Phase Transfer Catalyzed Synthesis of 3-Methyl-4*H*-pyrazolo[3,4-*d*]isoxazole from 3,5-Dimethyl-4-isoxazolyldiazonium tetrafluoroborate

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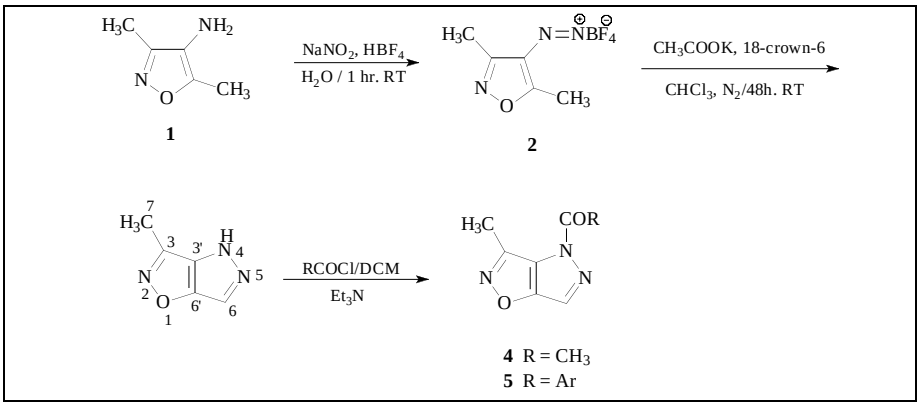

Reaction of 3,5-dimethyl-4-isoxazolyl-diazonium tetrafluoroborate (**2**) with two equivalents of potassium acetate and five mole percent of 18-crown-6 in ethanol-free chloroform produce 3-methyl-4*H*-pyrazolo[3,4-*d*]isoxazole (**3**) in good to excellent yield. Pyrazole (**3**) was subjected to acylation/aroylation to afford the corresponding 4-*N*-acetyl/aroyl derivatives by reaction with CH_3COCl/ArCOCl in Et_3N.

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INTRODUCTION

One of the more common routes to the indazole ring system is diazotization of *o*-toluidines in acidic or neutral aqueous solution [1-4]. A more successful preparation of indazole was the reaction of *o*-methylbenzenediazonium chloride with tetramethylammonium acetate in chloroform [5]. However, this synthesis required the isolation of an explosive diazonium chloride and the use of expensive and hygroscopic tetramethylammonium acetate. In view of this and as a sequel to our work on isoxazoles [6-10] we wish to report a facile phase transfer catalyzed synthesis of pyrazolo[3,4-*d*]isoxazole from non-explosive diazonium tetrafluoroborates and inexpensive potassium acetate [11].

RESULTS AND DISCUSSION

Diazotisation of 4-amino-3,5-dimethyl isoxazole (**1**) with sodium nitrite in fluoroboric acid has been carried out in water media for 1 hr. The reaction resulted in the formation of 3,5-dimethyl-4-isoxazolyl diazonium tetrafluoroborate (**2**), stable at room temperature and which is non-explosive, whose structure is established on the basis of spectral data and no specific precautions are needed in the handling during the reaction.

Reaction of 3,5-dimethyl-4-isoxazolyl diazonium tetrafluoroborate (**2**) with potassium acetate in presence of 18-crown-6 in ethanol-free chloroform at room temperature for 48 hr, followed by a very simple isolation procedure and recrystallization of the crude product gave a 90% yield of 3-methyl-4*H*-pyrazole[3,4-*d*] isoxazole. In the absence of 18-crown-6, no product was formed. For this heterogenous system, the crown ether transfers both the solid diazonium salt and the potassium acetate into solution where reaction occurs [12].

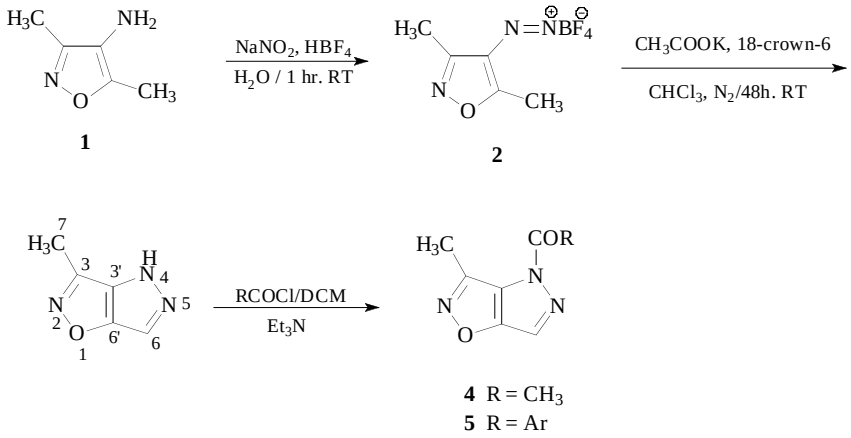
The structure of 3-methyl-4*H*-pyrazolo[3,4-*d*]isoxazole was assisted by elemental analysis, IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. To confirm further, the product **3** was subjected to acetylation and aroylation separately by using CH_3COCl/ArCOCl in Et_3N which led to the formation of 4-*N*-acetyl and 4-*N*-aroyl derivatives respectively (Table 1). These products are also in agreement with IR, ^{1}H NMR, ^{13}C NMR and mass spectral data.

Table 1

Physical and Analytical Data of Compounds **5**

Compd	Ar	Time (hr)	MP (°C)	Yield %
5a	C_6H_5	2.5	139-142	90
5b	4-CH_3-C_6H_4	3.0	145-147	95
5c	4-CH_3O-C_6H_4	3.0	123-125	90
5d	4-Cl-C_6H_4	2.5	167-169	90
5e	2-Cl-C_6H_4	3.0	173-174	95
5f	2,4-Cl_2-C_6H_3	2.5	181-184	95

Scheme 1



4 R = CH_3
5 R = Ar

CONCLUSION

In conclusion, we have successfully demonstrated the synthesis of pyrazole ring under phase transfer conditions which gave 90% yield, by utilizing non-explosive diazonium tetrafluoroborate and inexpensive potassium acetate. To the best of our knowledge this happens to be the first report to build pyrazole ring on isoxazole moiety under PTC conditions. Pyrazole (**3**) underwent smooth acylation/aryolation by treatment with CH_3COCl/ArCOCl in Et_3N to give the corresponding 4-*N*-acetyl/aroyl derivatives in high yields.

EXPERIMENTAL

Melting points were determined on a cintex melting-point apparatus and are uncorrected. The purity of the compounds was checked by TLC. TLC analyses were performed on precoated silica gel (E. merck Kieselgel $60F_{254}$) plates and visualization was done by exposing to iodine vapour. Ethylacetate and hexane (2:7) used as an eluent. IR spectrum was recorded in KBr on a Perkin Elmer spectrum BX series FT-IR spectrometer, ^{1}H NMR spectra on a Varian Gemini 300 MHz spectrometer using tetramethylsilane as internal standard, and mass spectra on a Jeol JMC D-300 spectrometer. C, H and N analyses were carried out on Carlo Erba 106 and Perkin-Elmer model 240 analysers.

Synthesis of 3,5-Dimethyl-4-isoxazolyl-diazonium tetrafluroborate (**2**). 4-Amino-3,5-dimethyl-isoxazole **1** (0.005 mole) was dissolved in 10 ml of fluoroboric acid (47%, 0.005 mole). To this sodium nitrite solution (1.0 g in 50 ml H_2O) was added drop wise at 0°C for 0.5 hr. The reaction mixture was stirred at room temperature for 1 hr. The solid obtained was collected by filtration and recrystallized from acetone.

Synthesis of 3-Methyl-4*H*-pyrazolo[3,4-*d*]isoxazole (**3**). The 3,5-dimethyl-4-isoxazolyl-diazonium tetrafluoroborate **2** (0.005 mole) was added in one portion to a stirred mixture of dried and powdered potassium acetate (0.01 mole) and 18-crown-6 (0.025 mole) in 20 ml of ethanol-free chloroform. After magnetic stirring under nitrogen atmosphere for 1 hr., the mixture was filtered and washed with chloroform. The filtrate and washings are combined, washed with water (3 x 50 ml), dried with Na_2SO_4 and evaporated *in vacuo*. The product was recrystallized from aq. methanol.

Synthesis of 1-[3-Methyl-4*H*-pyrazolo[3,4-*d*]isoxazol-4-yl]-1-ethanone (**4**). To a solution of 3-methyl-4*H*-pyrazolo[3,4-*d*]-isoxazole (0.005 mole) in dichloromethane (15 ml), acetylchloride (0.005 mole) was added with stirring at 20°C for 15 min. Triethylamine (5 ml) was added to it later and stirring continued for 3 hr at room temperature. The solid triethylamine hydrochloride was removed by filtration. The organic layer was washed with water (2 x 25 ml) and brine solution (2 x 25 ml) and concentrated under vacuum. The solid obtained was crystallized from ethanol.

Synthesis of 3-Methyl-4*H*-pyrazolo[3,4-*d*]isoxazol-4-yl-phenylmethanone (**5a-f**). **General Method**. To a solution of 3-methyl-4*H*-pyrazolo[3,4-*d*]isoxazole (0.005 mole) in dichloromethane (15 ml), aroyl chloride (0.005 mole) was added with stirring at 20°C for 30 min. Triethylamine (5 ml) was added to this solution later with stirring for 2-3 hr at room temperature. Triethylamine hydrochloride was removed by filtration. The filtrate was washed with water (2 x 25 ml) and brine solution (2 x 25 ml) and concentrated under vacuum. The product was recrystallized from methanol (Table 1).

3,5-Dimethyl-4-isoxazolyldiazanium tetrafluoroborate (**2**). This compound was obtained as colourless crystals, yield 85%, m.p. 110-113°C; IR: 2250 (N=N) cm^{-1}; ^{1}H NMR: δ 2.2 (s, 3H, CH_3), 2.5 (s, 3H, CH_3) ; MS : m/z 210 (M^+).

Anal. Calcd. for $C_5H_6N_3OBF_4$; C, 28.57; H, 2.85; N, 20.00. Found: C, 28.62; H, 2.89; N, 19.92%.

3-Methyl-4*H*-pyrazolo[3,4-*d*]isoxazole (**3**). This compound was obtained as colourless crystals; yield 90%, m.p. 139-142°C; IR: 3250 (NH) cm^{-1}; ^{1}H NMR: δ 2.4 (s, 3H, CH_3), 8.2 (s, 1H, =CH), 13.0 (bs, 1H,NH, D_2O exchangeable), ^{13}C NMR: δ 16 (C-7), 115 (C-3'), 136 (C-3), 146 (C-6), 162 (C-6'); MS: m/z 123 (M^+).

Anal. Calcd. for $C_5H_5N_3O$: C, 48.78; H, 4.06; N, 34.14. Found: C, 48.71; H, 4.12; N, 34.10%.

1-(3-Methyl-4*H*-pyrazolo[3,4-*d*]isoxazol-4-yl]-1-ethanone (**4**). This compound was obtained as colourless crystals; yield 85%, m.p. 128-130°C. IR: 1680 (C=O) cm^{-1}; ^{1}H NMR : δ 2.6 (s, 3H, CH_3), 2.8 (s, 3H, $COCH_3$), 7.8 (s, 1H, =CH); MS: m/z 165 (M^+).

Anal. Calcd. for $C_7H_7N_3O_2$: C, 50.09; H, 4.24; N, 25.45. Found C, 50.01; H, 4.19; N, 25.49%.

3-Methyl-4*H*-pyrazolo[3,4-*d*]isoxazol-4-yl(phenyl)methanone (**5a**). This compound was obtained as colourless crystals

m.p. 139-142°C. IR 1685 (C=O) cm^{-1}, ^1H NMR: δ 2.4 (s, 3H, CH_3), 7.0-8.0 (m, 5H, Ar-H), 8.2 (s, 1H, pyrazole-H), MS: m/z 227 (M^+).

Anal. Calcd. for $C_{12}H_9N_3O_2$: C, 63.43; H, 3.96; N, 18.50. Found C, 63.45; H, 3.98; N, 18.47%.

3-Methyl-4*H*-pyrazolo[3,4-*d*]isoxazol-4-yl-(*p*-tolyl)-methanone (**5b**). This compound was obtained as colourless crystals m.p. 145-147°C. IR 1680 (C=O) cm^{-1}, ^1H NMR: δ 2.4 (s, 3H, CH_3), 2.6 (s, 3H, CH_3), 7.0-8.0 (m, 4H, Ar-H), 8.2 (s, 1H, pyrazole H), MS: m/z 241 (M^+).

Anal. Calcd. for $C_{13}H_{11}N_3O_2$: C, 64.73; H, 4.56; N, 17.42. Found: C, 64.78; H, 4.50; N, 17.49%.

3-Methyl-4*H*-pyrazolo[3,4-*d*]isoxazol-4-yl-(*p*-methoxyphenyl)-methanone (**5c**). This compound was obtained as colourless crystals m.p. 123-125°C; IR 1680 (C=O) cm^{-1}, ^1H NMR: δ 2.3 (s, 3H, CH_3), 3.8 (s, 3H, OCH_3), 7.1-8.2 (m, 4H, Ar-H), 8.3 (s, 1H, pyrazole H); MS: m/z 257, (M^+).

Anal. Calcd for $C_{13}H_{11}N_3O_3$: C, 60.70; H, 4.28; N, 16.34. Found: C, 60.76; H, 4.34; N, 16.30%.

3-Methyl-4*H*-pyrazolo[3,4-*d*]isoxazol-4-yl-(*p*-chlorophenyl)-methanone (**5d**). This compound was obtained as colourless crystals m.p. 167-169°C; IR 1675 (C=O) cm^{-1}; ^1H NMR: δ 2.2 (s, 3H, CH_3), 7.1-8.1 (m, 4H, Ar-H), 8.1 (s, 1H, pyrazole-H); MS: m/z 261 (M^+).

Anal. Calcd. for $C_{12}H_9N_3O_2Cl$: C, 55.17; H, 3.06; N, 16.09. Found: C, 55.21; H, 3.1; N, 16.03%.

3-Methyl-4*H*-pyrazolo[3,4-*d*]isoxazol-4-yl-(*o*-chlorophenyl)-methanone (**5e**). This compound was obtained as colourless crystals m.p. 173-174°C. IR 1680 (C=O) cm^{-1}; ^1H NMR: δ 2.3 (s, 3H, CH_3), 7.0-7.9 (m, 4H, Ar-H), 8.2 (s, 1H, pyrazole-H); MS: m/z 261 (M^+).

Anal. Calcd. for $C_{12}H_8N_3O_2Cl$: C, 55.17; H, 3.06; N, 16.09. Found: C, 55.20; H, 3.01; N, 16.24%.

3-Methyl-4*H*-pyrazolo[3,4-*d*]isoxazol-4-yl-(2,4-dichlorophenyl)-methanone (**5f**). This compound was obtained as colourless crystals m.p. 181-184°C; IR 1675 (C=O) cm^{-1}; ^1H NMR: δ 2.4 (s, 3H, CH_3), 7.2-8.0 (m, 3H, Ar-H), 8.1 (s, 1H, pyrazole-H); MS: m/z 295 (M^+).

Anal. Calcd. for $C_{12}H_7N_3O_2Cl_2$: C, 48.81; H, 2.37; N, 14.23. Found: C, 48.87; H, 2.30; N, 14.25%.

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