 Hz, Ph both isomers), 6.98 (d, 2 H, *J* = 8.2 Hz, Ph both isomers), 8.07 (br s, 1 H, OH both isomers).

^{13}C NMR ($CDCl_3$): δ (both isomers) = 9.71, 15.03, 18.13, 20.19, 20.75, 45.99, 53.41, 113.10, 113.92, 115.78, 127.41, 130.13, 130.30, 145.05, 160.96, 163.00.

MS (EI, 70 eV): *m*/*z* (%) = 192 ($M^{+\cdot}$, 35), 177 (19), 134 (100), 118 (23), 91 (28).

Synthesis of 1-Alkyl(aryl)-1*H*-4-methylimidazole N^3-Oxides 7, 8, 10–13, 17; General Procedure

Method A: A mixture of the corresponding α-aminooxime (1.9 mmol), catalytic amounts of *p*-TsOH and the corresponding orthoester (methyl orthoformate or ethyl orthoacetate) (10 mL) was heated at reflux for 24 h. Then the solvent was removed in vacuo and the residue was purified by column chromatography (EtOAc–MeOH, 6:4).

Method B: A mixture of the corresponding α-aminooxime (1.9 mmol), the corresponding orthoester (methyl orthoformate or ethyl orthoacetate) (5.7 mmol) and AcOH (10 mL) was stirred at r.t. for the time indicated in Table 4. Then the solvent was removed in vacuo and the residue was purified by column chromatography (EtOAc–MeOH, 6:4).

4,5-Dimethyl-1-(2-phenylethyl)-1*H*-imidazole N^3-Oxide (7)

Brown oil.

IR (KBr): 2984, 2870, 1651, 1472, 1235, 1045, 723 cm^{-1}.

^{1}H NMR (methanol-d_4): δ = 2.04 (s, 3 H, C_5CH_3), 2.18 (s, 3 H, C_4CH_3), 3.00 (t, 2 H, *J* = 7.3Hz, CH_2Ph), 4.05 (t, 2 H, *J* = 7.3Hz, NCH_2), 7.28 (m, 5 H, Ph), 7.36 (br s, 1 H, 2-H).

^{13}C NMR (methanol-d_4): δ = 8.56, 12.60, 37.95, 56.14, 122.50, 127.44, 129.04, 129.07, 132.50, 134.81, 137.70.

MS (EI, 70 eV): *m*/*z* (%) = 200 ($M^{+\cdot}$ – 16, 100), 138 (28), 111 (42), 105 (47).

Anal. Calcd for $C_{13}H_{16}N_2O{\times}H_2O$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.80; H, 7.59; N, 11.92.

2,4,5-Trimethyl-1-(2-phenylethyl)-1*H*-imidazole N^3-Oxide (8)
Brown oil.

IR (KBr): 2984, 2870, 1653, 1472, 1258, 1044, 723 cm^{-1}.

^1H NMR (methanol-d_4): δ = 2.00 (s, 3 H, C_5CH_3), 2.10 (br s, 6 H, C_2CH_3, C_4CH_3), 2.87 (t, 2 H, J = 8.0 Hz, CH_2Ph), 3.91 (t, 2 H, J = 8.0 Hz, NCH_2), 7.03 (d, 2 H, J = 7.4 Hz, Ph), 7.26 (m, 3 H, Ph).

^{13}C NMR (methanol-d_4): δ = 9.10, 12.71, 13.26, 37.33, 45.80, 121.78, 127.30, 129.13, 129.19, 131.50, 138.07, 142.59.

MS (EI, 70 eV): m/z (%) = 214 ($M^{+\cdot}$ – 16, 98), 123 (100), 104 (31), 82 (21).

Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 72.66; H, 7.57; N, 11.95.

1-(2-Furylmethyl)-2,4,5-trimethyl-1*H*-imidazole N^3-Oxide (10)
Orange oil.

IR (KBr): 2975, 2870, 1651, 1472, 1208, 1148 cm^{-1}.

^1H NMR (methanol-d_4): δ = 2.11 (s, 3 H, C_5CH_3), 2.13 (s, 3 H, C_4CH_3), 2.39 (s, 3 H, C_2CH_3), 4.87 (s, 2 H, CH_2), 6.10 (d, 1 H, J = 3.4 Hz, Furyl), 6.29 (d, 1 H, J = 3.4 Hz, Furyl), 7.33 (t, 1 H, J = 3.4 Hz, Furyl).

^{13}C NMR (methanol-d_4): δ = 9.17, 12.71, 13.52, 41.07, 107.99, 110.78, 122.23, 131.58, 142.96, 143.03, 150.17.

MS (EI, 70 eV): m/z (%) = 190 ($M^{+\cdot}$ – 16, 18), 109 (6), 81 (100).

Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.70; H, 6.90; N, 13.22.

1-(*p*-Methoxyphenyl)-4,5-dimethyl-1*H*-imidazole N^3-Oxide (11)
Beige oil.

IR (KBr): 2984, 2870, 1647, 1516, 1472, 1256, 1042, 826 cm^{-1}.

^1H NMR (methanol-d_4): δ = 2.11 (s, 3 H, C_5CH_3), 2.24 (s, 3 H, C_4CH_3), 3.88 (s, 3 H, OCH_3), 7.11 (d, 2 H, J = 6.8 Hz, Ph), 7.36 (d, 2 H, J = 6.8 Hz, Ph), 8.32 (s, 1 H, 2-H).

^{13}C NMR (methanol-d_4): δ = 6.13, 8.04, 55.18, 115.03, 123.70, 126.30, 127.57, 127.74, 129.09, 161.08.

MS (EI, 70 eV): m/z (%) = 218 ($M^{+\cdot}$, 100), 202 ($M^{+\cdot}$ – 16, 49), 148 (72), 107 (15).

Anal. Calcd for $C_{12}H_{14}N_2O_2{\times}H_2O$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.89; H, 6.64; N, 11.57.

4,5-Dimethyl-1-(*p*-methylphenyl)-1*H*-imidazole N^3-Oxide (12)[1c]
IR (KBr): 2919, 2849, 1682, 1516, 1456, 1210, 1111, 818 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.08 (s, 3 H, C_5CH_3), 2.26 (s, 3 H, C_4CH_3), 2.43 (s, 3 H, $PhCH_3$), 7.13 (d, 2 H, J = 8.2 Hz, Ph), 7.29 (d, 2 H, J = 8.2 Hz, Ph), 7.89 (br s, 1 H, 2-H).

^{13}C NMR (methanol-d_4): δ = 7.74, 9.75, 21.49, 122.08, 124.84, 126.09, 127.77, 130.82, 132.88, 139.91.

MS (EI, 70 eV): m/z (%) = 202 ($M^{+\cdot}$, 30), 186 ($M^{+\cdot}$ – 16, 100), 144 (38), 91 (44).

Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 70.95; H, 6.64; N, 13.52.

2,4,5-Trimethyl-1-(*p*-methylphenyl)-1*H*-imidazole N^3-Oxide (13)[1b]
Colorless oil.

IR (KBr): 2920, 2850, 1680, 1515, 1456, 1209, 1110, 810 cm^{-1}.

^1H NMR (methanol-d_4): δ = 1.96 (s, 3 H, C_5CH_3), 2.16 (s, 3 H, C_4CH_3), 2.35 (s, 3 H, $PhCH_3$), 2.44 (s, 3 H, C_2CH_3), 7.13 (d, 2 H, J = 8.2 Hz, Ph), 7.39 (d, 2 H, J = 8.2 Hz, Ph).

^{13}C NMR (methanol-d_4): δ = 13.26, 21.20, 21.46, 24.85, 118.00, 120.40, 128.00, 129.83, 137.00, 139.50, 144.00.

MS (EI, 70 eV): m/z (%) = 216 ($M^{+\cdot}$, 29), 200 ($M^{+\cdot}$ – 16, 100), 144 (40), 91 (40).

Anal. Calcd for $C_{13}H_{16}N_2O{\times}0.5H_2O$: C, 69.33; H, 7.56; N, 12.44. Found: C, 68.99; H, 7.33; N, 12.57.

Synthesis of 4-Methyl-1-(*p*-methylphenyl)-1*H*-imidazole N^3-Oxide (17)

1-[(*p*-Methylphenyl)amino]acetone Oxime (16)
A mixture of chloroacetone (2.00 g, 21.0 mmol), *p*-toluidine (2.30 g, 21.0 mmol), K_2CO_3 (2.89 g, 21.0 mmol), KI (catalytic amounts) and acetone (50 mL) was heated at reflux for 10 h. Then the solvent was removed in vacuo. The residue was dissolved in EtOAc (30 mL) and washed with brine (3 × 10 mL). The organic layer was dried (Na_2SO_4) and evaporated in vacuo. The residue (1.40 g, 40%) was used in the next step without further purification.

^1H NMR ($CDCl_3$): δ = 2.20 (s, 6 H, $PhCH_3$, $COCH_3$), 2.40 (br s, 1 H, NH), 3.90 (s, 2 H, $HNCH_2$), 6.50 (d, 2 H, J = 8.3 Hz, Ph), 6.90 (d, 2 H, J = 8.3 Hz, Ph).

^{13}C NMR ($CDCl_3$): δ = 20.70, 27.80, 55.10, 113.40, 127.50, 130.20, 145.00, 204.80.

MS (EI, 70 eV): m/z (%) = 163 ($M^{+\cdot}$, 15), 120 (100).

A mixture of the α-aminocarbonyl compound (0.16 g, 1.0 mmol), hydroxylamine hydrochloride (0.07 g, 1.0 mmol), $NaOAc{\cdot}3H_2O$ (0.13 g, 1.0 mmol) and MeOH (5 mL) was stirred at reflux for 1 h and then at r.t. for 12 h. The solid residue (0.12 g, 67%) was used in the next step without further purification. Infrared spectroscopy confirmed the oxime formation.

4-Methyl-1-(*p*-methylphenyl)-1*H*-imidazole N^3-Oxide (17)
Beige solid; mp 202.0–203.0 °C (Lit.[1b] 197.0–199.0 °C).

^1H NMR ($CDCl_3$): δ = 2.32 (s, 3 H, C_4CH_3), 2.40 (s, 3 H, $PhCH_3$), 6.89 (s, 1 H, 5-H), 7.20 (d, 2 H, J = 8.5 Hz, Ph), 7.29 (d, 2 H, J = 8.5 Hz, Ph), 8.17 (br s, 1 H, *2-H*).

^{13}C NMR ($CDCl_3$): δ = 8.50, 21.34, 112.76, 121.04, 124.44, 131.12, 132.26, 135.00, 138.78.

MS (EI, 70 eV): m/z (%) = 188 ($M^{+\cdot}$, 40), 172 ($M^{+\cdot}$ – 16, 8).

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.02; H, 6.27; N, 14.48.

Crystallographic Study
The diffraction pattern of compound **18**, $C_8H_9NO_2$, was collected at 120K on an Enraf-Nonius KappaCCD diffractometer employing graphite mono-chromate MoKα radiation and φ and ω scans to explore the reciprocal space. Data were collected with the program COLLECT[10b] and reduced with DENZO and SCALEPACK.[10c] Compound **18** crystallizes in the orthorhombic space group $Pna2_1$ with a = 10.606(2), b = 7.669(2), c = 9.244(1) Å, and Z = 4. The structure was solved by direct[10d] and Fourier[10e] methods from 1012 reflections with $I>2\sigma(I)$ and refined by full-matrix least-squares[10e] to an agreement factor $R1$ = 0.0534. The H atoms were positioned stereochemically and refined with the riding model. Phenyl C–C bond lengths are in the range from 1.375(5) Å to 1.398(4) Å. Single C(Ph)–N and C(Ph)–O bond distances are 1.414(4) Å and 1.357(4) Å, respectively. The remaining single N–C and O–C(Me) bond lengths are 1.330(4) Å and 1.439(4) Å, respectively, and the double C=O bond distance is 1.229(4) Å. C(Ph)–O–C(Me) and C(Ph)–N–C bond angles are 116.8(3)° and 126.9(3)°, respectively. Listings of atomic coordinates and equivalent isotropic displacement parameters, full intra-molecular bond distances and angles, hydrogen coordinates and anisotropic displacement parameters were deposited in

the Cambridge Crystallographic Data Centre, reference number CCDC-237524.

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