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PAPER

Synthesis of 4(5)-phenacyl-imidazoles from isoxazole side-chain rearrangements

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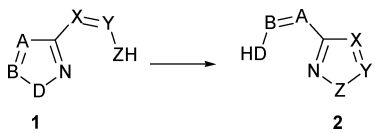
A novel base-induced rearrangement of isoxazoles into imidazole derivatives is reported. In the isoxazole series, this represents the first example of a three-atom side-chain rearrangement involving a CNC sequence. The reactions are carried out under nitrogen and produced 2-aryl-4(5)-phenacyl-5(4)-phenyl-imidazoles in high yields. In the presence of oxygen, a cascade rearrangement-oxidation reaction sequence was observed and imidazole derivatives bearing an oxidized side-chain were isolated.

Introduction

Imidazoles are an important class of heterocycles with a crucial role in biology.[1] Among the synthetic methodologies available for obtaining imidazole derivatives, heterocyclic rearrangements[2] represent a valid alternative whenever the target compounds are not accessible through classical approaches. In this context the reactivity and the availability of the appropriate heterocyclic precursor are key requirements for the success of this synthetic strategy.

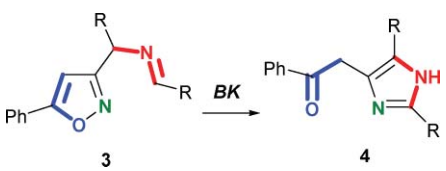
Among ring-transformations of five-membered heterocycles, the Boulton–Katritzky (*BK*) rearrangement is one of the most investigated reaction and is suitable for synthetic applications. It consists of an interconversion between azoles **1** and **2** (Chart 1) bearing a three-atom side-chain which is directly involved in the rearrangement through bond formation with the pivotal ring nitrogen.[3]



1 **2**

Chart 1

This type of reaction has been the subject of synthetic[4] and mechanistic studies,[5] and typically occurs on O–N bond containing heterocycles (**1**; D = O) such as isoxazoles, 1,2,5-oxadiazoles (furazans) and 1,2,4-oxadiazoles.[4,5] Although the effect of the type of side chain (X═Y-ZH) on the obtainment of different heterocycles has been extensively investigated,[4e,g] only few examples reported the involvement of a nucleophilic carbon (Z = C) in the side-chain.[6–10] Besides earlier studies on *N*-(1,2,4-oxadiazol-3-yl)-β-enaminoketones,[6] synthetic applications of BK rearrangements of 1,2,4-oxadiazole derivatives bearing an NCC,[7] NNC[8] or a CNC[9] side-chain sequence have been very recently exploited to obtain variously functionalized 1,2,4-triazoles[8] and imidazoles.[7,9] In the isoxazole series, instead, the only example involving a nucleophilic carbon at the side chain is related to the obtainment of pyrrole derivatives through a CCC side-chain sequence.[10] From a synthetic point of view, the possibility to change the heterocyclic moiety in the substrate **1** would result in changing the identity of the side-chain in the product **2**. In this context, we decided to extend the applicability of BK rearrangements, involving a CNC side-chain, to isoxazoles which are more aromatic[11] and less keen to rearrange than 1,2,4-oxadiazoles.[4b,12] Interestingly, by using *N*-(isoxazol-3-yl)benzyl aldimines **3** as starting compounds, the base-promoted BK rearrangement would produce the corresponding 4(5)-phenacylimidazoles **4** (Scheme 1). To the best of our knowledge, 4(5)-phenacylimidazoles have been rarely reported[13] despite the biological activity and synthetic interest of regioisomeric *N*-phenacyl-[14] and 2-phenacylimidazole derivatives.[15]



3 **4**

Scheme 1 CNC side-chain rearrangement of isoxazole.

Results and discussion

The synthesis of isoxazole-imines **3** has been achieved in two steps starting from the easily accessible 3-benzoyl-5-phenylisoxazole **5**.[16] In the first step, 3-(α-aminobenzyl)-isoxazole **6** was obtained in high yield (87%), by reacting isoxazole **5** with benzylamine in the presence of Montmorillonite K10 (Mont-K10) in toluene

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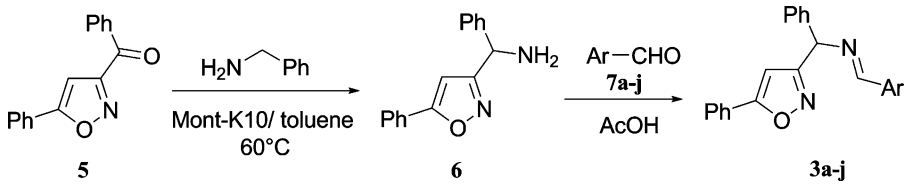


Scheme 2 Synthesis of imines **3**.

Table 1 Results for the synthesis of imines **3**

Entry	Product	Yield %[a]
1	**3a**: Ar = Ph	84
2	**3b**: Ar = 4-CH_3OPh	82
3	**3c**: Ar = 4-CH_3Ph	76
4	**3d**: Ar = 3-CH_3Ph	76
5	**3e**: Ar = 2-CH_3Ph	80
6	**3f**: Ar = 4-CF_3Ph	68
7	**3g**: Ar = 4-FPh	70
8	**3h**: Ar = 4-ClPh	53
9	**3i**: Ar = 4-BrPh	64
10	**3j**: Ar = 4-N(CH_3)$_2$Ph	57

[a] Isolated yield.

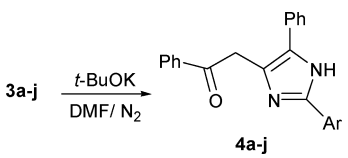
Table 2 Results for the synthesis of imidazoles **4**

Entry	Product	Yield %[a]
1	**4a**: Ar = Ph	85
2	**4b**: Ar = 4-CH_3OPh	90
3	**4c**: Ar = 4-CH_3Ph	95
4	**4d**: Ar = 3-CH_3Ph	98
5	**4e**: Ar = 2-CH_3Ph	97
6	**4f**: Ar = 4-CF_3Ph	95
7	**4g**: Ar = 4-FPh	85
8	**4h**: Ar = 4-ClPh	90
9	**4i**: Ar = 4-BrPh	88
10	**4j**: Ar = 4-N(CH_3)$_2$Ph	80

[a] Isolated yield.

at 60 °C for 24 h. The reaction consists of a biomimetic non-reductive transamination promoted by the heterogeneous catalyst and recently developed for the synthesis of similar 1,2,4-oxadiazole derivatives (Scheme 2).[9] In the second step, amine **6** was reacted with a series aromatic aldehydes **7a–j** at room temperature in acetic acid producing the corresponding imines **3a–j** which were isolated after crystallization as pure compounds and in good yields (Scheme 2, Table 1).

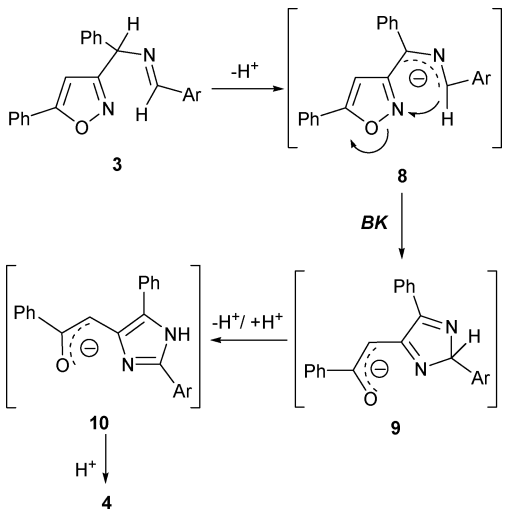
The general scheme of the *BK* reaction points out the key role of the potentially acidic *Z*-H proton which allows, under basic conditions, the formation of a negatively charged nucleophilic site in the side-chain. In our substrates, this role is taken on by the benzylic proton which could be abstracted by a strong base thus generating a terminal nucleophilic site in the CNC side-chain. Indeed, when imines **3a–j** were reacted at room temperature with an excess of *t*-BuOK in DMF under nitrogen for 8 h, the corresponding imidazole derivatives **4a–j** were produced in excellent yield (Scheme 3, Table 2).



Scheme 3 Rearrangement of imines **3** into imidazoles **4**.

The essential role of the base was confirmed by separate experiments performed in the absence of *t*-BuOK. For instance, refluxing compounds **3** in most common organic solvents (acetonitrile, benzene, toluene, DMF) or heating it above the melting temperature under solvent free-conditions led to decomposition of the starting material. Additionally, the attempts to perform thermal rearrangements in protic solvents (MeOH, EtOH) led to hydrolysis of imines **3** into the amine **6**. From a mechanistic point of view, the formation of imidazoles **4** could be explained through the initial formation of 2-aza-allylanion **8**, which undergoes an internal nucleophilic substitution at the pivotal N(2) of the isoxazole ring.

The resulting intermediate **9** will re-aromatize into its tautomer **10** producing the target imidazoles **4** after final protonation (Scheme 4).



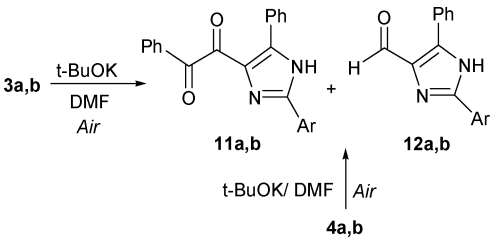
Scheme 4 Proposed mechanism for rearrangement of compounds **3**.

The driving force of the reaction could be identified either in the acidity of the benzylic proton, which is higher in **3** than in **4**, in the formation of a C–N(2) bond replacing the less stable O–N(2) one, or simply in the higher aromaticity of the imidazole ring with respect to the isoxazole one.[11]

Interestingly, the yields of final imidazoles **4** were not affected by either steric (Table 2: entries 3–5) or electronic (Table 2: entries 1, 2, 6) effects of the substituents on the *N*-benzylidene moiety. Additionally, no effect of the substituents was observed on the reaction rate. In the case of the synthesis of **4j**, some decomposition occurs during chromatographic purification.

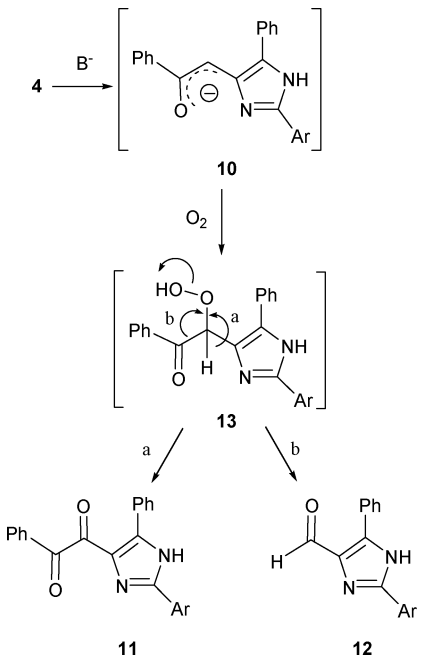
Additionally, a crucial experimental detail is that the rearrangement must be carried out under nitrogen in previously deoxygenated solvents in order to prevent oxidation of final imidazoles **4**.

In fact, in the presence of air, products resulting from the oxidation of phenacyl side-chain were observed. For instance, when representative compounds **3a,b** were reacted in DMF/*t*-BuOK under air, a complex mixture of products was formed with imidazoles **11a,b** and **12a,b** as major components. The formation of compounds **11** and **12** was also observed in a separate experiment starting from phenacyl imidazoles **4**, under the same reaction conditions (Scheme 5).



Scheme 5 Oxidative rearrangement of imines **3**.

The oxidation of the phenacyl side-chain of imidazoles **4** likely involves the hydroperoxide intermediate **13** which will decompose following either route a or b into products **11** or **12**, respectively (Scheme 6).[17] A tandem BK-oxidation reaction was once previously observed on similar substrates, but involved a copper-mediated oxidation process.[18]



Scheme 6 Proposed mechanism for oxidation of compounds **4**.

Conclusions

In conclusion, a Boulton–Katritzky rearrangement with the involvement of the CNC side-chain was observed for the first time in the isoxazole series. Synthetic application of this rearrangement allowed to obtain 4(5)-phenacyl-imidazoles in high yields and under mild conditions. Additionally, an air-promoted oxidative process of the obtained phenacyl-imidazoles was highlighted, opening the way to further functionalization of the imidazole side-chain.

Experimental section

Instrumentation and chemicals

Melting points were determined on a hot-stage apparatus and are uncorrected. FT-IR spectra were registered in Nujol mull. ^{1}H-NMR and ^{13}C-NMR spectra were recorded at 300 MHz and 62.5 MHz, respectively, residual solvent peak was used as reference. Electrospray (ESI) mass spectrometry experiments have been carried out on a LCQ-DECA (ThermoFinnigan, San Jose, CA) with spray voltage, 4.5 kV, capillary temperature 200 °C. Ultra pure helium He was the collision gas. CID collision energy: 0.5–1.0 eV (laboratory frame). Flash chromatography was performed by using silica gel (Merck, 0.040–0.063 mm) and mixtures of ethyl acetate and petroleum ether (fraction boiling in the range of 40–60 °C) in various ratios. 3-Benzoyl-5-phenylisoxazole **5** was obtained as previously reported.[16]

Phenyl(5-phenyl-isoxazol-3-yl)methanamine 6

To a solution of 3-benzoyl-5-phenylisoxazole **5** (500 mg, 2 mmol) in toluene (10 ml) benzylamine (2.5 mL, 10 mmol) and Montmorillonite K-10 (1 g) were added and the mixture kept in an oil bath at 60 °C under good stirring. After 24 h, the reaction mixture was cooled to room temperature, filtered off and washed with ethyl acetate. The filtrate was evaporated *in vacuo* to give the crude product, which was purified by flash chromatography to isolate the Phenyl(5-phenyl-isoxazol-3-yl)methanamine **6** (434 mg, 87%) as a white solid, mp 111–112 °C (from petroleum ether) (Found: C, 76.79; H, 5.63; N, 11.11. $C_{16}H_{14}N_2O$ requires C, 76.78; H, 5.64; N, 11.19%); ν_{max}(Nujol)/cm^{-1} 3365, 3290 and 1608; δ_H(300 MHz; $CDCl_3$) 1.80 (2 H, s, NH_2, exch. with D_2O), 5.37 (1 H, s, C*H*NH_2), 6.36 (1 H, s, C(4)H), 7.29–7.49 (8 H, m, Ph) and 7.70–7.74 (2 H, m, Ph); δ_C(62.5 MHz; $CDCl_3$) 53.0, 97.9, 125.8, 126.8, 127.4, 127.8, 128.8, 128.9, 130.1, 142.3, 168.1 and 170.0; *m*/*z*: 250 (M^+,100%).

General procedure for the synthesis of imines 3

To a solution of **6** (250 mg, 1 mmol) in glacial acetic acid (10 mL) was added the appropriate aldehyde **7a–j** (1.5 mmol). After 12 h at room temperature the solvent was removed *in vacuo* and the residual oil treated with petroleum ether. The formed precipitate was collected by filtration and crystallized from the appropriate solvent giving imines **3a–j**.

***N*-Benzylidene-phenyl-(5-phenyl-isoxazol-3-yl)methanamine 3a.** (284 mg, 84%) mp 135–136 °C (from petroleum ether) (Found: C, 81.64; H, 5.34; N, 8.29. $C_{23}H_{18}N_2O$ requires C, 81.63; H, 5.36; N, 8.28%); ν_{max}(Nujol)/cm^{-1} 1643; δ_H(300 MHz; $CDCl_3$) 5.87 (1 H, s, C*H*-N═C), 6.58 (1 H, s, C(4)H), 7.29–7.56 (11 H, m, Ph), 7.73–7.77 (2 H, m, Ph), 7.86–7.90 (2 H, m, Ph) and 8.54 (1 H, s, N═C*H*-Ph); δ_C(62.5 MHz; $CDCl_3$) 69.4, 98.4, 125.8, 127.1, 127.6, 128.6–128.8 (overlapped signals), 130.0, 131.2, 135.8, 140.9, 163.2, 166.5 and 169.9; *m*/*z*: 338 (M^+,100%).

***N*-(4-Methoxybenzylidene)-phenyl-(5-phenyl-isoxazol-3-yl)methanamine 3b.** (302 mg, 82%) mp 126–127 °C (from petroleum

ether) (Found: C, 78.20; H, 5.50; N, 7.61. $C_{24}H_{20}N_2O_2$ requires C, 78.24; H, 5.47; N, 7.60%); ν_{max}(Nujol)/cm^{-1} 1641 and 1606; δ_H(300 MHz; $CDCl_3$) 3.93 (3 H, s, OCH_3), 5.89 (1 H, s, C*H*-N=C), 6.64 (1 H, s, C(4)H), 7.02 (2 H, d, *J* 9.0, Ar), 7.36–7.52 (6 H, m, Ph), 7.59–7.61 (2 H, m, Ph), 7.80–7.84 (2 H, m, Ph), 7.85 (2 H, d, *J* 9.0, Ar) and 8.53 (1 H, s, N=C*H*-Ar); δ_C(62.5 MHz; $CDCl_3$) 55.4, 69.3, 98.5, 114.0, 125.8, 127.1, 127.5, 125.8, 127.8, 128.6, 128.8, 130.0, 130.2, 141.2, 162.1, 162.4, 166.7 and 169.9; *m*/*z*: 368 (M^+,100%).

***N*-(4-Methylbenzylidene)-phenyl-(5-phenyl-isoxazol-3-yl)methanamine 3c.** (268 mg, 76%) mp 172–173 °C (from petroleum ether) (Found: C, 81.75; H, 5.70; N, 7.93. $C_{24}H_{20}N_2O$ requires C, 81.79; H, 5.72; N, 7.95%); ν_{max}(Nujol)/cm^{-1} 1641; δ_H(300 MHz; $CDCl_3$) 2.48 (3 H, s, CH_3), 5.92 (1 H, s, C*H*-N=C), 6.65 (1 H, s, C(4)H), 7.24 (2 H, d, *J* 8.1, Ar), 7.37–7.50 (6H, m, Ph), 7.63–7.60 (2 H, m, Ph), 7.81–7.86 (4 H, m, Ph+Ar) and 8.57 (1 H, s, N=C*H*-Ar); δ_C(62.5 MHz; $CDCl_3$) 21.5, 69.4, 98.5, 125.8, 127.2, 127.5, 127.6, 128.5, 128.6, 128.8, 129.3, 130.0, 133.3, 141.1, 141.6, 163.1, 166.6 and 169.9; *m*/*z*: 352 (M^+,100%).

***N*-(3-Methylbenzylidene)-phenyl-(5-phenyl-isoxazol-3-yl)methanamine 3d.** (268 mg, 76%) mp 109–110 °C (from petroleum ether) (Found: C, 81.76; H, 5.76; N, 7.97. $C_{24}H_{20}N_2O$ requires C, 81.79; H, 5.72; N, 7.95%); ν_{max}(Nujol)/cm^{-1} 1643; δ_H(300 MHz; $CDCl_3$) 2.49 (3 H, s, CH_3), 5.93 (1 H, s, C*H*-N=C), 6.65 (1 H, s, C(4)H), 7.34–7.51 (8 H, m, Ph+Ar), 7.60–7.62 (2 H, m, Ph), 7.69–7.71 (1 H, m, Ar), 7.81–7.83 (3 H, m, Ph+Ar) and 8.58 (1 H, s, N=C*H*-Ar); δ_C(62.5 MHz; $CDCl_3$) 21.3, 69.5, 98.5, 125.8, 126.1, 127.2, 127.5, 127.6, 128.5, 128.6, 128.8 (overlapped signals), 130.0, 132.1, 135.8, 138.4, 141.0, 163.5, 166.5 and 170.0; *m*/*z*: 352 (M^+,100%).

***N*-(2-Methylbenzylidene)-phenyl-(5-phenyl-isoxazol-3-yl)methanamine 3e.** (282 mg, 80%) mp 95–96 °C (from petroleum ether) (Found: C, 81.77; H, 5.76; N, 7.96. $C_{24}H_{20}N_2O$ requires C, 81.79; H, 5.72; N, 7.95%); ν_{max}(Nujol)/cm^{-1} 1634 and 1600; δ_H(300 MHz; $CDCl_3$) 2.57 (3 H, s, CH_3), 5.86 (1 H, s, C*H*-N=C), 6.59 (1 H, s, C(4)H), 7.20–7.47 (9 H, m, Ph+Ar), 7.54–7.57 (2 H, m, Ph), 7.73–7.77 (2 H, m, Ar), 8.05 (1 H, dd, *J* 1.2 and 7.5, Ar) and 8.85 (1 H, s, N=C*H*-Ar); δ_C(62.5 MHz; $CDCl_3$) 19.6, 70.2, 98.4, 125.8, 126.1, 127.1, 127.6 (overlapped signals), 128.4, 128.7, 128.8, 130.0, 130.7, 131,0, 133.7, 138.2, 141.1, 162.1, 166.7 and 170.0; *m*/*z*: 352 (M^+,100%).

***N*-(4-Trifluoromethylbenzylidene)-phenyl-(5-phenyl-isoxazol-3-yl)methanamine 3f.** (276 mg, 68%) mp 75–76 °C (from petroleum ether) (Found: C, 70.95; H, 4.27; N, 6.93. $C_{24}H_{17}F_3N_2O$ requires C, 70.93; H, 4.22; N, 6.89%); ν_{max}(Nujol)/cm^{-1} 1643 and 1610; δ_H(300 MHz; $CDCl_3$) 5.92 (1 H, s, C*H*-N=C), 6.57 (1 H, s, C(4)H), 7.27–7.44 (6 H, m, Ph), 7.53–7.57 (2 H, m, Ph), 7.70 (2 H, d, *J* 8.2, Ar), 7.74–7.84 (2 H, m, Ph), 7.99 (2 H, d, *J* 8.2, Ar) and 8.58 (1 H, s, N=C*H*-Ar); δ_C(62.5 MHz; $CDCl_3$) 69.6, 98.4, 124.2 (q, *J* 207, CF_3), 125.6, 125.8, 127.4, 127.9, 128.8 (overlapped signals), 128.9, 130.2, 132.7 (q, *J* 32, *C*-CF_3), 138.8, 140.5, 161.8, 166.2 and 170.2; *m*/*z*: 406 (M^+,100%).

***N*-(4-Fluorobenzylidene)-phenyl-(5-phenyl-isoxazol-3-yl)methanamine 3g.** (249 mg, 70%) mp 152–153 °C (from petroleum ether) (Found: C, 75.52; H, 4.83; N, 7.90. $C_{23}H_{17}FN_2O$ requires C, 75.51; H, 4.81; N, 7.86%); ν_{max}(Nujol)/cm^{-1} 1643 and 1599; δ_H(300 MHz; $CDCl_3$) 5.85 (1 H, s, C*H*-N=C), 6.56 (1 H, s, C(4)H), 7.13 (2 H, t, *J* 8.7, Ar), 7.29–7.48 (6 H, m, Ph), 7.53–7.55 (2 H, m, Ph), 7.74–7.77 (2 H, m, Ph), 7.88 (2 H, dd, *J* 2.7 and 8.7, Ar) and 8.50 (1 H, s, N=C*H*-Ar); δ_C(62.5 MHz; $CDCl_3$) 69.4, 98.4, 115.7 (d, *J* 22), 125.8, 127.1, 127.5, 127.7, 128.7, 128.9, 130.1, 130.5 (d, *J* 9), 132.1, 140.9, 161.8, 164.6 (d, *J* 250, C–F), 166.4 and 170.0; *m*/*z*: 356 (M^+,100%).

***N*-(4-Chlorobenzylidene)-phenyl-(5-phenyl-isoxazol-3-yl)methanamine 3h.** (197 mg, 53%) mp 138–139 °C (from petroleum ether) (Found: C, 74.13; H, 4.65; N, 7.53. $C_{23}H_{17}ClN_2O$ requires C, 74.09; H, 4.60; N, 7.51%); ν_{max}(Nujol)/cm^{-1} 1645; δ_H(300 MHz; $CDCl_3$) 5.86 (1 H, s, C*H*-N=C), 6.54 (1 H, s, C(4)H), 7.29–7.24 (8 H, m, Ph+Ar), 7.51–7.54 (2 H, m, Ph), 7.72–7.75 (2 H, m, Ph), 7.80 (2 H, d, *J* 8.4, Ar) and 8.49 (1 H, s, N=C*H*-Ar); δ_C(62.5 MHz; $CDCl_3$) 69.4, 98.3, 125.7, 127.1, 127.3, 127.4, 127.6, 128.6, 128.8, 129.7, 130.0, 134.2, 137.2, 140.6, 161.8, 166.2 and 170.0; *m*/*z*: 374 [$(M+2)^+$, 32.2%], 372 (M^+,100).

***N*-(4-Bromobenzylidene)-phenyl-(5-phenyl-1,2,4-isoxazol-3-yl)-methanamine 3i.** (266 mg, 64%) mp 156–157 °C (from petroleum ether) (Found: C, 66.18; H, 4.14; N, 6.73. $C_{23}H_{17}BrN_2O$ requires C, 66.20; H, 4.11; N, 6.71%); ν_{max}(Nujol)/cm^{-1} 1645; δ_H(300 MHz; $CDCl_3$) 5.86 (1 H, s, C*H*-N=C), 6.54 (1 H, s, C(4)H), 7.29–7.45 (6 H, m, Ph), 7.51–7.59 (4 H, m, Ph+Ar), 7.73–7.76 (4 H, m, Ph+Ar) and 8.48 (1 H, s, N=C*H*-Ar); δ_C(62.5 MHz; $CDCl_3$) 69.4, 98.3, 125.7 (overlapped signals), 127.0, 127.3, 127.7, 128.6, 128.7, 129.9, 130.0, 131.8, 134.6, 140.6, 161.9, 166.2 and 170.0; *m*/*z*: 418 [$(M+2)^+$, 97.5%], 416 (M^+,100).

***N*-(4-Dimethylaminobenzylidene)-phenyl-(5-phenyl-isoxazol-3-yl)methanamine 3j.** (217 mg, 57%) mp 150–151 °C (from petroleum ether) (Found: C, 78.74; H, 6.10; N, 11.00. $C_{25}H_{23}N_3O$ requires C, 78.71; H, 6.08; N, 11.02%); ν_{max}(Nujol)/cm^{-1} 1645 and 1610; δ_H(300 MHz; $CDCl_3$) 3.03 (6 H, s, 2 × NCH_3), 5.79 (1 H, s, C*H*-N=C), 6.58 (1 H, s, C(4)H), 6.71 (2 H, d, *J* 8.7, Ar), 7.28–7.45 (6 H, m, Ph), 7.52–7.55 (2 H, m, Ph), 7.73–7.74 (4 H, m, Ph+Ar) and 8.39 (1 H, s, N=C*H*-Ar); δ_C(62.5 MHz; $CDCl_3$) 40.2, 69.2, 98.6, 111.5, 124.1, 125.8, 127.2, 127.3, 127.6, 128.5, 128.8, 129.9, 130.0, 141.6, 152.4, 162.9, 167.0 and 169.7; *m*/*z*: 381 (M^+,100%).

General procedure for *BK* rearrangement of imines 3: Synthesis of imidazoles 4

To a solution of imine **3** (1 mmol) in DMF (5 ml) was added *t*-BuOK (560 mg, 5 mmol). After 8 h of stirring at room temperature under nitrogen, the reaction mixture was diluted with water and extracted with diethyl ether (4 × 50 mL). The combined organic layers were dried over sodium sulfate and evaporated *in vacuo*. The crude product was chromatographed giving 2-aryl-4(5)-phenacyl-5(4)-phenyl-imidazoles **4a–j**.

4(5)-Phenacyl-2,5(4)-diphenyl-imidazole 4a. (287 mg, 85%) mp 79–80 °C (from petroleum ether) (Found: C, 81.66; H, 5.33; N, 8.30. $C_{23}H_{18}N_2O$ requires C, 81.63; H, 5.36; N, 8.28%); ν_{max}(Nujol)/cm^{-1} 1687; δ_H(300 MHz; $CDCl_3$) 4.58 (2 H, s, CH_2), 7.35–7.69 (11 H, m, Ph), 7.89–7.96 (2 H, m, Ph), 8.07–8.09 (2 H, m, Ph) and 10.69 (1 H, br s, NH, exch. with D_2O); δ_C(62.5 MHz; $CDCl_3$) 35.6, 124.8, 125.2, 126.9, 127.2, 127.3, 128.2, 128.5, 128.6, 128.7 overlapped signals, 130.0, 133.6, 136.3, 145.9, 152.4 and 197.4; *m*/*z*: 338 (M^+,28%), 233 (100).

2-(4-Methoxyphenyl)-4(5)-phenacyl-5(4)-phenyl-imidazole 4b. (331 mg, 90%) mp 127–128 °C from (petroleum ether) (Found: C, 78.27 H, 5.50; N, 7.58. $C_{24}H_{20}N_2O_2$ requires C, 78.24; H, 5.47; N, 7.60%); ν_{max}(Nujol)/cm^{-1} 1688; δ_H(300 MHz; $CDCl_3$) 3.74 (3 H, s, OCH_3), 4.38 (2 H, s, CH_2), 6.83 (2 H, d, *J* 8.4, Ar), 7.29–7.61 (8 H, m, Ph), 7.90 (2 H, d, J 8.4, Ar), 8.07–8.09 (2 H, m, Ph) and 10.24 (1 H, br s, NH, exch. with D_2O); δ_C(62.5 MHz; $CDCl_3$) 36.6, 55.7, 114.6, 114.9, 125.6, 125.7, 128.9–129.2 (overlapped signals), 130.2, 133.9, 136.7, 145.9, 159.3 and 197.9; *m*/*z*: 368 (M^+, 31%), 263 (100).

2-(4-Methylphenyl)-4(5)-phenacyl-5(4)-phenyl-imidazole 4c. (334 mg, 95%) mp 155–156 °C (from petroleum ether) (Found: C, 81.81; H, 5.69; N, 7.96. $C_{24}H_{20}N_2O$ requires C, 81.79; H, 5.72; N, 7.95%); ν_{max}(Nujol)/cm^{-1} 3315 and 1670; δ_H(300 MHz; $CDCl_3$) 2.43 (3 H, s, CH_3), 4.53 (2 H, s, CH_2), 7.24–7.68 (10 H, m, Ph+Ar), 7.89 (2 H, d, *J* 5.7, Ar), 8.06–8.08 (2 H, m, Ph) and 10.07 (1 H, br s, NH, exch. with D_2O); δ_C(62.5 MHz; $CDCl_3$) 21.2, 35.5, 124.7, 125.1, 126.9, 127.1, 128.2, 128.5, 128.6, 128.7 (overlapped signals), 129.4, 130.1, 133.5, 136.4, 136.9, 145.7 and 197.5; *m*/*z*: 352 (M^+, 28%), 247 (100).

2-(3-Methylphenyl)-4(5)-phenacyl-5(4)-phenyl-imidazole 4d. (345 mg, 98%) mp 129–130 °C (from petroleum ether) (Found: C, 81.78; H, 5.70; N, 7.93. $C_{24}H_{20}N_2O$ requires C, 81.79; H, 5.72; N, 7.95%); ν_{max}(Nujol)/cm^{-1} 1676; δ_H(300 MHz; $CDCl_3$) 2.37 (3 H, s, CH_3), 4.50 (3 H, s, CH_2), 7.13 (1 H, d, J 6.6, Ar), 7.29–7.49 (8 H, m, Ph+Ar), 7.57–7.62 (1 H, m, Ph), 7.84–7.87 (2 H, m, Ph), 8.00–8.03 (2 H, m, Ph) and 10.56 (1 H, br s, NH, exch. with D_2O); δ_C(62.5 MHz; $CDCl_3$) 21.4, 36.1, 124.2, 124.7, 125.1, 127.9, 128.4–128.7 (overlapped signals), 129.9, 133.5, 136.3, 138.3, 145.7 and 197.4; *m*/*z*: 352 (M^+, 27%), 247 (100).

2-(2-Methylphenyl)-4(5)-phenacyl-5(4)-phenyl-imidazole 4e. (341 mg, 97%) mp 165–166 °C (from petroleum ether) (Found: C, 81.83; H, 5.73; N, 7.94. $C_{24}H_{20}N_2O$ requires C, 81.79; H, 5.72; N, 7.95%); ν_{max}(Nujol)/cm^{-1} 1676; δ_H(300 MHz; $CDCl_3$) 2.31 (3 H, s, CH_3), 4.29 (2 H, s, CH_2), 7.26–7.60 (10 H, m, Ph+Ar), 7.88–7.93 (4 H, m, Ph) and 10.45 (1 H, br s, NH, exch. with D_2O); δ_C(62.5 MHz; $CDCl_3$) 20.1, 35.9, 124.6, 125.1, 125.7, 128.1, 128.3, 128.4 (overlapped signals), 128.5, 128.6, 128.7, 130.1, 130.4, 130.6, 133.3 (overlapped signals), 137.7, 145.7 and 197.3; *m*/*z*: 352 (M^+, 25%), 247 (100).

2-(4-Trifluoromethylphenyl)-4(5)-phenacyl-5(4)-phenyl-imidazole 4f. (386 mg, 95%) mp 181–182 °C (from petroleum ether) (Found: C, 70.95; H, 4.25; N, 6.92. $C_{24}H_{17}F_3N_2O$ requires C, 70.93; H, 4.22; N, 6.89%); ν_{max}(Nujol)/cm^{-1} 1683; δ_H(300 MHz; $CDCl_3$) 4.61 (2 H, s, CH_2), 7.37–7.55 (5 H, m, Ph+Ar), 7.62–8.04 (9 H, m, Ph+Ar) and 10.62 (1H, br s, NH, exch. with D_2O); δ_C(62.5 MHz; $CDCl_3$) 34.2, 121.1, 124.23 (q, *J* 271, CF_3), 124.9, 125.2, 125.5, 126.8, 127.4, 128.8 (overlapped signals), 129.7, 134.0, 136.0, 138.3, 146.5 and 196.9; *m*/*z*: 406 (M^+, 32%), 301 (100).

2-(4-Fluorophenyl)-4(5)-phenacyl-5(4)-phenyl-imidazole 4g. (303 mg, 85%) mp 139–140 °C (from petroleum ether) (Found: C, 77.54; H, 4.79; N, 7.90. $C_{23}H_{17}FN_2O$ requires C, 77.51; H, 4.81; N, 7.86%); ν_{max}(Nujol)/cm^{-1} 1676; δ_H(300 MHz; $CDCl_3$) 4.51 (2 H, s, CH_2), 7.13 (2 H, t, *J* 8.7, Ar), 7.32–7.64 (8 H, m, Ph+Ar), 7.86–7.89 (2 H, m, Ph), 8.00–8.03 (2 H, m, Ph) and 10.71 (1 H, br s, NH, exch. with D_2O); δ_C(62.5 MHz; $CDCl_3$) 35.2, 115.7 (d, *J* 21), 124.8, 125.1, 128.2, 128.4, 128.7, 128.8 (overlapped signals), 128.9, 129.1 (d, *J* 8), 129.9, 133.8, 145.8, 162.1 (d, *J* 245, C–F) and 197.6; *m*/*z*: 356 (M^+, 31%), 251 (100%).

2-(4-Chlorophenyl)-4(5)-phenacyl-5(4)-phenyl-imidazole 4h. (335 mg, 90%) mp 164–165 °C (from petroleum ether) (Found: C, 74.12; H, 4.63; N, 7.54. $C_{23}H_{17}ClN_2O$ requires C, 74.09; H, 4.60; N, 7.51%); ν_{max}(Nujol)/cm^{-1} 1676; δ_H(300 MHz; $CDCl_3$) 4.48 (2 H, s, CH_2), 7.36–7.61 (10 H, m, Ph+Ar), 7.80–7.84 (2 H, m, Ph), 7.98–8.00 (2 H, m, Ph) and 10.70 (1 H, br s, NH, exch. with D_2O); δ_C(62.5 MHz; $CDCl_3$) 35.5, 125.2 (overlapped signals), 128.4 (overlapped signals), 128.8 (overlapped signals), 129.8, 132.9, 133.8, 136.1, 146.1 and 197.3; *m*/*z*: 374 [$(M+2)^+$, 10%], 372 (M^+,32), 267 (100).

2-(4-Bromophenyl)-4(5)-phenacyl-5(4)-phenyl-imidazole 4i. (366 mg, 88%) mp 133–134 °C (from petroleum ether) (Found: C, 66.25; H, 4.13; N, 6.68. $C_{23}H_{17}BrN_2O$ requires C, 66.20; H, 4.11; N, 6.71%); ν_{max}(Nujol)/cm^{-1} 1680; δ_H(300 MHz; $CDCl_3$) 4.53 (2 H, s, CH_2), 7.30–7.65 (10 H, m, Ph+Ar), 7.78–8.02 (4 H, m, Ph) and 10.62 (1 H, br s, NH, exch. with D_2O); δ_C(62.5 MHz; $CDCl_3$) 36.3, 121.0, 124.8, 125.2, 128.2, 128.3, 128.4, 128.7, 128.8, 129.0, 129.8, 131.8, 132.2, 133.9, 136.1, 146.1 and 197.2; *m*/*z*: 418 [$(M+2)^+$, 23%], 416 (M^+,24), 313 (97), 311 (100).

2-(4-*N*,*N*-Dimethylaminophenyl)-4(5)-phenacyl-5(4)-phenyl-imidazole 4j. (305 mg, 80%) mp 102–103 °C (from petroleum ether) (Found: C, 78.75; H, 6.09; N, 11.06. $C_{25}H_{23}N_3O$ requires C, 78.71; H, 6.08; N, 11.02%); ν_{max}(Nujol)/cm^{-1} 1683 and 1608; δ_H(300 MHz; $CDCl_3$) 2.99 (6 H, s, $2 \times NCH_3$), 4.56 (2 H, s, CH_2), 6.86 (2 H, d, *J* 8.1, Ar), 7.31–7.57 (8 H, m, Ph+Ar), 7.84–7.87 (2 H, m, Ph), 8.04–8.07 (2 H, m, Ph) and 9.99 (1 H, br s, NH, exch. with D_2O); δ_C(62.5 MHz; $CDCl_3$) 36.2, 39.8, 111.3, 111.9, 118.8, 124.6, 125.8, 127.3, 127.6 (overlapped signals), 128.0, 130.0, 132.7, 135.1, 145.9, 149.3 and 196.8; *m*/*z*: 381 (M^+, 27%), 276 (100).

General procedure for rearrangement of imines 3 in the presence of oxygen

To a solution of imine **3a,b** (1 mmol) in DMF (5 ml) was added *t*-BuOK (560 mg, 5 mmol). After 6 h of stirring at room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate (4 × 50 mL). The combined organic layers were dried over sodium sulfate, evaporated *in vacuo* and the residue was chromatographed.

Reaction of compound 3a. Chromatography of the residue gave **11a** (183 mg, 52%) and **12a** (94 mg, 38%).

1-(2,5-Diphenyl-*1H*-imidazol-4-yl)-2-phenyl-ethane-1,2-dione 11a. mp 81–82 °C (from petroleum ether) (Found: C, 78.43 H, 4.60; N, 7.97. $C_{23}H_{16}N_2O_2$ requires C, 78.39; H, 4.58; N, 7.95%); ν_{max}(Nujol)/cm^{-1} 1681 and 1676; δ_H(300 MHz; $CDCl_3$) 7.61–7.68 (8 H, m, Ph), 7.77–7.82 (1 H, m, Ph), 7.96–8.07 (6 H, m, Ph) and 13.63 (1 H, br s, NH, exch. with D_2O); δ_C(62.5 MHz; $CDCl_3$) 126.1, 127.1, 127.9, 128.5, 129.0, 129.4 (overlapped signals), 129.7, 130.0, 133.1, 134.7, 140.5, 147.4, 190.6 and 195.4; ESI–MS(–) (*m*/*z*): 351 $[M - H]^-$; ESI-MS^2: 323$[M–H–CO]^-$, 246, 220, 218.

2,4(5)-Diphenyl-imidazole-5(4)-carbaldehyde 12a. mp 220–221 °C (from petroleum ether) (Found: C, 77.45, H, 4.90; N, 11.30. $C_{16}H_{12}N_2O$ requires C, 77.40; H, 4.87; N, 11.28%);

ν_{max}(Nujol)/cm^{-1} 3261, 1645 and 1624; δ_H(300 MHz; DMSO-d_6) 7.54–7.61 (6 H, m, Ph), 7.94–7.96 (2 H, m, Ph), 8.29–8.39 (2 H, m, Ph), 9.92 (1 H, s, CHO) and 13.70 (1 H, br s, NH, exch. with D_2O); δ_C(62.5 MHz; DMSO-d_6) 126.1, 126.9, 128.7, 128.8, 129.0, 129.4, 130.2, 130.9, 133.0, 150.1, 151.5 and 179.7; ESI–MS(+) (*m*/*z*): 249 $[MH]^+$; ESI-MS^2: 221$[MH\text{-}CO]^+$, 146, 118.

Reaction of compound 3b. Chromatography of the residue gave **11b** (118 mg, 31%) and **12b** (28 mg, 10%).

1-[2-(4-Methoxy-phenyl)-5-phenyl-*1H*-imidazol-4-yl]-2-phenyl-ethane-1,2-dione 11b. mp 156–157 °C (from ethanol) (Found: C, 75.40, H, 4.78; N, 7.37. $C_{24}H_{18}N_2O_3$ requires C, 75.38; H, 4.74; N, 7.33%); ν_{max}(Nujol)/cm^{-1} 3298, 1654 and 1649; δ_H(300 MHz; DMSO-d_6) 3.85 (3 H, s, OCH_3), 7.12 (2 H, d, *J* 8.4, Ar), 7.40–7.47 (3 H, m, Ph), 7.55–7.60 (2 H, m, Ph), 7.69–7.74 (1 H, m, Ph), 7.88–7.96 (4 H, m, Ph), 8.00 (2 H, d, *J* 8.4, Ar) and 13.42 (1 H, br s, NH, exch. with D_2O); δ_C(62.5 MHz; DMSO-d_6) 55.5, 113.9, 120.4, 126.1, 128.9, 129.4 (overlapped signals), 130.9, 132.8, 133.2, 134.6, 140.8, 147.1, 160.6, 190.4 and 195.5; ESI–MS(+) (*m*/*z*): 383 $[MH]^+$; ESI-MS^2: 355$[MH\text{-}CO]^+$.

2-(4-Methoxy-phenyl)-4(5)-phenyl-imidazole-5(4)carbaldehyde 12b. mp 219–220 °C (from petroleum ether) (Found: C, 77.40, H, 5.10; N, 10.3. $C_{17}H_{14}N_2O_2$ requires C, 73.37; H, 5.07; N, 10.07%); ν_{max}(Nujol)/cm^{-1} 3257 and 1634; δ_H(300 MHz; DMSO-d_6) 3.88 (3 H, s, OCH_3), 7.12 (2 H, d, *J* 8.5, Ar), 7.54–7.60 (3 H, m, Ph), 7.89 (2 H, d, *J* 8.5, Ar), 8.25 (2 H, m, Ph), 9.87 (1 H, s, CHO) and 13.60 (1 H, br s, NH, exch. with D_2O); δ_C(62.5 MHz; DMSO-d_6) 55.4, 114.3, 125.3, 126.8, 128.5, 128.8, 129.0 (overlapped signals) 130.2, 131.8, 150.0, 160.1 and 179.6; ESI–MS(+) (*m*/*z*): 279 $[MH]^+$; ESI-MS^2: 264$[MH\text{-}CH_3]^{+\bullet}$, 251, 236, 176.

General procedure for base-induced oxidation of imidazoles 4

To a solution of imidazole **4a,b** (1 mmol) in DMF (5 ml) was added *t*-BuOK (560 mg, 5 mmol). After 6 h of stirring at room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate (4 × 50 mL). The combined organic layers were dried over sodium sulfate, evaporated *in vacuo* and the residue was chromatographed.

Reaction of compound 4a. Chromatography of the residue gave **11a** (215 mg, 61%) and **12a** (35 mg, 14%).

Reaction of compound 4b. Chromatography of the residue gave **11b** (256 mg, 67%) and **12b** (14 mg, 5%).

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