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Net Rearrangements of 4-acetyl-3-(4-substituted phenylamino)-2-(5-nitropyridin-2-yl)isoxazol-5(2H)-ones to Imidazo [1, 2-a]pyridines by Flash-Vacuum-Pyrolysis (F.V.P)

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ABSTRACT

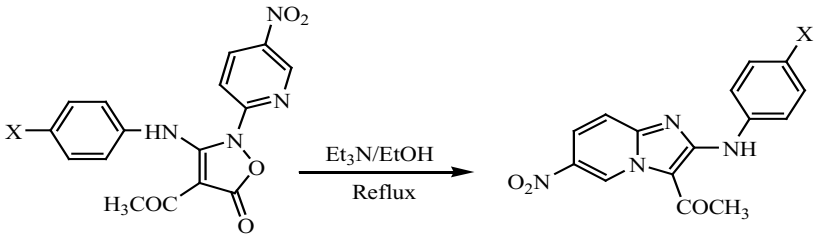
4-acetyl-3-(4-substituted phenylamino)-2-(5-nitropyridin-2-yl) isoxazol-5(2H)-ones, rearranged under Flash-Vacuum-Pyrolysis (F.V.P) conditions accompanied by elimination of carbon dioxide to give imidazo[1, 2-a]pyridines in high to excellent yields (90-95%).

Key words: Isoxazolones, Imidazopyridines, Flash-Vacuum-Pyrolysis.

INTRODUCTION

The thermal or photochemical loss of nitrogen and carbon dioxide from triazoles and isoxazole-5-ones, respectively, have been reported.[1]

We have reported that the reaction of 4-acetyl-3-(4-substituted phenylamino)-2-(5-nitropyridin-2-yl) isoxazol-5(2H)-ones (1,X: Br, Me)[2] with triethylamine in ethanol, give imidazo annulated compounds (2, X: Br (84%), Me (75%) as net products, Scheme 1.

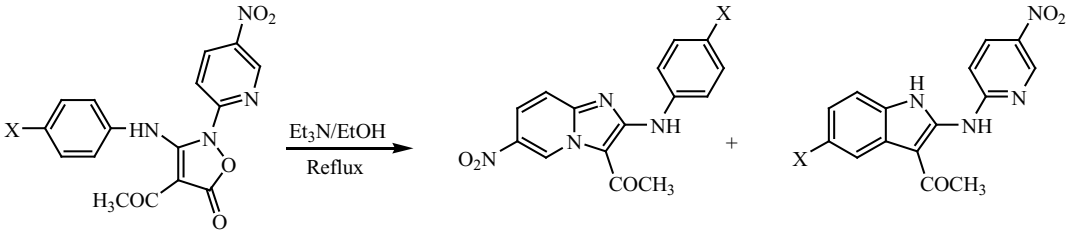


1, X: Br, Me

2, X: Br, Me

Scheme 1

However, the reaction of 4-acetyl-3-(4-substituted phenylamino)-2-(5-nitropyridin-2-yl) isoxazol-5(2H)-ones (1, X: OMe) with triethylamine gives imidazo (2, X: OMe, 59%) and indole (3, 20%)[2] annulated compounds respectively, Scheme 2.



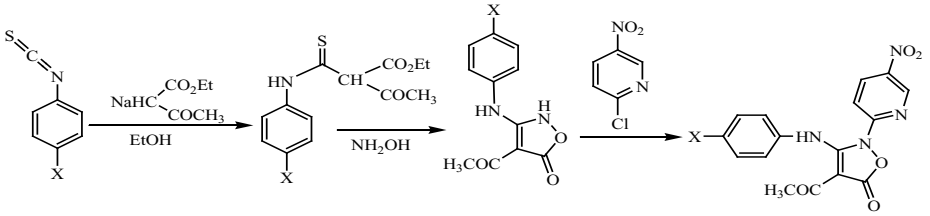
1, X: OMe 2, X: OMe 3, X: OMe

Scheme 2

Here we describe the net rearrangement of 4-acetyl-3-(4-substituted phenylamino)-2-(5-nitropyridin-2-yl) isoxazol-5(2H)-ones (1, X: Br, Me and 3) to Imidazo[1, 2-a]pyridines (2, X: Br, Me, OMe) under Flash-Vacuum-Pyrolysis (F.V.P) conditions.

RESULTS AND DISCUSSION

The required isoxazolones (1) were synthesized by reaction of 2-chloro-5-nitropyridine with 2H-isoxazolones (6) which in turn were made by modification of the procedure of Worrall.[3, 4] Thus, the reaction of the sodium salt of ethylacetoacetate in ethanol with arylisothiocyanates (4) gave the thiocarbamates (5) in high yield (70-90%) and this converted to corresponding isoxazolone (6) by reaction with 2 equiv of hydroxylamine. N-arylation of isoxazolone (6) with 2-chloro-5-nitropyridine in solid phase condition gave the corresponding N-substituted isoxazolones (1) in fair yield (70-85%), Scheme 3.

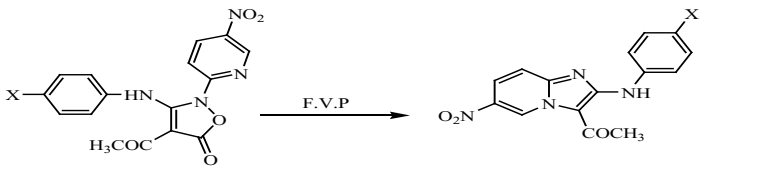


4 5 6 1

X: Br, Me, OMe X: Br, Me, OMe X:Br, Me, OMe X: Br, Me, OMe

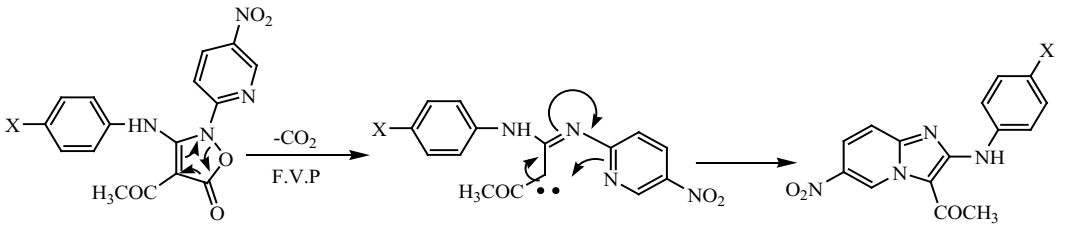
Scheme 3

The rearrangement of (1) as shown in Scheme 4, proceeded in 90-95% yield under F.V.P conditions accompanied by elimination of carbon dioxide for 60 min. The reaction pathway leading to net Imidazo[1,2-a]pyridines which is consist the electronic requirement of the reaction as shown in Scheme 5 or with the alternative pathway suggested by Prager and Co-workers.[5]



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

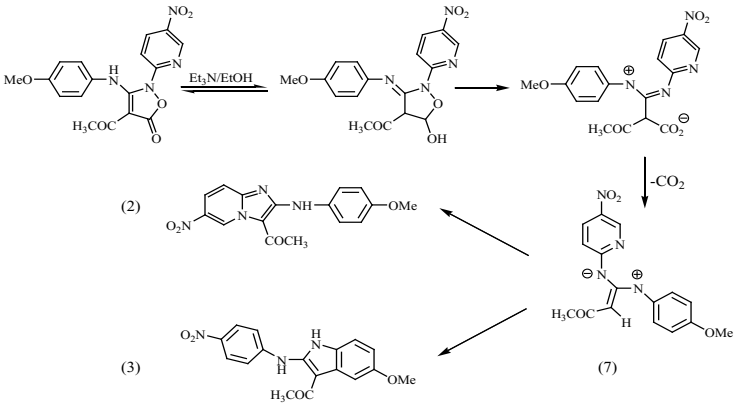
Scheme 4



X: Br, Me, OMe

Scheme 5

With a number of imidazopyridine structures in hand, the structures of all imidazopyridines were confirmed by ^{1}H-NMR, ^{13}C-NMR, FT-IR, MASS spectra or microanalyses. 4-methoxy derivative (1, Ar: $MeOC_6H_4$) reacts in refluxing ethanol with triethylamine to form a mixture of imidazopyridine (2, Ar: $MeOC_6H_4$) and indole (3) in a 2:1 ratio, respectively, but it only rearranges to imidazopyridine under F.V.P conditions. The exact mechanism of this synthetic method has been unclear so far. However, we think that the zwitterionoic (7) plays a role under refluxing ethanol with triethylamine, (scheme 6). This is consistent with electronic requirements of the reaction. The zwitterionoic (7) probably can be stabilised by ethanol as protic solvent, however under F.V.P conditions it can not be produced.



Scheme 6

EXPERIMENTAL

General

Freshly distilled solvents were used throughout, and anhydrous solvents were dried according to Perrin and Amarego.[6] ^{1}H-NMR and ^{13}C-NMR spectra were recorded, in deuteriochloroform, unless otherwise stated, at 500 and 125 MHz respectively, with a Bruker DRX-500 Avance spectrometer. Tetramethylsilane was used as an internal standard and all signals due to amino protons were removed by exchange with D_2O. Infrared spectra were recorded on a Unicam Matsson 1000 Fourier-Transform Spectrometer. Mass spectra were recorded on a Varian Matt 311 spectrometer and relative abundance of fragments are quoted in parentheses after the m/z values. Melting points were determined on a Philip Harris C4954718 apparatus and are uncorrected. Micronalyses were preformed on a Carlo–Erba Analyzer 1104.

4-acetyl-3-(4-bromo phenylamino) isoxazol-5(2H)-ones (6, X: 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 (5, X: 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 (6, X: Me).

This compound was prepared as described above using Ethyl-2-(4-methylphenyl) carbamothioyl)-3-oxobutanoate (5, X: 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-methoxy phenylamino) isoxazol-5(2H)-ones (6, X: OMe)

This compound was prepared as described above using Ethyl-2-(4-methoxyphenyl) carbamothioyl)-3-oxobutanoate (5, X: OMe) Refluxing for 24 hours gave the desired product (80%) which was recrystallized from ethanol/acetone (1:1) as a white solid, m.p: 206-207 ºC (dec.); ^{1}H-NMR (D_6-DMSO+$CDCl_3$)δ(ppm) 2.3 (s, J= 7.0Hz, 3H, CH_3), 3.35 (s, 3H, OMe), 6.38 (d, J=8.5Hz, 2H, Ar), 6.94 (d, J= 8.5Hz, 2H, Ar), 6.96 (bs,1H, NH), 7.70(bs,1H,NH).

^{13}C-NMR(D_6-DMSO+$CDCl_3$)δ(ppm) 15.64, 55.55, 73.5 ,114.6, 118.6, 135.73, 153.7, 165.73, 168.14, 174.81.

FT-IR ν_{max} 3407, 1708, 1615, 1554, 1248, 1077, 792 cm^{-1}.

4-acetyl-3-(4-bromo phenylamino) -2-(5-nitropyridin-2-yl) isoxazol-5(2H)-ones(1, X: Br)

A mixture of 2-chloro-5-nitropyridine (48.5 mg, 0.30 mmol) and 4-acetyl-3-(4-bromo phenylamino) isoxazol-5(2H)-ones (6, X: Br), 100 mg, 0.30 mmol) was heated neat under nitrogen in an oil bath at 130 ºC for 2 hours. The residue was recrystallized from ethanol to give the desired isoxazolone as yellow crystals (112 mg, 82%), m.p: 218 ºC.

^{1}H-NMR(D_6-DMSO+$CDCl_3$) δ(ppm) 2.25 (s, J=7.0Hz, 3H, CH_3), 6.87 (d, J=8.5Hz, 2H,Ar), 7.18 (d, J=8.5Hz, 2H, Ar), 7.73 (d, J=9.1Hz,1H, Ar), 8.40 (dd, J_1=9.1Hz, J_2=2.3Hz, 1H, Ar), 8.75 (d, J=2.3Hz, 1H, Ar), 10.29 (bs, 1H, NH).

^{13}C-NMR (D_6-DMSO+$CDCl_3$) δ (ppm) 14.41, 79.05, 114.63, 119.46, 124.11, 132.46, 135.08, 137.21, 141.66, 143.79, 153.92, 158.31, 161.38, 165.88.

FT-IR ν_{max} 3140, 2965, 1773, 1683, 1591, 1531, 1324, 1188, 1114, 1010, 961, 832 cm^{-1}.

MS m/z 419(M+, 27%), 417(M+, 30%), 406(74), 404(77), 279(100), 251(20), 184(35), 182(36), 157(29), 155(29), 102(22), 72(23), 44(59).

4-acetyl-3-(4-methyl phenylamino)-2-(5-nitropyridin-2-yl) isoxazol-5(2H)-ones(1, X: Me) This compound was prepared as described for above using the corresponding isoxazolone (6, X: Me) and 2-chloro-5-nitropyridine to give the desired product after recrystalization from

ethanol yellow needles (85%), m.p: 156-158 ºC, after recrystalization from ethanol.

^{1}H-NMR ($CDCl_3$)δ(ppm) 2.29 (s,J=7.05Hz, 3H, CH_3), 2.35 (s, 3H, Me), 7.04 (d, J=8.5Hz, 2H, Ar), 7.07 (d, J=8.5Hz, 2H, Ar), 7.54 (d, J= 9.0Hz, 1H, Ar), 8.55 (dd, J_1=9.0Hz, J_2=2.5Hz, 1H, Ar), 8.91 (d, J=2.5Hz, 1H, Ar), 10.33 (s, 1H, NH).

^{13}C-NMR ($CDCl_3$)δ(ppm) 14.66, 21.35, 79.05, 115.42, 122.40, 130.29, 134.74, 135.36, 136.83, 141.89, 143.92, 154.28, 160.88, 163.62, 164.19.

FT-IR ν_{max} 3177, 1762, 1700, 1600, 1515, 1338, 1208, 1123, 976, 838 cm^{-1}.

MS m/z 355(M+, 13%), 354(100), 294(57), 269(16), 248(40), 230(16), 220(16), 158(39), 144(13), 118(21), 117(20), 107(16), 91(67), 78(16), 65(20), 44(33).

4-acetyl-3-(4-methoxy phenylamino) -2-(5-nitropyridin-2-yl) isoxazol-5(2H)-ones (1, X: OMe).

This compound was prepared as described for above using the corresponding isoxazolone (6, X: OMe) and 2-chloro-5-nitropyridine to give the desired product Yellow needles (80%), m.p: 186-188 ºC.

^{1}H-NMR ($CDCl_3$)δ(ppm) 2.30 (s, J=7.0Hz, 3H, CH_3), 3.77 (s, 3H, OMe), 6.79 (d, J=8.7Hz, 2H,Ar), 7.10 (d, J=8.7Hz, 2H, Ar), 7.52 (d, J=9.0Hz, 1H, Ar), 8.54 (dd, J_1=9Hz, J_2=2.1Hz, 1H, Ar), 8.93 (bd, J=2.1Hz, 1H, Ar), 10.26 (s,1H,NH).

^{13}C-NMR ($CDCl_3$)δ(ppm) 14.72, 55.89, 78.87, 114.85, 115.59, 124.34, 130.74, 134.68, 141.93, 143.95, 154.33, 158.40, 161.38, 163.69, 164.32.

FT-IR ν_{max} 3823, 1785, 1700, 1592, 1345, 1207, 1115, 1030, 838 cm^{-1}.

MS m/z 370 (M^+, 10%), 356(100), 310(49), 295(43), 264(21), 249(13), 221(14), 193(12), 194(10), 174(21), 146(10), 134(34), 133(22), 123(17), 92(16), 77(29), 44(37).

1-(2-(4-bromo phenylamino) -6-nitroimidazo[1,2-a] pyridine-3-yl) ethanone (2, X: Br)

Pyrolysis (580°C, 0.01 mm Hg, sublimation flask 110°C, 60 min) of isoxazolone (1, X: Br) (100 mg, 0.23 mmol) gave pale cream needles (81.17 mg, 90%), m.p: 195-196 ºC.

^{1}H-NMR(D_6-DMSO)δ(ppm)2.55(s, J=7.0Hz, 3H, CH_3), 7.49 (d, J=8.5Hz, Ar), 7.68 (d, J=9.7Hz, 1H, Ar), 7.74 (d, J=8.5Hz , 2H, Ar), 8.19 (dd, J_1=9.7Hz, J_2=1.6Hz, 1H, Ar), 8.87 (bd, J=1.6Hz, 1H, Ar), 9.88 (s,1H,NH).

^{13}C-NMR (D_6-DMSO)δ(ppm)15.25, 99.72, 114.62, 114.97, 121.76, 123.93, 127.61, 132.38, 137.66, 140.01, 147.17, 155.28, 160.87.

FT-IR ν_{max} 3285, 2955, 1643, 1611, 1555, 1475, 1331, 1294, 1201, 1102, 1079, 1002, 820 cm^{-1}.

MS m/z 375(M+, 62%), 374(M^+,64%), 360(5), 358(6), 279(100), 251(16), 233(14), 205(12), 184(11), 182(12), 157(12), 155(12), 102(14), 78(13), 77(11).

1-(2-(4-methyl phenylamino) -6-nitroimidazo[1,2-a] pyridine-3-yl) ethanone (2, X:Me)

Pyrolysis (580°C, 0.01 mm Hg, sublimation flask 110°C, 60 min) of isoxazolone (1, X: Me) (100 mg, 0.26 mmol) gave the desired imidazole as pale cream needles (82.34 mg, 93%), m.p: 187-188 ºC.

^{1}H-NMR (D_6-DMSO)δ(ppm) 2.35 (s, J=6.9Hz, 3H, CH_3), 2.55 (s, 3H, Me), 7.19 (d, J=8.2Hz, 2H, Ar), 7.51 (d, J=9.7Hz, 1H, Ar), 7.59 (bd, J=8.2Hz, 2H, Ar), 8.15 (bd, J=6.7Hz, 1H, Ar), 8.85 (bs, 1H, NH), 9.84 (bs, 1H, Ar).

^{13}C-NMR ($CDCl_3$)δ(ppm): 15.03, 61.44, 98.99, 114.30, 119.33, 122.80, 127.26, 130.07, 132.93, 137.11, 147.34, 157.76, 161,15 .

FT-IR ν_{max} 3455, 1662, 1608, 1555, 1308, 1208, 1015, 822 cm^{-1}.

MS m/z 310 (M^+, 100%), 294(48), 248(27), 220(9), 144(10), 118(13), 91(20), 78(6), 65(6).

1-(2-(4-methoxy phenyl amino) -6-nitroimidazo [1,2-a] pyridine-3-yl) ethanone(2, X: OMe)

Pyrolysis (580°C, 0.01 mm Hg, sublimation flask 110°C, 60 min) of isoxazolone (1, X: OMe) (100 mg, 0.25 mmol) gave the title compound as a red solid (84.55 mg, 95%), m.p: 160-161 ºC;

^{1}H-NMR ($CDCl_3$)δ(ppm) 2.52 (s, J=7.1Hz, 3H, CH_3), 3.73 (s, 3H, OMe), 6.86 (dd, J_1=8.7Hz, J_2= 2.5Hz, 1H, Ar), 6.92 (d, J=9.1Hz, 1H, Ar), 7.32 (d, J=8.7Hz, 1H, Ar), 7.45 (bs, 1H, Ar), 8.42 (dd, J_1=9.1Hz, J_2=2.6Hz, 1H, Ar), 9.26 (d, J=2.6Hz, 1H, Ar), 10.72 (bs, 1H, NH).

^{13}C-NMR ($CDCl_3$)δ(ppm) 15.02, 50.43, 89.99, 103.86, 111.00, 111.69, 112.14, 125.67, 126.89, 133.76, 138.65, 145.26, 145.59, 156.41, 156.58.

FT-IR ν_{max} 3345, 1642, 1615, 1500, 1331, 1215, 1117, 1035, 838 cm^{-1}.

MS m/z 326(M^+, 70%), 310(100), 295(27), 264(32), 249(13), 221(29), 193(12), 194(10), 150(13), 78(6), 77(5).

CONCLUSION

In conclusion we have shown that a variety of 4-acetyl-3-(4-substituted phenylamino)-2-(5-nitropyridin-2-yl) isoxazol-5(2H)-ones, rearranged under Flash-Vacuum-Pyrolysis (F.V.P) conditions to give imidazo [1,2-a] pyridines. 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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