A CONVENIENT AND NEW ONE-STEP SYNTHESIS OF 1H-IMIDAZOLE-2-CARBOXAMIDES

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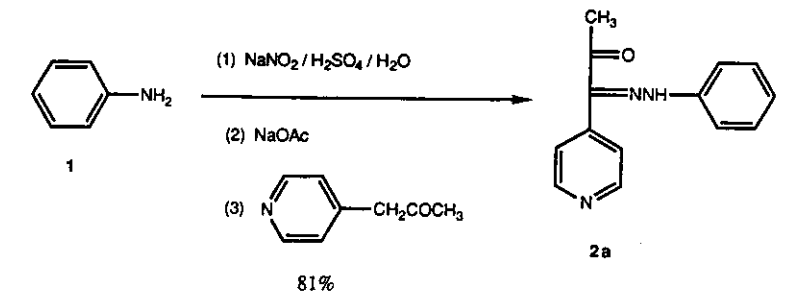
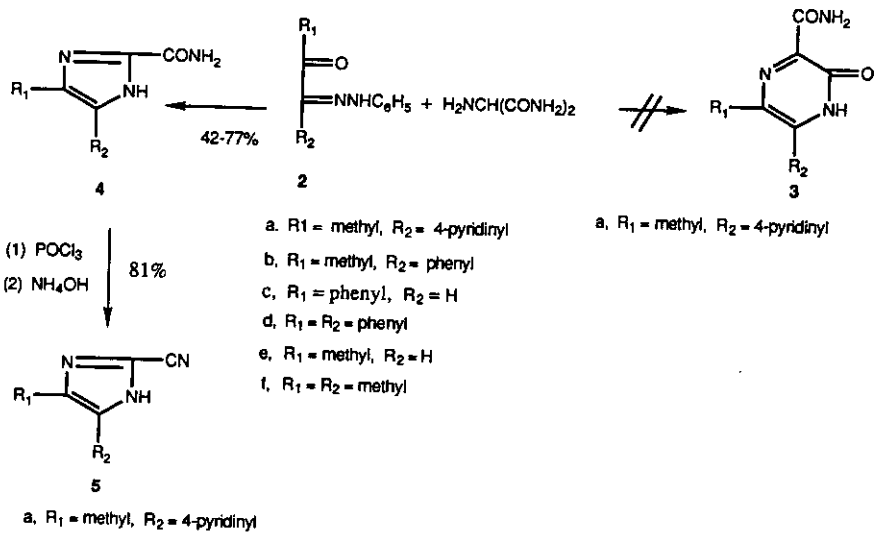
Abstract - 1,2-Diketone monophenylhydrazones (2) reacted with aminomalonamide in 1-methyl-2-pyrrolidinone to provide 1H-imidazole-2-carboxamides (4). The condensation of 1-(4-pyridinyl)-2-propanone with phenyldiazonium chloride gave 1-phenylhydrazono-1-(4-pyridinyl)-2-propanone (2a). 4-Methyl-5-(4-pyridinyl)-1H-imidazole-2-carboxamide (4a) was converted to the corresponding nitrile (5a) by the action of phosphorous oxychloride.

The imidazole nucleus is found in a variety of natural products such as vitamin B_{12} and its derivatives,[1] histidine derivatives,[2] as well as imidazole nucleosides and nucleotides.[3] It is also a key feature of cardiotonic agents such as pimobenden[4] and adibenden,[5] potential anti-tumor agents[6] and anti-ulcer agents.[7] Due to its high thermal stability, it also has been incorporated into high temperature polymers.[8] While there are numerous syntheses of imidazoles, few have wide general application.[9] Furthermore, a literature search failed to reveal a direct synthesis of 1H-imidazole-2-carboxamides which are useful intermediates for the preparation of imidazole-2-carboxylic acids and nitriles. This manuscript describes a convenient and novel one-step synthesis of 1H-imidazole-2-carboxamides from aminomalonamide and 1,2-diketone monophenylhydrazones.

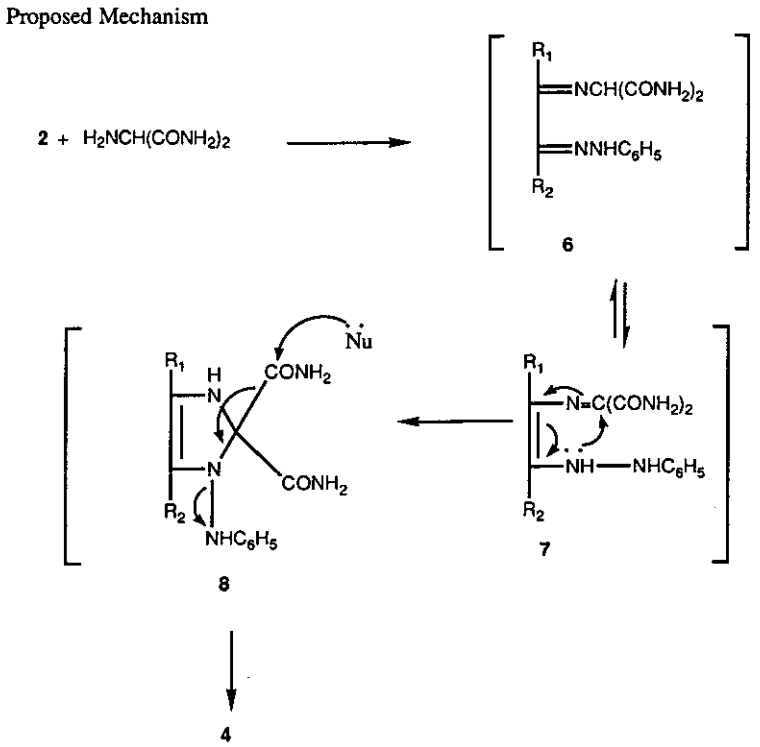
3,4-Dihydro-6-methyl-3-oxo-5-(4-pyridinyl)pyrazine-2-carboxamide (3a) was needed as an intermediate in one of the projects in our laboratory. Pyrazinonecarboxamides[10] and pyrazinones[11]

have been prepared by the condensation of 2-ketocarboxaldehydes with aminomalonamide and glycinamide, respectively. It seemed reasonable that a similar reaction between aminomalonamide and 1-phenylhydrazono-1-(4-pyridinyl)-2-propanone (**2a**) may result in the formation of **3a**. However, this reaction gave 4-methyl-5-(4-pyridinyl)-1H-imidazole-2-carboxamide (**4a**) instead of **3a**. The structure of **4a** is supported by its spectral data. The mass spectrum gave a strong peak at 203 (MH^+), ^{13}C nmr spectrum indicated ten carbon atoms, and ^1H nmr spectrum was consistent with the presence of -NH-, $-CONH_2$, methyl and 4-pyridinyl groups. The ir spectrum showed a primary amide group which was confirmed by the conversion of **4a** to nitrile (**5a**). This reaction was found to be general, and other 1,2-diketone monophenylhydrazones gave the corresponding 1H-imidazole-2-carboxamides in 42-77% yield.





Proposed Mechanism. The first step in the proposed mechanism for the formation of 4 involves the condensation of aminomalonamide with the keto group of 2 to form intermediate (6). The alternative tautomer (7) then undergoes cyclization to give intermediate (8) which in turn loses one of the carboxamide groups and the anilino group to yield 4.



In conclusion, the procedure described herein provides a convenient route to 1H-imidazole-2-carboxamides. Furthermore, it allows variation of the alkyl and aryl substituents in position 4 and 5.

EXPERIMENTAL

1-Phenylhydrazono-2-propanone was purchased from K&K Laboratories and other known 1,2-diketone monophenylhydrazones were prepared according to published procedures.[12] Melting points were determined in open capillaries in an oil bath and are uncorrected. The nmr

spectra were obtained on a Varian HA-100 spectrometer using tetramethylsilane as the internal standard, and chemical shifts are reported in parts per million and are given in δ units. Compounds (**4b-f**) were isolated by column chromatography on silica gel using diethyl ether to 10% methanol in diethyl ether as the eluent.

1-Phenylhydrazono-1-(4-pyridinyl)-2-propanone (2a): To a stirred mixture of aniline (9.3 g, 0.1 mol), concentrated sulphuric acid (7 ml, 0.13 mol), and water (100 ml) cooled in an ice-salt bath was added a solution of sodium nitrite (8.5 g, 0.12 mol) in water (35 ml) at 0-5°C over 20 min. The resulting orange solution was further stirred for 20 min and then treated with sodium acetate trihydrate (21.4 g, 0.13 mol). To the resulting solution was added 95% 1-(4-pyridinyl)-2-propanone[13] (15 ml, 0.12 mol). The resulting mixture was further stirred for 30 min and then the light orange product was collected, washed with water, and recrystallized from ethanol to give 19.5 g (81%) of **2a**: mp 215-217°C; ms m/z: 240 (MH^+); ^{1}H nmr (DMSO-d_6) δ: 11.18 (br s, 1H, NH), 8.70 (d, J=5.9 Hz, 2H, H-2, H-6 of pyridine), 7.44-6.91 (m, 7H, aromatic), 2.52 (s, 3H, CH_3). Anal. Calcd for $C_{14}H_{13}N_3O$: C, 70.28; H, 5.48; N, 17.56. Found: C, 70.18; H, 5.43; N, 17.38.

General Procedure. 4-Methyl-5-(4-pyridinyl)-1H-imidazole-2-carboxamide (4a). A stirred mixture of **2a** (21 g, 0.08 mol), aminomalonamide (18 g, 0.16 mol), and 1-methyl-2-pyrrolidinone (100 ml) was heated on a steam bath for 48 h and then more aminomalonamide (9 g, 0.08 mol) was added and the resulting mixture was heated for 24 h more. Next, the insoluble material was filtered off and washed with hot methanol (300 ml). This solid was discarded and the filtrate was concentrated to near dryness under reduced pressure to give a brown solid which was treated with boiling water (300 ml) and the resulting mixture was cooled to room temperature. The tan solid was collected and recrystallized from methanol to afford 11.9 g (74%) of light tan crystals of **4a**: mp 278-280°C; ms m/z: 203 (MH^+); ^{1}H nmr (DMSO-d_6) δ: 13.15 (br s, 1H, -NH-), 7.85 (s, 1H, $CONH_2$), 8.55, 7.72 (A_2B_2, J=5.5 Hz, 4H, -C_5H_4N), 7.55 (s, 1H, -$CONH_2$), 2.51 (s, 3H, CH_3); ^{13}C nmr (DMSO-d_6) δ: 160.04 ($CONH_2$), 149.74 (C-2, C-6 of pyridine), 141.91, 139.73, 133.60, 129.74, 120.17 (C-3, C-5 of pyridine), 11.48 (CH_3); ir (KBr) 1664 cm^{-1} ($CONH_2$). Anal. Calcd for $C_{10}H_{10}N_4O$: C, 59.40; H, 4.98; N, 27.71. Found: C, 59.27; H, 4.89; N, 27.59.

4-Methyl-5-phenyl-1H-imidazole-2-carboxamide (4b): yield 77%; mp 238-240°C (EtOH); ms m/z: 202 (MH^+); ^1H nmr (CF_3CO_2D) δ: 7.66 (s, 5H, C_6H_5), 2.68 (s, 3H, CH_3). Anal. Calcd for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.43; H, 5.40; N, 20.87.

4-Phenyl-1H-imidazole-2-carboxamide (4c): yield 51%; mp 208-211°C (i-PrOH) (lit.[14], mp 211-212°C); ms m/z: 188 (MH^+); ^1H nmr (CF_3CO_2D) δ: 7.88 (s, 1H, 5-H), 8.01-7.50 (m, 5H, C_6H_5).

4,5-Diphenyl-1H-imidazole-2-carboxamide (4d): yield 71%; mp 248-250°C (i-PrOH) (lit.[14], mp 250-253°C); ms m/z: 264 (MH^+); ^1H nmr (CF_3CO_2D) δ: 7.56 (m, 2xC_6H_5).

4-Methyl-1H-imidazole-2-carboxamide (4e): yield 42%; mp 249-251°C (i-PrOH); ms m/z: 126 (MH^+); ^1H nmr (CF_3CO_2D) δ: 7.44 (s, 1H, 5-H), 2.57 (s, 3H, CH_3). Anal. Calcd for $C_5H_7N_3O$: C, 47.99; H, 5.64; N, 33.58. Found: C, 47.74; H, 5.63; N, 33.29.

4,5-Dimethyl-1H-imidazole-2-carboxamide (4f): yield 46%; mp 296-298°C (EtOH); ms m/z: 140 (MH^+); ^1H nmr (DMSO-d_6) δ: 12.43 (br s, 1H, -NH-), 7.49 (s, 1H, $CONH_2$), 7.18 (s, 1H, $CONH_2$), 2.10 (s, 3H, CH_3), 2.04 (s, 3H, CH_3). Anal. Calcd for $C_6H_9N_3O$: C, 51.79; H, 6.52; N, 30.20. Found: C, 51.68; H, 6.48; N, 30.22.

4-Methyl-5-(4-pyridinyl)-1H-imidazole-2-carbonitrile (5a). A stirred mixture of **4a** (5 g, 24.7 mmol) and phosphorous oxychloride (300 ml, 3.22 mol) was heated under reflux for 7 h to give a brown solution. After cooling to room temperature, the unreacted phosphorous oxychloride was removed under reduced pressure. The residue was quenched with ice and treated with concentrated aqueous ammonia until slightly basic. The resulting mixture was acidified with acetic acid. The resulting brown precipitate was collected, washed with water, and recrystallized from methanol after charcoal treatment to yield 3.5 g (81%) of light orange crystals of **5a**: mp 283-285°C (decomp.); ms m/z: 185 (MH^+); ^1H nmr (CF_3COOD) δ: 8.94, 8.43 (A_2B_2, J=5.6 Hz, 4H, C_5H_4N), 2.82 (s, 3H, CH_3); ir (KBr) 2230 cm^{-1} (CN). Anal. Calcd for $C_{10}H_8N_4$: C, 65.21; H, 4.38; N, 30.42. Found: C, 65.30; H, 4.41; N, 30.45.

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