A CONVENIENT APPROACH TO THE SYNTHESIS OF THE IMIDAZO[5,1-*b*]OXAZOLE RING SYSTEM

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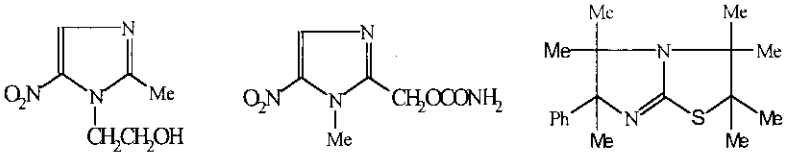
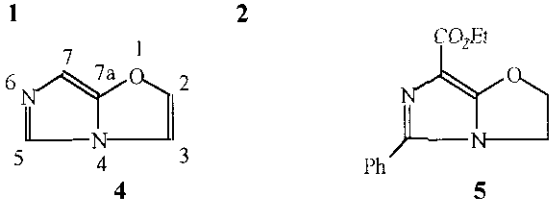
Abstract - Reaction of 4(5)-bromo-2-methyl-5(4)-nitroimidazole with phenacyl bromide derivatives led to 4-bromo-2-methyl-1-phenacyl-5-nitro- and 5-bromo-2-methyl-1-phenacyl-4-nitroimidazoles. Treatment of the latter isomers with potassium *tert*-butoxide in dry THF yielded imidazo[5,1-*b*]oxazoles.

In general nitroimidazoles have found useful applications as therapeutic agents.[1] Metronidazole **(1)** has been used extensively in the treatment of trichomonal and protozoal infections.[2] Other studies have shown that metronidazole **(1)** as well as other nitroimidazoles, like ronidazole **(2)** can radiosensitize hypoxic tumour cells.[3] Tetramizole **(3)**, a fused 5-membered ring heterocycle derived from imidazole, has found clinical application as a potent broad spectrum anthelmintic agent in domestic animals.[4] Thus, interest in the synthesis of other nitro- fused imidazoles continues due to its potential use as radiosensitizers or antiprotozoal agents.[5,6]

The chemistry of derivatives in the imidazo[5,1-*b*]oxazole ring system **(4)** has been little explored. Although there is an isolated example of the 2,3-dihydroimidazo[5,1-*b*]oxazole derivative **(5)**, prepared through a Cornforth rearrangement.[7] Herein we describe a convenient approach to the synthesis of the fully unsaturated imidazo[5,1-*b*]oxazole nucleus **(4)**.

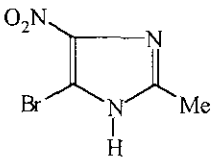


1 **2** **3**



4 **5**

4(5)-Bromo-2-methyl-5(4)-nitro-imidazole **(6)** (prepared by bromination with NBS in DMF of **9**) has shown to be a useful reagent for the building of condensed imidazole derivatives, such as tetrahydroimidazo[1,5-*c*]-1,2,4-triazines **(7)**,[8,9] and derivatives of imidazo[1,5-*a*]imidazole **(8)**.[10] Thus, it was reasoned that bromonitroimidazole **(6)** could also be used in the construction of the desired imidazo[5,1-*b*]oxazole ring system.



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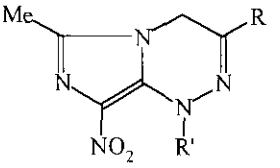
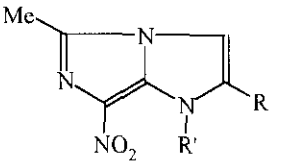


7

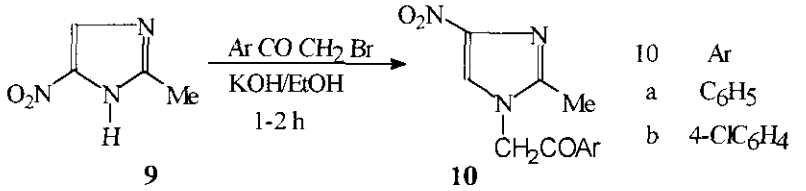
R= Alk, Ar.
R'= H, Alk, Ar.



8

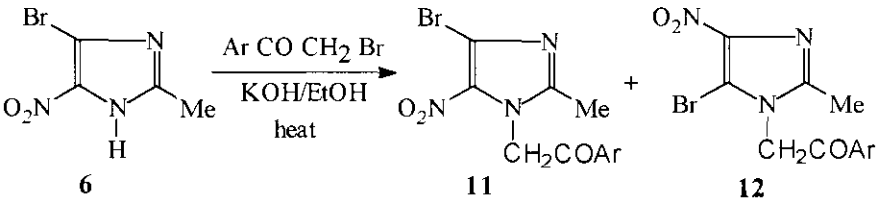
R= Me, Ph.
R'= H, Alk, Ph.

Indeed reaction of 2-methyl-5(4)-nitroimidazole **(9)** with phenacyl bromides in basic medium (KOH/EtOH) produced only one isomer **(10a-b)** according to previous observations.[8] In this process, reaction time was important and more than 2 h caused lower yields of phenacylnitroimidazoles with starting nitroimidazole **(9)** being recovered. However reaction of bromo derivative **(6)** with phenacyl bromides gave the mixture of isomers **(11)** and **(12)** in a 1:3 ratio, determined by both HPLC and ^{1}H-NMR spectroscopy analyses. Structure of compounds **(11)** and **(12)** was further confirmed by X-Ray analysis. Interestingly reaction time had no effect in this latter process and in some cases more than 5 h were needed to take the reaction to completion. Compounds **(11a-f)** were separated from **12a-f** by column chromatography in the yields shown in Table 1 and fully characterized through spectroscopic measurements. Compound **(12a)** was also prepared by bromination of **10a** with Br_2 in aqueous DMF.[9,11]



9 **10**

10	Ar
a	C_6H_5
b	4-ClC_6H_4



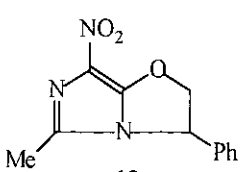
6 **11** **12**

Ar = **a)** C_6H_5, **b)** 4-ClC_6H_4, **c)** 4-$MeOC_6H_4$, **d)** 4-MeC_6H_4, **e)** 4-FC_6H_4, **f)** 3-$CF_3C_6H_4$

Table 1. 4-Bromo-1-phenacyl-2-methyl-5-nitro- and 5-Bromo-1-phenacyl-2-methyl-4-nitroimidazoles (11) and (12).

Entry	Aryl	mp (°C)	Lit. mp (°C)	Yield (%)
11 a	C_6H_5	182 - 183	---	19.5
11 b	4-ClC_6H_4	179 - 181	---	22.85
11 c	4-$MeOC_6H_4$	114 - 116	---	18.25
11 d	4-MeC_6H_4	147 - 148	---	19.02
11 e	4-FC_6H_4	163 - 165	---	22.08
11 f	3-$CF_3C_6H_4$	142 - 143	---	17.54
12 a	C_6H_5	189 - 190	190 - 191[8]	58.50
12 b	4-ClC_6H_4	210 - 212	203 - 204[8]	68.55
12 c	4-$MeOC_6H_4$	187 - 189	---	54.75
12 d	4-MeC_6H_4	217 - 218	219 - 221[8]	57.71
12 e	4-FC_6H_4	232 - 233	---	66.25
12 f	3-$CF_3C_6H_4$	146 - 148	---	52.63

In an attempt to prepare the 2,3-dihydroimidazo[5,1-*b*]oxazole **(13)**, compound **(12a)** was treated with sodium borohydride in different media (alkaline, acidic, neutral), but in all cases product **(14)** was isolated, thus showing the great susceptibility of bromo to nucleophilic displacement. Compound **(14)** was also obtained by sodium borohydride reduction of **10a** and this experiment in fact was an indirect method to confirm the structure of **10a**. The experiment also suggested that a nucleophilic base should be avoided in the further cyclization process. Thus, treatment of products **(12a-f)** with *t*BuOK in dry THF yielded the bicyclic imidazo[5, 1-*b*]oxazoles **(15a-f)** in the yields shown in Table 2. The bicyclic compound **(15a-f)** were characterized by spectroscopic analysis. Thus in the ^{1}H-NMR spectra of products **(15a-f)**, the H-3 proton appeared as a singlet, downfield in the range 8.8-9.1 ppm.



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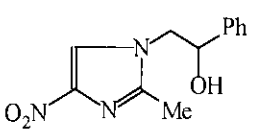

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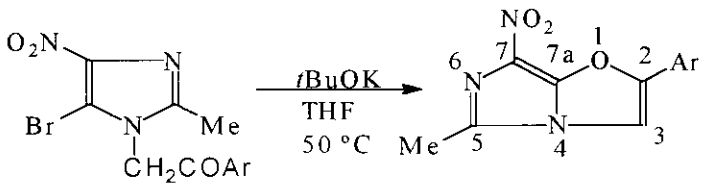

12 a-f **15 a-f**

Table 2. 2-Aryl-5-methyl-7-nitroimidazo[5,1-*b*]oxazole (15a-f)

Entry	Aryl	mp (°C)	Yield (%)
15 a	C_6H_5	238 - 240	60.33
15 b	4-ClC_6H_4	250 - 251	65.70
15 c	4-$MeOC_6H_4$	143 - 145	60.13
15 d	4-MeC_6H_4	269 - 271	50.24
15 e	4-FC_6H_4	233 - 235	50.07
15 f	3-$CF_3C_6H_4$	236 - 238	48.65

In conclusion the greater acidity of the methylene hydrogens in compounds **(12a-f)** and the bromo susceptibility to nucleophilic displacement allowed reaction of them with *t*BuOK and ultimately permitted the formation of imidazo[5, 1-*b*]oxazole derivatives through a nucleophilic intramolecular sustitution. The competitive base reaction with the hydrogens of the nitroimidazole methyl substituent was expected but not observed.

EXPERIMENTAL

All reactions were carried out under nitrogen. Melting point were measured on an electrothermal melting point apparatus and are uncorrected. IR spectral data were obtained from a Perkin Elmer FT 1600 infrared spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectral data were obtained using a Bruker DPX 300 MHz NMR spectrometer. Chemical shifts are given in ppm downfield from TMS ($\delta_H = 0$). MS were obtained with a JOEL JMSAX505HA instrument. Column chromatography was carried out with silica gel (Merck 60, 70-230 mesh) as the adsorbent.

2-Methyl-5-nitroimidazole and 2-bromo-4-chloroacetophenone were purchased from Aldrich Chem. Co. Other 2-bromo-substituted acetophenones were prepared following literature procedures.

4(5)-Bromo-2-methyl-5(4)-nitroimidazole (6). To a srirring warm solution (55 °C) of 2-methyl-5-nitro-imidazole (15 g, 180.02 mmol) in anhydrous DMF (60 mL), NBS (42.01 g, 236.02 mmol) was slowly added (1 h). After addition was completed, temperature was increased to 80 °C and stirring was continued for 4 h.

The reaction mixture was allowed to cool to 5 °C and poured onto crushed ice. The formed precipitate was filtered, washed with cold water, dried and further recrystallized from EtOH to yield the title compound as white needles, (17.92 g, 74%), mp 268-270 °C (lit.,[12] 270-271 °C). IR (ν max) 1526, 1358 cm^{-1}.^{1}H-NMR (DMSO-d_6) δ 2.33 (3H, Me). MS m/z; 206 (M^+), 205 (M^+-1, 100%).

4-Bromo-1-phenacyl-2-methyl-5-nitroimidazole (11a) and 5-bromo-1-phenacyl-2-methyl-4-nitroimidazole (12a). To a stirring suspension of 4(5)-bromo-2-methyl-5(4)-nitroimidazole (2 g, 9.71 mmol), KOH (0.54 g, 9.64 mmol) in absolute EtOH (60 mL), phenacyl bromide (2.14 g, 10.21 mmol) was slowly added. The reaction mixture was gently refluxed for 2 h, cooled, and poured onto 188 g of crushed ice. The precipitate was filtered, washed with 50 mL of water and dried *in vacuo* overnight. The crude mixture was purified by column chromatography (silica gel, 1:1 hexane-ethyl acetate) to afford 0.61 g (19.5 %) of compound **(11a)** as yellow crystals, mp 182-183 °C (from ethanol). IR (ν max) 1704, 1518, 1336 cm^{-1}.^{1}H-NMR (DMSO-d_6): δ 8.10 (dd, J= 8.0 Hz, J= 2.4 Hz, 2H, H-2'), 7.90 (dd, J= 8.0 Hz, J= 2.4 Hz, 1H, H-4'), 7.78 (dd, J = 8.0 Hz, J= 2.4 Hz, 2H, H-3'), 6.06 (s, 2H, CH_2), 2.47 (s, 3H, Me); ^{13}C-NMR (DMSO-d_6) δ 192.69 (C=O), 151.97, 136.07, 135.38, 134.65, 130.0, 129.69, 120.69, 54.69 (CH_2), 14.62 (Me). Anal. Calcd for $C_{12}H_{10}N_3O_3Br$: C, 44.44; H, 3.08; N, 12.96. Found: C, 44.15; H, 3.21; N, 13.01. The more polar fraction afforded 1.8 g of **12a** (58.5%) as yellow crystals (from ethanol), mp 189-190 °C (lit.,[8]190-191 °C) . IR (ν max) 1700, 1524, 1338 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 8.18 (dd, J = 7.85 Hz, J = 2.35 Hz, 2H, H-2'), 7.82 (dd, J = 7.85 Hz, J = 2.35 Hz, 1H, H-4'), 7.69 (dd, J = 7.85 Hz, J = 2.35 Hz, 2H, H-3'), 5.95 (s, 2H, CH_2), 2.42 (s, 3H, Me); ^{13}C-NMR (DMSO-d_6) δ 191.84 (C=O), 147.96, 144.06, 135.36, 134.44, 129.92, 129.20, 108.08, 53.63 (CH_2), 14.72 (Me).

X-Ray crystal data of 11a. $C_{12}H_{10}N_3O_3Br$: crystal dimension 0.28 X 0.58 X 0.60 monoclinic, space group $P2_1/n$, a= 7.9857 (6) Å, b= 13.0121 (13) Å, c= 12.3563 (7) Å, α= 90 °, β= 97.871 (5) °, γ= 90°, V= 1271.9 (2) $Å^3$, Z=4, D_{calcd}= 1.693 mgm^{-3}, R=0.0559, R_w=0.1385.The data were collected on a Siemens P4 diffractometer with graphite monochromated Mo-K α radiation (λ= 0.71073Å).

X-Ray crystal data of 12a. $C_{12}H_{10}N_3O_3Br$: crystal dimension 0.25 X 0.52 X 0.56 monoclinic, space group $P2_1/c$, a= 7.7618 (8) Å, b= 22.635 (2) Å, c= 8.1014 (8) Å, α= 90 °, β= 115.018 (6) °, γ= 90°, V= 1289.8 (2) $Å^3$, Z=4, D_{calcd}= 1.669 mgm^{-3}, R=0.0553, R_w=0.1311.The data were collected on a Siemens P4 diffractometer with graphite monochromated Mo-K α radiation (λ= 0.71073Å).

4-Bromo-1-(4'-chlorophenacyl)-2-methyl--5-nitroimidazole (11b) and 5-bromo-1-(4'-chlorophenacyl)-2-methyl-4-nitroimadazole (12b). 4(5)-Bromo-2-methyl-5(4)-nitroimidazole (2 g, 9.71 mmol) reacted with

2-bromo-4'-chloroacetophenone (2.4 g, 10.28 mmol) following the procedure described above to afford 0.76 g (22.85%) of compound **(11b)** as yellow needles, mp 179-181 °C (from ethanol). IR (ν max) 1704, 1518, 1336 cm^{-1}.^{1}H-NMR (DMSO-d_6) δ 8.10 (d, J= 7.9 Hz, 2H, H-2') 7.75 (d, J= 8.7 Hz, 2H, H-3'), 6.49 (s, 2H, CH_2), 2.40 (s, 3H, Me). ^{13}C-NMR (DMSO-d_6) δ 190.82 (C=O), 151.08, 139.76, 135.52, 133.59, 130.44, 129.22, 119.72, 53.61 (CH_2), 13.87 (Me). Anal. Calcd for $C_{12}H_9N_3O_3BrCl$: C, 40.16; H, 2.51; N, 11.71. Found: C, 40.25; H, 2.70; N, 11.80. The more polar fraction afforded 2.02 g (68.55%) of compound **(12b)** as pale yellow crystals (from ethanol), mp 210-212 °C (lit.,[8] 203-204 °C). IR (ν max) 1696, 1524, 1332 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 8.15 (d, J= 8.65, 2H, H-2'), 7.73 (d, J= 8.65 Hz, 2H, H-3'), 5.90 (s, 2H, CH_2), 2.37 (s, 3H, Me). ^{13}C-NMR (DMSO-d_6) δ 190.67 (C=O), 146.53, 143.07, 139.63, 132.35, 130.36, 129.17, 107.79, 52.48 (CH_2), 13.48 (Me).

4-Bromo-1-(4'-methoxyphenacyl)-2-methyl-5-nitroimidazole (11c) and 5-bromo-1-(4'-methoxyphenacyl)-2-methyl-4-nitroimadazole (12c). 4(5)-Bromo-2-methyl- 5(4)-nitroimidazole (2.5 g, 12.14 mmol) reacted with 2-bromo-4'-methoxyacetophenone (2.9 g, 12.71 mmol) following the procedure described above to afford 0.775 g (18.25%) of compound **(11c)** as a light yellow solid, mp 114-116 °C (from isopropanol) IR (ν max) 1688, 1523, 1333 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 7.97 (dd, J= 7.65 Hz, J= 2.1 Hz, 2H, H-2'), 7.07 (dd, J= 7.65 Hz, J= 2.1 Hz, 2H, H-3'), 5.91 (s, 2H, CH_2), 3.83 (s, 3H, -OMe) 2.39 (s, 3H, Me), ^{13}C-NMR (DMSO-d_6) δ 190.38 (C=O), 164.5, 151.02, 135.47, 131.05, 127.24, 119.86, 114.67, 56.12 (-OMe), 53.63 (CH_2), 13.87 (Me). Anal. Calcd for $C_{13}H_{12}N_3O_4Br$: C, 44.06; H, 3.39; N, 11.86. Found: C, 44.0; H, 3.35; N, 11.90. The more polar fraction afforded 2.33 g (54.75%) of compound **(12c)** as amorphous crystals, mp 187-189 °C (from isopropanol). IR (ν max) 1689, 1524, 1335 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 8.11 (dd, J= 6.95 Hz, J= 1.9 Hz, 2H, H-2'), 7.15 (dd, J= 6.95 Hz, J= 1.9 Hz, 2H, H-3'), 5.83 (s, 2H, CH_2), 3.89 (s, 3H, -OMe), 2.35 (s, 3H, Me). ^{13}C-NMR (DMSO-d_6) δ 190.81 (C=O), 164.25, 146.53, 143.15, 130.89, 126.55, 114.27, 107.86, 55.76 (-OMe), 52.12 (CH_2), 13.49 (Me). Anal. Calcd for $C_{13}H_{12}N_3O_4Br$: C, 44.06; H, 3.39; N, 11.86. Found: C, 43.96; H, 3.40; N, 11.80.

4-Bromo-1-(4'-methylphenacyl)-2-methyl- 5-nitroimidazole (11d) and 5-bromo- 1-(4'-methylphenacyl)-2-methyl-4-nitroimadazole (12d). 4(5)-Bromo-2-methyl-5(4)-nitroimidazole (2.5 g, 12.14 mmol) reacted with 2-bromo-4'-methylacetophenone (2.58 g, 12.12 mmol) following the procedure described above to afford 0.78 g (19.02%) of compound **(11d)** as yellow needles, mp 147-148 °C (from ethanol). IR (ν max) 1696, 1523, 1337 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 7.97 (dd, J = 8.4 Hz, J= 3.1 Hz, 2H, H-2'), 7.96 (dd, J= 8.4 Hz, J= 3.1 Hz, 2H, H-3'), 5.98 (s, 2H, CH_2), 2.43 (s, 6H, Ar-Me, Me). ^{13}C-NMR (DMSO-d_6) δ 191.33 (C=O), 150.64, 145.08, 135.02, 131.38, 129.52, 128.35, 119.63, 53.47 (CH_2), 21.27 (Ar-Me), 13.46 (Me). Anal. Calcd for $C_{13}H_{12}N_3O_3Br$: C, 46.15; H, 3.55; N, 12.42. Found: C, 46.05; H, 3.65; N, 12.51. The more polar

fraction afforded 2.34 g (57.71%) of compound **(12d)** as white needles, mp 217-218 °C (lit.,[8] 219-221 °C). IR (ν max) 1687, 1522, 1325 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 8.03 (d, J= 8.15 Hz, 2H, H-2'), 7.44 (d, J= 8.15 Hz, 2H, H-3'), 5.86 (s, 2H, CH_2), 2.43 (s, 3H, Ar-Me), 2.36 (s, 3H, Me). ^{13}C-NMR (DMSO-d_6) δ 190.89 (C=O), 146.5, 145.39, 143.17, 131.20, 129.54, 128.52, 107.81, 52.34 (CH_2), 21.29 (Ar-Me), 13.46 (Me).

4-Bromo-1-(4'-fluorophenacyl)-2-methyl-5-nitroimidazole (11e) and 5-bromo-1-(4'-fluorophenacyl)-2-methyl-4 -nitroimadazole (12e). 4(5)-Bromo-2-methyl- 5(4)-nitroimidazole (1.15 g, 5.58 mmol) reacted with 2-bromo-4'-fluoroacetophenone (1.33 g, 6.14 mmol) following the procedure described above to afford 0.42 g (22.08%) of compound **(11e)** as a brown solid, mp 163-165 °C (from ethanol). IR (ν max) 1695, 1528, 1334 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 8.17 (dd, J = 8.9 Hz, J = 5.5 Hz, 2H, H-2'), 7.47 (d, J = 8.9 Hz, 2H, H-3'), 6.01 (s, 2H, CH_2), 2.43 (s, 3H. Me). ^{13}C-NMR (DMSO-d_6) δ 191.49 (C=O), 166.45, 151.57, 132.31, 131.56, 131.52, 120.62, 117.04, 54.41 (CH_2), 14.36 (Me). Anal. Calcd for $C_{12}H_9N_3O_3BrF$: C, 42.10; H, 2.63; N, 12.28. Found: C, 41.90; H, 2.60; N, 12.40. The more polar fraction afforded 1.26 g (66.25%) of compound **(12e)** as a pale yellow solid, mp 232-233 °C (from ethanol). IR (ν max) 1698, 1524, 1357 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 8.23 (dd, J = 8.95 Hz, J = 5.5 Hz, 2H, H-2'), 7.49 (dd, J = 8.85 Hz, J = 5.4 Hz, 2H, H-3'), 5.90 (s, 2H, CH_2), 2.37 (s, 3H, Me); ^{13}C-NMR (DMSO-d_6) δ 190.12 (C=O), 167.49, 146.49, 146.14, 131.60, 130.45, 116.14, 107.66, 52.40 (CH_2), 13.47 (Me). Anal. Calcd for $C_{12}H_9N_3O_3BrF$: C, 42.10; H, 2.63; N, 12.28. Found: C, 41.82; H, 2.73; N, 12.37.

4-Bromo-1-(3'-trifluoromethylphenacyl)-2-methyl-5-nitroimidazole (11f) and 5-bromo-1-(4'-trifluoromethylphenacyl)-2-methyl- 4-nitroimadazole (12f). 4(5)-Bromo-2-methyl-5(4)-nitroimidazole (1.8 g, 8.74 mmol) reacted with 2-bromo-3'-trifluoromethylacetophenone (2.56 g, 9.6 mmol) following the procedure described above to afford 0.6 g (17.54%) of compound **(11f)** as a brown solid, mp 142-143 °C (from isopropanol). IR (ν max) 1709, 1530, 1328 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 8.37 (s, 1H, H-2'), 8.36 (d, J = 6.7 Hz, 1H, H-6'), 8.15 (d, J = 7.9 Hz, 1H, H-4'), 7.89 (dd, J = 8.15 Hz, J = 5.0 Hz, 1H, H-5'), 6.11 (s, 2H, CH_2), 2.45 (s, 3H, Me). ^{13}C-NMR (DMSO-d_6) δ 191.29 (C=O), 150.76, 147.50, 134.65, 132.19, 130.70, 130.44, 129.51, 124.76, 119.84, 117.21, 53.76 (CH_2), 13.48 (Me). Anal. Calcd for $C_{13}H_9N_3O_3BrF_3$: C, 39.79; H, 2.29; N, 10.71. Found: C, 39.4; H, 2.35; N, 10.8. The more polar fraction afforded 1.8 g (52.63%) of compound **(12f)** as a light brown solid, mp 146-148°C (from isopropanol). IR (ν max) 1709, 1529, 1328 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 8.46 (s, 1H, H-2'), 8.41 (d, J= 7.8 Hz, 1H, H-6'), 8.16 (d, J= 7.8 Hz, 1H, H-4'), 7.89 (dd, J= 7.8 Hz, J= 5.0 Hz, 1H, H-5'), 6.04 (s, 2H,CH_2), 2.38 (s, 3H, Me); ^{13}C-NMR (DMSO-d_6) δ 190.87 (C=O), 146.54, 143.27, 134.37, 132.30, 130.89, 130.36, 129.85, 125.51, 125.11, 107.79, 52.71 (CH_2), 13.47 (Me). Anal. Calcd for $C_{13}H_9N_3O_3BrF_3$: C, 39.79; H, 2.29; N, 10.71. Found: C, 39.85; H, 2.32; N, 10.84.

2-Phenyl-5-methyl-7-nitroimidazo[5,1-*b*]oxazole (15a). 5-Bromo-1-phenacyl-2-methyl-4-nitroimidazole (0.3 g, 0.93 mmol) and potassium *tert*-butoxide (0.16 g, 1.4 mmol) were stirred in dry THF (10 mL) at 50 °C, until starting material was consumed as monitored by TLC. Reaction mixture was cooled, 5% NH_4Cl solution (5 mL) was added and THF exchanged for ethyl acetate. The organic phase was washed with water (10 mL), dried (anh. Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel, 1:1 hexane-ethyl acetate). The title compound was isolated (0.137 g , 60.33%) as a yellow solid, mp 238-240 °C (from ethanol). IR (ν max) 1592, 1398, 1134 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 8.95 (s, 1H, H-3), 7.86 (d, J= 9.6 Hz, 2H, H-2'), 7.70 (d, J = 9.6 Hz, 2H, H-3'), 7.52 (d, J = 9.6 Hz, 1H, H-4'), 2.50 (s, 3H, Me). ^{13}C-NMR (DMSO-d_6) δ 154.06, 134.61, 129.4, 129.4, 128.24, 125.95, 124.88, 124.19, 109.0 (C-3), 12.49 (Me). MS m/z; 243 (M^+), 171 (M^+ -72, 100%). Anal. Calcd for $C_{12}H_9N_3O_3$: C, 59.02; H, 4.13; N, 17.20. Found: C, 59.04; H, 4.14; N, 17.21.

2-(4'-Chlorophenyl)-5-methyl-7-nitroimidazo[5,1-*b*]oxazole (15b). Obtained in 65.71% as a light brown solid, mp 250-251 °C (from ethanol) following the procedure described above. IR (ν max) 1490, 1358, 1260 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 8.74 (s, 1H, H-3), 7.78 (dd, J = 8.3 Hz, J = 4.45 Hz, 2H, H-2'), 7.63 (dd, J = 8.3 Hz, J = 4.45 Hz, 2H, H-3'), 2.47 (s, 3H, Me); ^{13}C-NMR (DMSO-d_6) δ 153.61, 145.74, 135.29, 130.0, 128.97, 126.32, 125.48, 120.71, 107.8 (C-3), 13.35 (Me). MS m/z; 277 (M^+), 205 (M^+-72, 100%). Anal. Calcd for $C_{12}H_8N_3O_3Cl$: C, 51.91; H, 2.90; N, 15.13; Cl, 12.77. Found: C, 51.94; H, 2.91; N, 15.13; Cl, 12.74.

2-(4'-Methoxyphenyl)-5-methyl-7-nitroimidazo[5,1-*b*]oxazole (15c). Obtained in 60.13% as a light brown solid, mp 143-145°C (from isopropanol) following the procedure described above. IR (ν max) 1510, 1358, 1246 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 8.69 (s, 1H, H-3), 7.74 (dd, J = 8.65 Hz, J = 2.2 Hz, 2H, H-2'), 7.14 (dd, J= 8.65 Hz, J = 2.2 Hz, 2H, H-3'), 3.85 (s, 3H, -OMe), 2.48 (s, 3H, Me), ^{13}C-NMR (DMSO-d_6) δ 160.58, 154.06, 145.17, 128.08, 125.99, 120.59, 118.53, 114.76, 113.35 (C-3), 55.35 (-OMe), 12.88 (Me). MS m/z; 273 (M^+), 201 (M^+-72, 100%) Anal. Calcd for $C_{13}H_{11}N_3O_4$: C, 57.14; H, 4.06; N, 15.38. Found: C, 57.16; H, 4.09; N, 15.35.

2-(4'-Tolyl)-5-methyl-7-nitroimidazo[5,1-*b*]oxazole (15d). Obtained in 50.24% as a brown solid, mp 269-271 °C (from ethanol) following the procedure described above. IR (ν max) 1591, 1357, 1261 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 8.77 (s, 1H, H-3), 7.68 (dd, J = 7.75 Hz, J = 1.65, 2H, H-2'), 7.36 (dd, J = 7.75 Hz, J = 1.65, 2H, H-3'), 2.46 (Ar-Me), 2.36 (s, 3H, Me); ^{13}C-NMR (DMSO-d_6) δ 154.08, 146.22, 140.15, 129.23, 128.28, 124.26 , 123.29, 122.87, 105.50 (C-3), 20. 87 (Ar-Me), 12.05 (Me). MS m/z; 257 (M^+), 185 (M^+-72, 100%). Anal. Calcd for $C_{13}H_{11}N_3O_3$: C, 60.69; H, 4.30; N, 16.36. Found: C, 60.64; H, 4.32; N, 16.35.

2-(4'-Fluorophenyl)-5-methyl-7-nitroimidazo[5,1-*b*]oxazole (15e). Obtained in 50.07% as a light yellow solid, mp 233-235 °C (from ethanol) following the procedure described above. IR (ν max) 1525, 1358, 1200 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 8.82 (s,1H, H-3), 7.86 (dd, J= 8.9 Hz, J= 5.0 Hz, 2H, H-2'), 7.44 (dd, J= 8.95 Hz, J= 7.0 Hz, 2H, H-3') 2.46 (s, 3H, Me); ^{13}C-NMR (DMSO-d_6) δ 163.83, 152.24, 145.54, 133.15, 130.81, 124.80, 123.40, 115.79, 106.82 (C-3), 13.47 (Me). MS m/z; 261 (M^+), 189 (M^+-72, 100%). Anal. Calcd for $C_{12}H_8N_3O_3F$: C, 55.18; H, 3.09; N, 16.09; F, 7.27. Found: C, 55.16; H, 3.12; N, 16.11; F, 7.25.

2-(3'-Trifluorophenyl)-5-methyl-7-nitroimidazo[5,1-*b*]oxazole (15f). Obtained in 48.65% as a light brown solid, mp 236-238 °C (isopropanol) following the procedure described above. IR (ν max) 1574, 1358, 1256 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 9.11 (s, 1H, H-3), 8.14 (s, 1H, H-2'), 8.11 (d, J = 7.8 Hz, 1H, H-6'), 7.90-7.65 (m, 2H, H-4', H-5'), 2.48 (s, 3H, Me). ^{13}C-NMR(DMSO-d_6) δ 152.47, 145.22, 138.10, 130.74, 129.92, 128.53, 128.30, 127.86, 127.27, 122.01, 121.50, 107.90 (C-3), 12.84 (Me). MS m/z; 311 (M^+), 239 (M^+-72, 100%). Anal. Calcd for $C_{13}H_8N_3O_3F_3$: C, 50.17; H, 2.59; N, 13.50; F, 18.31. Found: C, 50.12; H, 2.61; N, 13.46; F, 18.34.

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