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ORIGINAL ARTICLE

Flash-Vacuum-Pyrolysis (F.V.P) of 4-acetyl-3-(4-substitute-dphenylamino)-2-(benzoxazol-2-yl)-isoxazol-5(2H)-ones

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ABSTRACT
*Flash-vacuum-pyrolysis (F.V.P) of the 4-acetyl-3-(4-substitutedphenylamino)-2-(benzoxazol-2-yl)-isoxazol-5-(2H)-ones (**4**) at 900°C and 0.4 mm Hg has been investigated and net product, 1-(2-(4-substitutedphenylamino)-imidazo-[2,1-b]-benzoxazol-3-yl)-ethanone in high to excellent yields (80-85%).*
Key Words: *Isoxazolones; 2-chlorobenzo[d]oxazole; Imidazobenzoxazol; Flash-Vacuum-Pyrolysis (F.V.P).*

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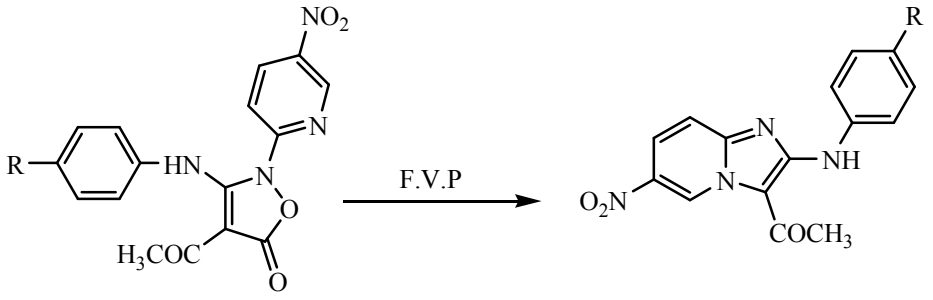
INTRODUCTION

Flash-vacuum-pyrolysis (F.V.P) or flash-vacuum-thermolysis (F.V.T) is a process by which a substrate is distilled through a hot tube and the products are collected afterwards in a cold trap. The thermal behaviour of a large variety of heterocyclic compounds has been investigated in connection with mechanistic and/or synthetic studies[1-3].

Though flash-vacuum-pyrolyses (F.V.P) of a few substituted and annulated isoxazoles [4-6] as well as of different isoxazolones [7-9] were investigated (revealing the preferential fission of the N-O bond, and the extrusion of CO_2, respectively) reports on the gas-phase chemistry of oxazoles are very scarce.

The loss of nitrogen and carbon dioxide from triazoles and isoxazole-5-ones, respectively, has been reported [10] by Prager and Co-workers.

In previous studies we have shown[11] rearrangement of 4-acetyl-3-(4-substituted phenylamino)- isoxazol-5(2H)-ones substituted on nitrogen with an 2-chloro-5-nitropyridine group (**1**, R: Br, Me, OMe) to Imidazo [1, 2-a] pyridines (**2**, R: Br, Me, OMe) under Flash-Vacuum-Pyrolysis (F.V.P) conditions.

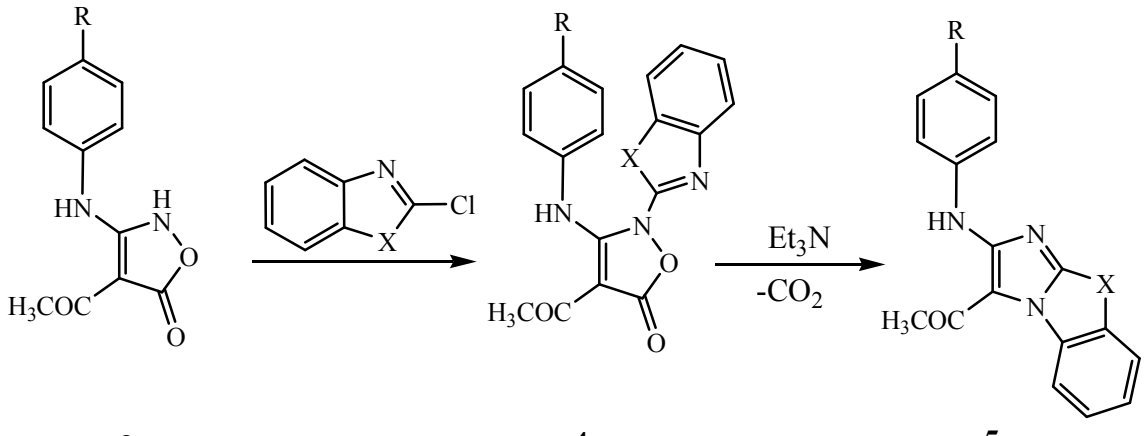


1, R: Br, Me, OMe

2, R: Br (90%), Me (93%), OMe (95%)

We have recently reported [12] synthesis of new N-substituted derivatives of P-substituted 4-acetyl-3-(4-substitutedphenylamino)-5(2H)-one **3** with a 2-chloro benzoxazol group substituted on N-2 **4**, and their

rearrangement in the presence of triethylamine to produce 1-(2-(4-substitutedphenylamino)-imidazo [2,1-b] benzoxazol-3-yl)-ethanone **5**, as shown in (Scheme I).



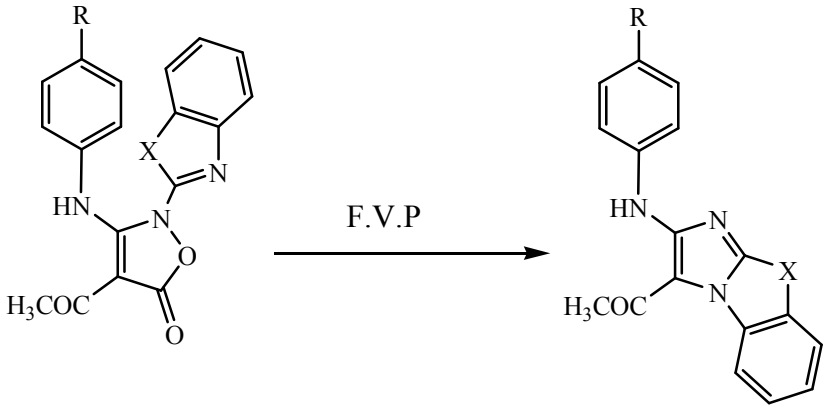
3 **4** **5**

X= O

R= Br, Me, NO_2

Scheme I

In this paper we report results of (F.V.P) of 4-acetyl-3-(4-substitutedphenylamino) -2-(benzoxazol-2-yl)-isoxazol-5(2H)-ones as shown in (Scheme II).



4 **5**

X= O

R= Br, Me, NO_2

X= O

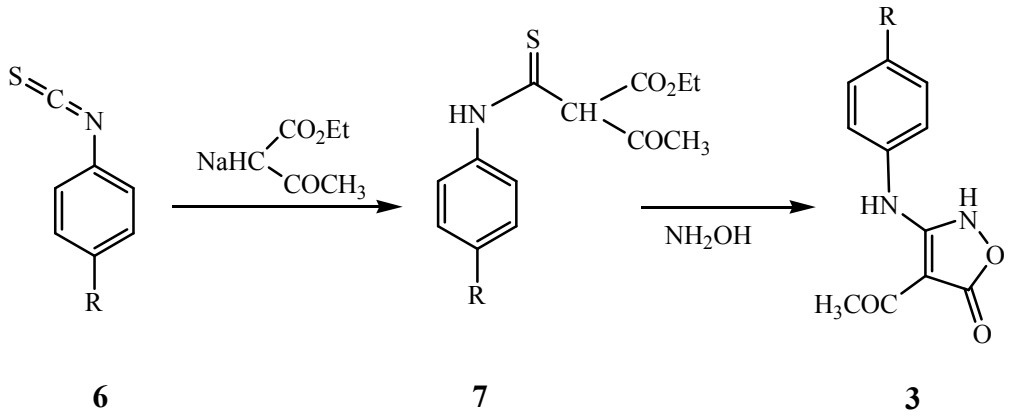
R= Br, Me, NO_2

Scheme II

RESULTS AND DISCUSSION

Were performed Net Rearrangements 4-acetyl-3-(4-substitutedphenylamino)-2-(benzoxazol-2-yl)-isoxazol-5(2H)-ones (1) at 900oC and 0.4 mm Hg. whereas at 700°C a conversion of only 15% was achieved, the increase of temperature at 900°C brought the conversion to 85%.

The required isoxazolones **4** were synthesized by reaction of 2-chlorobenzoxazol with 2H-isoxazolones **3**, which in turn were made by a modification of the procedure of Worrall [14, 15]. Thus, the reaction of the sodium salt of ethylacetoacetate in ethanol with 4-phenylisothiocyanates **6** gave the thiocarbamates **7** in high yield, and these were converted to the corresponding isoxazolone **3** by reaction with 2 equiv of hydroxylamine (Scheme III).

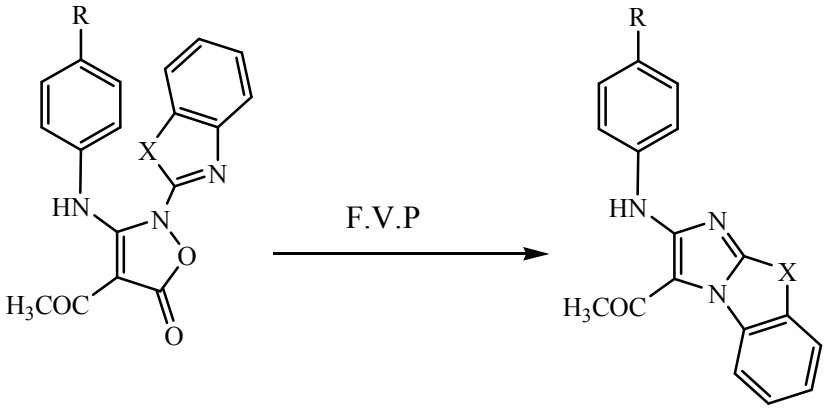


6 **7** **3**

R= Br, Me, NO_2

Scheme III

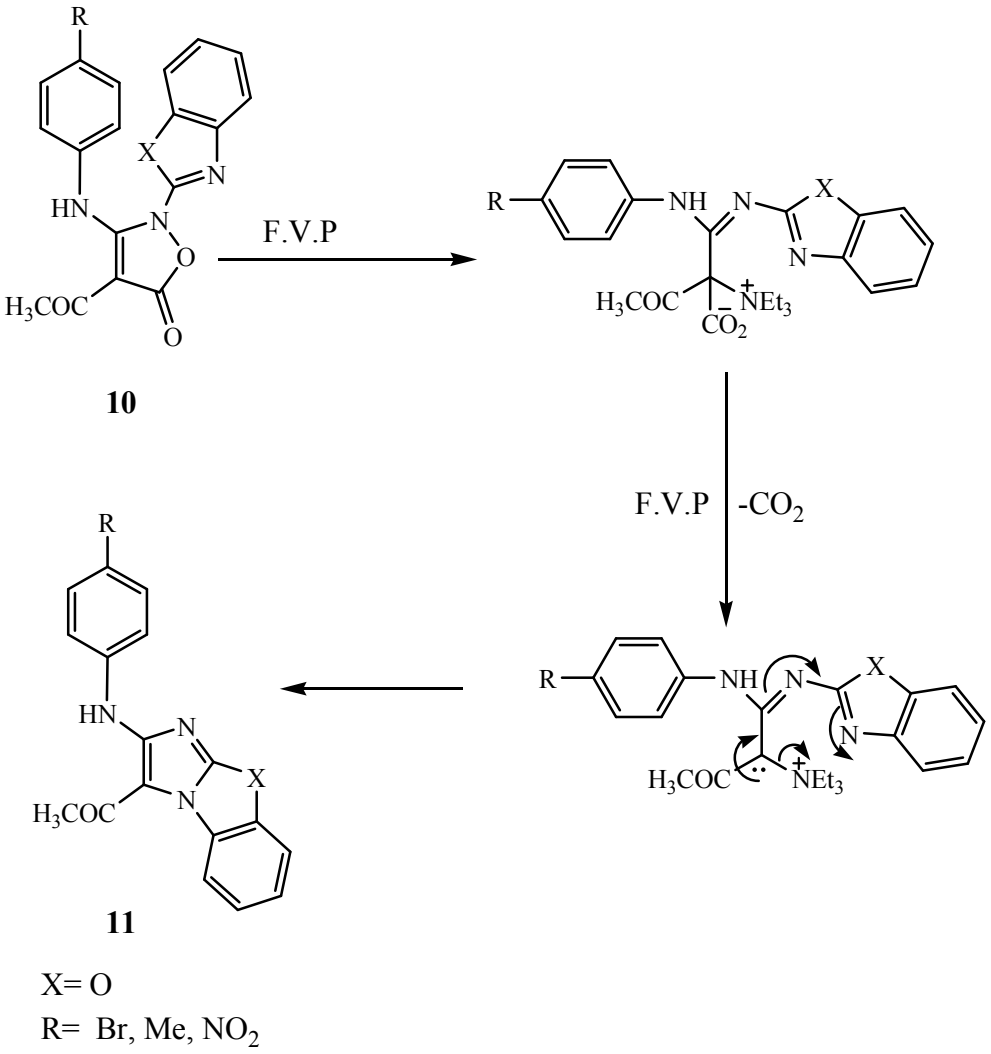
N-arylation of **3** with 2-chlorobenzoxazol in toluene under reflux conditions gave the corresponding N-substituted isoxazolones **4** in medium yield. The rearrangement of (**4**) as shown in Scheme 4, proceeded in 80-85% yield under Flash-vacuum-pyrolysis (F.V.P) conditions accompanied by elimination of carbon dioxide for 60 min. The reaction pathway leading to net imidazo-[2,1-b]-benzoxazole which is consist the electronic requirement of the reaction as shown in (Scheme IV) or with the alternative pathway suggested by Prager and Co-workers [16].



4 **5**

X= O
R= Br, Me, NO_2

X= O
R= Br, Me, NO_2



Scheme IV

The reaction products were examined by **GC/MS** analysis and by **^{1}H-NMR**, **^{13}C-NMR** and **FT-IR** spectroscopy.

EXPERIMENTAL

Freshly distilled solvents were used throughout, and anhydrous solvents were dried according to Perrin and Armarego.[13] Melting points were determined on a Philip Harris C4954718 apparatus and are uncorrected. Infrared spectra were recorded on a Thermonicolet (Nexus 670) FT-infrared spectrometer, using sodium chloride cells and measured as Nujol mulls or KBr. ^{1}H (300 MHz) and [13] C (300 MHz) NMR measurements were recorded on a Bruker 300 spectrometer in DMSO-d_6 or $CDCl_3$ using TMS as the internal reference. High resolution mass spectra were recorded on a Varian Matt 311 spectrometer. Mass spectra were registered in a HP 5973 MSD connected to HP 6890 GC interfaced by a Pentium PC and relative abundances of fragments are quoted in parentheses after the m/z values. Microanalyses were performed on a Leco Analyzer 932.

4-acetyl-3-(4-bromo phenylamino) isoxazol-5(2H)-ones (3, R: Br).

To a solution of hydroxylamine hydrochloride (7.06 g, 102 mmol) in water (30 mL), sodium bicarbonate (10.17 g, 102 mmol) was added slowly. Ethanol (80 mL) was added and the resulting potassium chloride was filtered off. Ethyl-2-(4-bromophenyl) carbamothioyl)-3-oxobutanoate (7, R: Br) 12.71g, 34 mmol) was added to the filtrate and the mixture was stirred at room temperature for 24 hours. The reaction mixture was acidified with dilute HCl and the white precipitate was collected and recrystallized from acetone to give the title product (8.78 g, 79%) as colourless needles, m.p: 200-202 ºC (dec.);

^{1}H-NMR (D_6-DMSO)δ(ppm): 2.25(s, J=7.1Hz, 3H, CH_3), 7.37(d, J=8.4Hz, 2H, Ar), 7.57(d, J=8.4Hz, 2H, Ar), 8.30 (bs, 1H, NH), 9.39 (bs, 1H, NH).
^{13}C-NMR (D_6-DMSO)δ(ppm) 15.31, 74.69, 118.02, 125.08, 132.94, 137.10, 163.53, 164.74, 167.39.
FT-IR ν_{max} 3250, 2950, 2740, 1723, 1696, 1666, 1607, 1563, 1456, 1398, 1316, 1183, 1018, 818 cm^{-1}.

4-acetyl-3-(4-methyl phenylamino) isoxazol-5(2H)-ones (3, R: Me)
This compound was prepared as described above using Ethyl-2-(4-methylphenyl) carbamothioyl)-3-oxobutanoate (7, R: Me) and Refluxing for 24 hours gave colourless crystals (85%), m.p: 164-166 ºC (dec.).
^{1}H-NMR (D_6-DMSO+$CDCl_3$)δ(ppm) 2.30 (s, J=7.0Hz, 3H, CH_3), 2.35 (s, 3H, Me), 6.78 (d, J=9.2Hz, 2H, Ar), 6.79 (bs, 1H, NH), 6.80(d, J=9.2Hz, 2H, Ar), 8.85 (bs, 1H, NH).
^{13}C-NMR (D_6-DMSO+$CDCl_3$,400 MHz)δ(ppm) 14.52, 20.85, 74.69, 121.53, 130.13, 133.29, 135.64, 163.59, 165.51, 166.74.
FT-IR ν_{max} 3669, 2979, 2746, 1705, 1669, 1615, 1331, 1208, 1115, 1023, 800 cm^{-1}.

4-acetyl-3-(4-nitrophenylamino)isoxazole-5(2H)-ones (3, R: NO_2)
The compound was prepared as described above using Ethyl-2-(4-nitrophenyl) carbamothioyl)-3-oxobutanoate (7, R: NO_2) (1.3 g, 4 mmol) and refluxing for 24 h to give the desired product as colourless crystals (0.5 g,65%), m.p. 162-164 ºC.
^{1}H-NMR (d_6-DMSO + $CDCl_3$)(δppm): 2.3 (s, J=7.0Hz, 3H, CH_3), 6.72 (d, J=9.2Hz, 2H), 6.84(bs, 1H, NH), 7.94 (d, J=9.2Hz, 2H), 8.8 (bs, 1H, NH).
^{13}C-NMR (d_6-DMSO+ $CDCl_3$)(δppm): 15.4, 74.69, 118.02, 125.08, 132.94, 137.10, 165.50, 167.74, 171.39.
FT-IR : 3669, 2979, 2746, 1705, 1669, 1615, 1350, 1331, 1208, 1115, 1023, 800 cm^{-1}.

4-acetyl-3-(4-bromophenylamino)-2-(benzoxazol-2-yl)-isoxazol-5(2H)-ones (4, R: Br)
4-acetyl-3-(4-bromophenylamino)-isoxazole-5(2H)-one (3, R: Br) (116 mg, 0.4 mmol) and 2-chlorobenzoxazol (46 mg, 0.3 mmol) were refluxed in toluene (8 mL) for 72 h. The solvent was removed under reduced pressure. On addition of n-hexane (10 mL) to the residue (colourless oil) a white precipitate was formed. The precipitate was filtered and recrystallized from ethanol to give 4-acetyl-3-(4-bromophenylamino)-2-(benzoxazol-2-yl)-isoxazol-5(2H)-ones as white prisms (81.8 mg, 61%) m.p. 156-157 ºC.
^{1}H-NMR (d_6-DMSO)(δppm): 2.3 (s, J=7.0Hz, 3H, CH_3), 6.37(d, J=8.4Hz, 2H), 7.3 (d, J=8.4Hz, 2H), 7.6 (t, J=8.4Hz, 2H), 8.7 (d, J=8.4Hz, 2H), 8.30 (bs, 1H, NH).
^{13}C-NMR (d_6-DMSO)(δppm): 26.1, 59.96, 84, 119.02, 124, 126.3, 132.94, 137.10, 163.53, 164.74, 167.39.
FT-IR : 3250, 2950, 2740, 1723, 1696, 1666, 1607, 1563, 1456, 1402, 1398, 1301, 1183, 1018, 818 cm^{-1}.
MS *m/z*: (%) 413.4 (M+, 12%), 411 (M+, 11%), 405 (82), 397 (71), 371 (48), 369 (40), 334 (25), 294 (28), 291 (27), 290 (100), 262 (30), 224 (27), 177 (33), 161 (34), 150 (40), 135 (26), 134 (33), 108 (29), 44 (65).

4-acetyl-3-(4-methylphenylamino)-2-(benzoxazol-2-yl)-isoxazol-5(2H)-ones (4, R: Me)
This compound was prepared as described above, using the corresponding isoxazolone (3, R: Me) (61 mg, 0.27 mmol) and 2-chlorobenzoxazole (41.3 mg, 0.27 mmol) to give the desired product as white prisms (44 mg, 51%) after recrystalization from ethanol, m.p. 160-163 ºC.
^{1}H-NMR (d_6-DMSO)(δppm): 2.3 (s, J=7.0Hz, 3H, CH_3), 2.35 (s, 3H, Me), 6.37(d, J=8.4Hz, 2H), 7.5 (d, J=8.4Hz, 2H), 7.8 (t, J=8.4Hz, 2H), 8.3 (d, J=8.4Hz, 2H), 8.33 (bs, 1H, NH).
^{13}C-NMR (d_6-DMSO)(δppm): 24.3, 26.1, 59.96, 84, 118.02, 121, 125.3, 132.94, 137.10, 163.53, 164.74, 167.39.
FT-IR : 3250, 2950, 2740, 1723, 1696, 1666, 1607, 1563, 1456, 1402, 1398, 1301, 1183, 1018, 818 cm^{-1}.
MS *m/z*: (%) 349.1 (M+, 12%), 341 (48), 325 (40), 314 (25), 294 (28), 291 (27), 290 (100), 262 (30), 224 (27), 177 (33), 161 (34), 150 (40), 135 (26), 134 (33), 108 (29), 44 (65).

4-acetyl-3-(4-nitrophenylamino)-2-(benzoxazol-2-yl)-isoxazol-5(2H)-ones (4, R: NO_2)
This compound was prepared as described above, using the corresponding isoxazolone (3, R: NO_2) (89 mg, 0.34 mmol) and 2-chlorobenzoxazole (52.1 mg, 0.34 mmol) to give the desired product as white prisms (43 mg, 49%) after recrystalization from ethanol, m.p. 168-170 ºC.
^{1}H-NMR (d_6-DMSO)(δppm):): 2.3 (s, J=7.0Hz, 3H, CH_3), 6.7(d, J=8.4Hz, 2H), 7.6 (t, J=8.4Hz, 2H), 7.9 (d, J=8.4Hz, 2H), 8.3 (d, J=8.4Hz, 2H), 8.33 (bs, 1H, NH).
^{13}C-NMR (d_6-DMSO)(δppm): 26.1, 59.96, 84, 118.02, 121, 125.3, 132.94, 137.10, 163.53, 164.74, 167.39.

FT-IR : 3250, 2950, 2740, 1723, 1696, 1666, 1607, 1563, 1456, 1450, 1402, 1398, 1301, 1183, 1018, 818 cm^{-1}.
MS *m/z*: (%) 380.1 (M+, 12%), 372 (48), 356 (40), 334 (25), 294 (28), 291 (27), 290 (100), 262 (30), 224 (27), 177 (33), 161 (34), 150 (40), 135 (26), 134 (33), 108 (29), 44 (65).

1-(2-(4-bromophenylamino)-imidazo-[2,1-b]-benzoxazol-3-yl)-ethanone (5, R: Br)
Flash-vacuum-pyrolysis (900°C, 0.4 mm Hg, sublimation flask 150°C, 60 min) of isoxazolone (4, R: Br) (90.2 mg, 0.22 mmol) gave pale cream needles (80.17 mg, 83%), m.p: 180-184 ^{o}C.
^{1}H-NMR (d_6-DMSO)(δppm): 2.55 (t, J=7.1Hz, 3H), 6.6(d, J=8.4Hz, 2H), 7.2 (t, J=8.4Hz, 1H), 7.3 (t, J=8.4Hz, 1H), 7.5 (d, J=8.4Hz, 2H), 8.2 (bs, 1H, NH).
^{13}C-NMR (d_6-DMSO)(δppm): 26.6, 46, 84, 118.02, 121, 125.3, 132.94, 137.10, 143.53, 144.74, 147.39.
FT-IR : 3250, 2950, 2740, 1723, 1696, 1666, 1607, 1563, 1456, 1450, 1402, 1398, 1301, 1183, 1018, 818 cm^{-1}.
MS *m/z*: (%) 369.1 (M+, 12%), 357 (48), 340 (40), 334 (25), 298 (28), 295 (27), 293 (100), 262 (30), 224 (27), 179 (33), 161 (34), 153(40), 145 (26), 134 (33), 108 (29), 44 (65).

1-(2-(4-methylphenylamino)-imidazo-[2,1-b]-benzoxazole-3-yl)-ethanone (5, R: Me)
Flash-vacuum-pyrolysis (900°C, 0.4 mm Hg, sublimation flask 150°C, 60 min) of isoxazolone (4, R: Me) (76.7 mg, 0.22 mmol) gave the desired imidazole as pale cream needles (82.34 mg, 85%), mp 153-157 ^{o}C.
^{1}H-NMR (d_6-DMSO)(δppm): 2.35 (s, J=7.1Hz, 3H), 2.55 (s, J=7.1Hz, 3H), 6.3 (d, J=8.4Hz, 2H), 6.9 (d, J=8.4Hz, 2H), 7.3 (t, J=8.4Hz, 1H), 7.5 (t, J=8.4Hz, 1H), 7.7 (d, J=8.4Hz, 2H), 8.2 (bs, 1H, NH).

^{13}C-NMR (d_6-DMSO)(δppm): 24.3, 26.7, 84, 118.02, 121, 125.3, 132.94, 137.10, 143.53, 144.74, 147.39.
FT-IR : 3250, 2950, 2740, 1723, 1696, 1666, 1607, 1563, 1456, 1450, 1402, 1398, 1301, 1183, 1018, 818 cm^{-1}.
MS *m/z*: (%) 305.11 (M+, 12%), 300 (48), 298 (28), 295 (27), 293 (100), 262 (30), 224 (27), 179 (33), 161 (34), 153(40), 145 (26), 134 (33), 108 (29), 44 (65).

1-(2-(4-nitrophenylamino)-imidazo-[2,1-b]-benzoxazole-3-yl)-ethanone (5, R: NO_2)
Flash-vacuum-pyrolysis (900°C, 0.4 mm Hg, sublimation flask 150°C, 60 min) of isoxazolone (4, R: NO_2) (83.6 mg, 0.22 mmol) gave the desired imidazole as pale cream needles (76.22 mg, 80%), mp. 199-204 ^{o}C.
^{1}H-NMR (d_6-DMSO)(δppm): 2.55 (s, J=7.1Hz, 3H), 6.7 (d, J=8.4Hz, 2H), 7.3 (t, J=8.4Hz, 1H), 7.5 (t, J=8.4Hz, 1H), 7.9 (d, J=8.4Hz, 2H), 8.6 (bs, 1H, NH).
^{13}C-NMR (d_6-DMSO)(δppm): 26.6, 70.96, 84, 118.02, 121, 125.3, 132.94, 137.10, 143.53, 144.74, 147.39.
FT-IR : 3250, 2950, 2740, 1723, 1696, 1666, 1607, 1563, 1456, 1450, 1402, 1398, 1353, 1301, 1183, 1018, 818 cm^{-1}.
MS *m/z*: (%) 336.11 (M+, 11%), 323 (48), 310 (40), 304 (25), 298 (28), 295 (27), 293 (100), 262 (30), 224 (27), 179 (33), 171 (34), 153(40), 149 (26), 134 (33), 108 (29), 44 (65).

CONCLUSION

In conclusion we have shown that a variety of N-substituted isoxazolones **4**, rearranged under Flash-Vacuum-Pyrolysis (F.V.P) conditions to give imidazo-[2,1-b]-benzoxazole. These rearrangements, therefore, appear to be generally applicable to the synthesis of imidazoheterocycles which are suitable synthetic intermediates for a series of polycyclic heterocycles with possible pharmaceutical applications.
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