Reactivity Of 4,6-Dimethyl-2-Oxo-5-(Phenyldiazenyl)-1,2-Dihydropyridine-3-Carbonitrile Towards Some Carbon Electrophiles

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Abstract: The present study aimed to investigate the reactivity of 4,6-Dimethyl-2-oxo-5-(phenyldiazenyl)-1,2-dihydropyridine-3-carbonitrile **(1)** towards some carbon electrophiles. Electrophilic reaction of **1** with allyl / propargyl bromides and epichlorohydrine in presence of mild base (K_2CO_3) gave the corresponding N-alkylated derivatives **3-5**, respectively and not O-analogues **3'-5'**. Furthermore, reaction of **1** with 4-acetoxybutyl bromide, 2-acetoxyethoxymethyl bromide, 3-chloropropanole and 1,3-dicloroisopropanole in presence of K_2CO_3 gave the corresponding N-acyclonucleosides **6-9,** respectively. Although, the same results were obtained at using strong base NaH. Carring out the mannich reaction on the starting pyridine derivative **1** confirmed the N-regioselectively of the reaction. The structural assignments of new compounds were based on their elemental analysis and spectral (IR, ^{1}H NMR and ^{13}C NMR) data.

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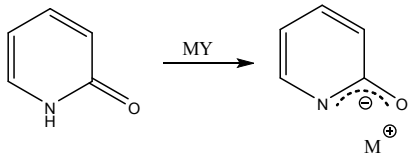
Introduction

The alkylation of 2-pyridone have received great attention from many chemists [1-6]. However the majority of the literature data on the alkylation of pyridin-2-(1*H*)-one indicates three products (*N*, *O*-alkylation or mixture). There is some factors effect on this selectivity; according to the literature [4] the presence of the powerful electron-withdrawing groups at pyridine ring directs the regioselective formation of *O*-alkylated products by inducing a higher charge density on the oxygen than on the nitrogen. While electron donating group directs the regioselectivity formation of *N*-alkylated products by inducing a higher charge density on the ring and subsequence give the N-products. Although we found these results in our previous literature [1,2], additionally, the steric factor at 6 position effect on the regioselectivty of the alkylation of pyridin-2(1*H*)-one derivatives. Mannich reaction is a three-component condensation reaction involving active hydrogen containing compound, formaldehyde and a secondary amine [7]. The aminomethylation of aromatic substrates by Mannich reaction is of considerable importance for the synthesis and modification of biologically active compounds [8], although the Mannich reaction is one chemical methods to prove the regioselectivity of alkylation process,[9] and in continuation of our study program in the chemistry of 2-pyridones [1-3], i report herein the behavior of 4,6-dimethyl-2(1*H*)-pyridone towards some carbon electrophiles.

Results and Discussion

The pyridin-2(1*H*)-one in general react with metal salts to form ambident anion, which form two isomeric products in its reaction with electrophilic reagents (*N*-substituted, *O*-substituted derivatives or mixture) (Fig. 1).

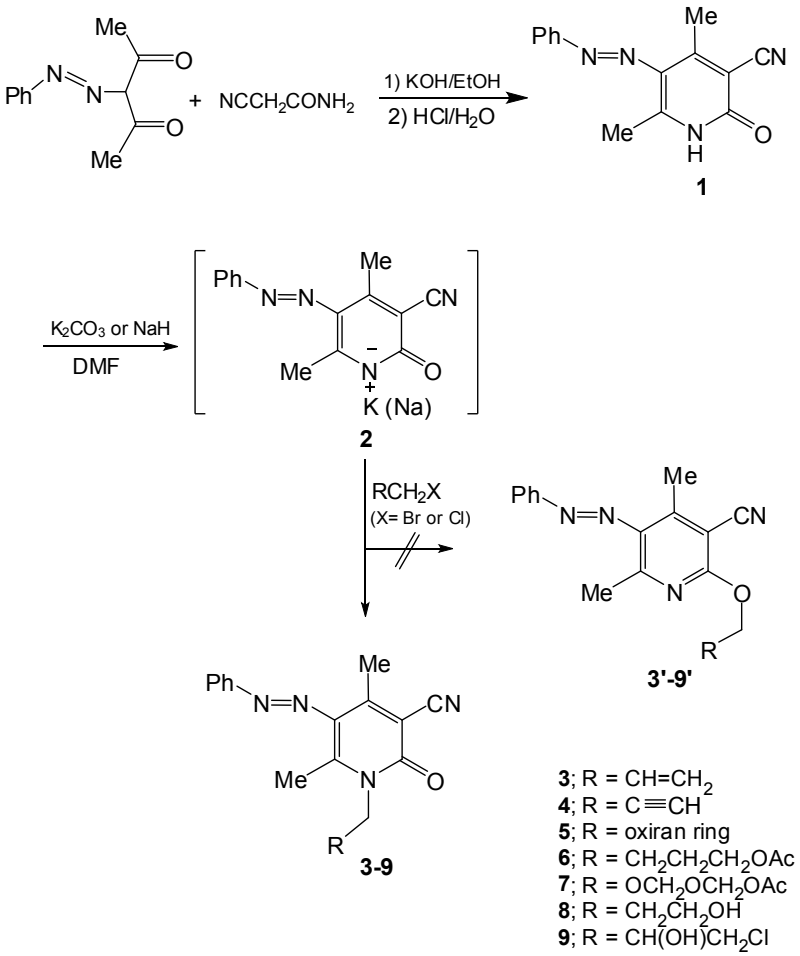


M = K, Y = CO_3
M = Na, Y = H

Fig. 1: Formation of ambident anion of pyridin-2(1*H*)-one

The alkylation reaction of the pyridin-2(1*H*)-one derivatives **1** was discussed in the present work considering different alkylating reagents, using 4,6-Dimethyl-2-oxo-5-(phenyldiazenyl)-1,2-dihydropyridine-3-carbonitrile **(1)** as starting material. It was prepared in analogy to the method described before [10] by reaction of 3-(phenyldiazenyl)pentane-2,4-dione with cyanoacetamide in presence of potassium hydroxide followed by neutralization with hydrochloric acid. Reaction of pyridin-2(1*H*)-one derivatives **1** with some alkylating agent, namely, allyl / propargyl bromide and epichlorohydrine in presence of potassium carbonate as mild base in DMF

afforded the corresponding *N*-alkylating derivatives **3-5** and not O-analogues **3'-5'** (Scheme 1). The IR spectra of compounds **3-5** showed the characteristic peaks for the amidic carbonyl (C=O) in between 1650-1651 cm^{-1}, which confirmed that the alkylation occurred regioselectivity on the nitrogen atom and not on the oxygen, while the C≡N and N=N peaks appeared in between 2215-2226 cm^{-1} and 1556-1558 cm^{-1}, respectively. The ^{1}H and ^{13}C NMR spectra of compounds **3-5** are agreement with the structure (see the experimental part).



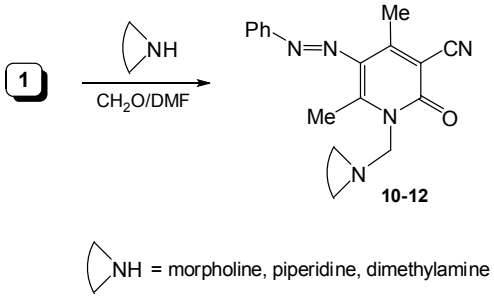
Scheme 1: *N*-Alkylation of pyridin-2(1*H*)-one dreivative **1**.

The reaction of **1** with one equivalent of 4-acetoxybutyl bromide [11], 2-acetoxyethoxymethyl bromide [11], 3-chlorobutanol and 1,3-dichloroisopropanol as precursor for the synthesis of acyclic nucleoside **6-9,** took place in the presence of anhydrous potassium carbonate in DMF to give the *N*-acyclic nucleoside analogous **6-9** and not the *O*-derivatives **6'-9'** in 66–80% yield (Scheme 1). More efficiently, carrying out the same reaction in the presence of sodium hydride as a catalyst in anhydrous DMF provided the same *N*-products **6-9** but in higher yields (85-88%) within short time (3–5 hours) with no change in regioselectivity (Scheme 1). The IR spectrum of compounds **6-9** showed absorption bands in between 1641-1650 cm^{-1} corresponding to the amidic carbonyl (C=O), which provided the formation of *N*-acyclic nucleoside derivatives and not the *O*-derivatives. The ^{1}H NMR spectra of nucleoside **6-8** showed two triplet and one singlet signals at 3.23, 3.87 and 5.39 ppm, corresponding to H-1' in compounds **6,8** and **7**, respectively. While the H-1' and H-1" protons in compound **9** appeared as two doublet of doublet at 3.42 and 3.68 ppm with coupling constatant 5.49, 5.81 and 11.61 Hz, respectively.

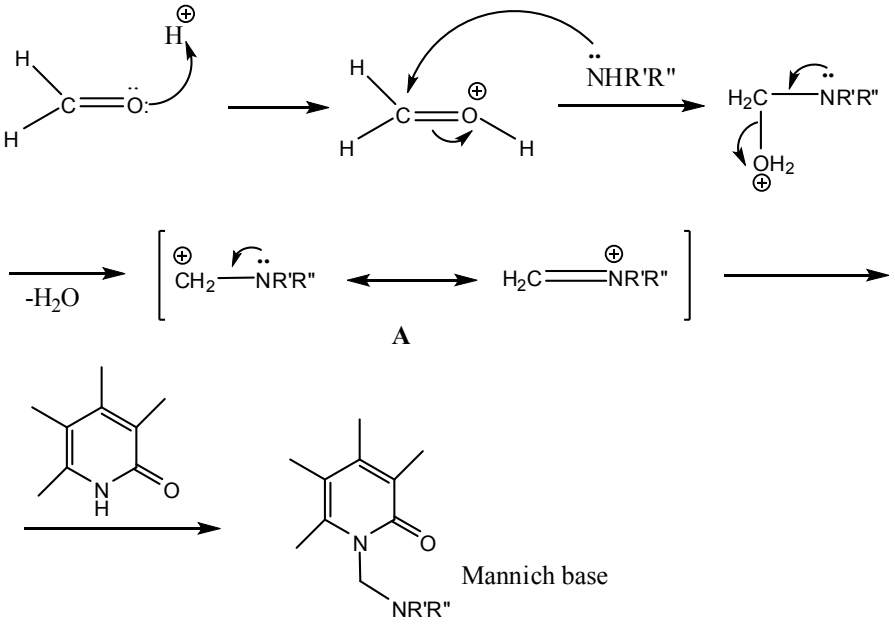
Transformation of 4,6-dimethylpyridine derivative **1** into mannich bases is important reaction to confirm the regeioselectivety of the previous alkylation reactions at nitrogen atom and not the

oxygen atom. The one pot multi-component Mannich reaction involving pyridine derivative **1**, formaldehyde and secondary amines (namely morpholine, pipridine and dimethylamine) in DMF to give the corresponding Mannich bases derivatives **10-12** in good yield (89-92%) **(**Scheme 2). The IR spectra of compounds **10-12** showed an absorption bands at 1633-1644 cm^{-1} corresponding to the amidic carbonyl (C=O).

The condensation can occur by the reaction of the secondary amine with formaldehyde to give condensation product **(A)**, which attacks the substrated pyridine to give the corresponding Mannich bases as shown in Scheme 3.



Scheme 2: Mannich reaction of pyridin-2(1*H*)-one dreivative **1**.



Scheme 3: The proposed mechanism of Mannich reaction.

In summary, the reaction of 2-pyridone with some carbon electrophiles gave the *N*-isomer, which may be attributed to the presence of two electron-donating and small sized methyl groups at 4 and 6 positions. The regioselectivity of this reaction was proofed by formation of mannich bases and comparing the spectroscopic data of the products.

Experimental

All melting points are uncorrected and were measured using an Electro thermal IA 9100 apparatus. TLC was performed on Merck Silica Gel 60F254 with detection by ultraviolet (UV) light. The IR spectra (KBr disc) were recorded on a Pye Unicam Sp-3-300 or a Shimadzu FTIR 8101 PC infrared spectrophotometer. The operation frequency was 300 MHz for ^{1}H and 75.5 MHz for ^{13}C NMR using JOEL-JNM-LA 300 MHz spectrometer. The coupling constants (J) are given in hertz. The chemical shifts are expressed on the δ (ppm) scale using TMS as the standard reference. Elemental analyses were determined on a Perkin Elmer 240 (microanalysis; Cairo University, Cairo, Egypt).

General Procedure For Alkylation Of Pyridin-2(1*H*)-One (1)

Method A:

A mixture of pyridin-2(1*H*)-one **1** (0.01 mol) and potassium carbonate (0.01 mol) was stirred in dry DMF (15 mL) for 1 hour; then the alkylating agent (0.011 mol) was added. The reaction mixture was stirred for overnight at room temperature, heated for 2-5 h, filtered off, and the solvent was evaporated

under reduced pressure. The residue was dried and crystallized from ethanol.

Method B:

A mixture of pyridin-2(1*H*)-one **1** (0.01 mol) and sodium hydride (0.011 mol) was stirred in dry DMF (15 mL) for 15 minutes; then the alkylating agent (0.011 mol) was added. The reaction mixture was stirred for 3-5 hours at room temperature and the solvent was evaporated under reduced pressure. The residue was extracted with methylene chloride and crystallized from ethanol.

1-Allyl-4,6-dimethyl-2-oxo-5-(phenyldiazenyl)-1,2-dihydropyridine-3-carbonitrile (3)

Method **A**: yield 88%. Orange crystals, mp 112-114ºC. IR (KBr, cm^{-1}): 2217 (C≡N), 1650 (C=O, amide), 1556 (N=N). ^{1}H NMR (DMSO-d_6, δ ppm): δ = 2.56 (s, 3H, CH_3), 2.69 (s, 3H, CH_3), 4.85 (d, 2H, *J* = 5.23 Hz, H-1'), 5.12 (d, 1H, *J* = 10.62 Hz, H-3'), 5.46 (d, 1H, *J* = 17.80 Hz, H-3"), 6.15 (m, 1H, H-2'), 7.50-7.82 (m, 5H, Ph-H). ^{13}C NMR (DMSO-d_6, δ ppm): δ = 18.55 23.09 (2CH_3), 62.1 (C-1'), 110.2 (C-3'), 116.3 (C≡N), 119.0 (C-2'), 125.2, 126.7, 128.0, 128.4, 132.5, 142.8, 151.0, 156.1 and 163.8 (Ar-C, and C=O). Anal. Calcd for $C_{17}H_{16}N_4O$ (292.34): C, 69.85; H, 5.52; N, 19.17. Found: C, 69.81; H, 5.55; N, 19.24.

4,6-Dimethyl-2-oxo-5-(phenyldiazenyl)-1-(prop-2-ynyl)-1,2-dihydropyridine-3-carbonitrile (4)

Method **A**: yield 85%. Orange crystals, mp 76-78ºC. IR (KBr, cm^{-1}): 2226 (C≡N), 1651 (C=O, amide), 1557 (N=N). ^{1}H NMR (DMSO-d_6, δ ppm): δ = 2.56 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 3.79 (t, 1H, *J* = 1.76 Hz, H-3'), 4.92 (dd, 2H, *J* = 1.76, 11.31 Hz, H-1'), 7.49-7.80 (m, 5H, Ph-H). Anal. Calcd for $C_{17}H_{14}N_4O$ (290.32): C, 70.33; H, 4.86; N, 19.30. Found: C, 70.28; H, 4.83; N, 19.34.

4,6-Dimethyl-1-(oxiran-2-ylmethyl)-2-oxo-5-(phenyldiazenyl)-1,2-dihydropyridine-3-carbonitrile (5)

Method **A**: yield 73%. Orange syrup, IR (KBr, cm^{-1}): 2215 (C≡N), 1650 (C=O, amide), 1568 (N=N). ^{1}H NMR (DMSO-d_6, δ ppm): δ = 2.55 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 2.85 (m, 1H, H-3'), 2.93 (m, 1H, H-3"), 4.26-4.38 (m, 2H, H-2' & H-1'), 5.01 (m, 1H, H-1"), 7.49-7.81 (m, 5H, Ph-H). Anal. Calcd for $C_{17}H_{16}N_4O_2$ (308.33): C, 66.22; H, 5.23; N, 18.17. Found: C, 66.16; H, 5.28; N, 18.21.

4-(3-Cyano-4,6-dimethyl-2-oxo-5-(phenyldiazenyl)pyridin-1(2H)-yl)butyl acetate (6)

Method **A**: yield 80%; method **B**: yield 88%. Orange crystals, mp 68-70ºC. IR (KBr, cm^{-1}): 2224 (C≡N), 1736 (C=O, acetoxy), 1650 (C=O, amide), 1556 (N=N). ^{1}H NMR (DMSO-d_6, δ ppm): δ = 1.61 (m, 2H, H-2'), 1.68 (m, 2H, H-3'),1.98 (s, 3H, CH_3CO), 2.55 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 3.23 (t, 2H, *J* = 5.18 Hz, H-1'), 4.31 (t, 2H, *J* = 5.64 Hz, H-4'), 7.49-7.82 (m, 5H, Ph-H). Anal. Calcd for $C_{20}H_{22}N_4O_3$ (366.41): C, 65.56; H, 6.05; N, 15.29; Found: C, 65.53; H, 6.11; N, 15.34.

2-((3-Cyano-4,6-dimethyl-2-oxo-5-(phenyldiazenyl)pyridin-1(2H)-yl)methoxy)ethyl acetate (7)

Method **A**: yield 78%; method **B**: yield 86%. Orange syrup, IR (KBr, cm^{-1}): 2215 (C≡N), 1733 (C=O, acetoxy), 1641 (C=O, amide), 1567 (N=N). ^{1}H NMR (DMSO-d_6, δ ppm): δ = 2.01 (s, 3H, CH_3CO), 2.56 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 4.12 (t, 2H, J = 5.7 Hz, H-3'), 4.51 (t, 2H, J = 5.7 Hz, H-4'), 5.39 (s, 2H, H-1'), 7.51-7.82 (m, 5H, Ph-H). Anal. Calcd for $C_{19}H_{20}N_4O_4$ (368.39): C, 61.95; H, 5.47; N, 15.21; Found: C, 61.89; H, 5.44; N, 15.27.

1-(3-Hydroxypropyl)-4,6-dimethyl-2-oxo-5-(phenyldiazenyl)-1,2-dihydropyridine-3-carbonitrile (8)

Method **A**: yield 66%; method **B**: yield 85%. Orange crystals, mp 143-145ºC. IR (KBr, cm^{-1}): 2218 (C≡N), 1644 (C=O, amide), 1564 (N=N). ^{1}H NMR (DMSO-d_6, δ ppm): δ = 1.90 (m, 2H, H-2'), 2.55 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 3.87 (t, 2H, H-1'), 4.92 (t, 2H, H-3'), 4.56 (t, 1H, OH), 7.51-7.82 (m, 5H, Ph-H). Anal. Calcd for $C_{17}H_{18}N_4O_2$ (310.35): C, 65.79; H, 5.85; N, 18.05. Found: C, 65.83; H, 5.81; N, 18.10.

1-(3-Chloro-2-hydroxypropyl)-4,6-dimethyl-2-oxo-5-(phenyldiazenyl)-1,2-dihydropyridine-3-carbonitrile (9)

Method **A**: yield 67%; method **B**: yield 85%. Orange crystals, mp 105-107ºC. IR (KBr, cm^{-1}): 2220 (C≡N), 1649 (C=O, amide), 1569 (N=N). ^{1}H NMR (DMSO-d_6, δ ppm): δ = 2.56 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 3.42 (dd, 1H, J = 5.49, 11.61 Hz, H-1'), 3.68 (dd, 1H, J = 5.81, 11.61 Hz, H-1"), 3.96 (m, 1H, H-3'), 4.15 (m, 1H, H-3"), 4.36 (m, 1H, H-2'), 4.43 (t, 1H, OH), 7.50-7.82 (m, 5H, Ph-H). Anal. Calcd for $C_{17}H_{17}ClN_4O_2$ (344.80): C, 59.22; H, 4.97; Cl, 10.28; N, 16.25. Found: C, 59.27; H, 5.03; N, 16.29.

General synthetic procedure for Mannich bases (10-12): A mixture of pyridine-2(1*H*)-one **1** (0.01 mol), morpholine, piperidine or dimethylamine (0.015 mol) and formaldehyde (1 mL, 37%) in DMF was stirred at room temperature for 3 h. then 20 mL of cooled water was added and keep the reaction mixture in refrigerator for overnight. The formed solid was filtered off, dried and recrystalysed from ethanol.

4,6-Dimethyl-1-(morpholinomethyl)-2-oxo-5-(phenyldiazenyl)-1,2-dihydropyridine-3-carbonitrile (10)

Orange crystals, yield 92%. mp 137-139ºC. IR (KBr, cm^{-1}): 2223 (C≡N), 1644 (C=O, amide), 1589 (N=N). ^{1}H NMR (DMSO-d_6, δ ppm): δ = 2.43 (t, 4H, J = 5.13 Hz, 2NC$\underline{H}_2$-morpholine), 2.55 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 3.71 (t, 4H, J = 5.13 Hz, 2OC$\underline{H}_2$-morpholine), 5.16 (s, 2H, N-CH_2-N), 7.50-7.81 (m, 5H, Ph-H). ^{13}C NMR (DMSO-d_6): δ = 18.56 (CH_3),

23.10 (CH_3), 51.92, 66.3 (4$\underline{C}H_2$-morpholine), 80.1 (N-CH_2-N), 107.6, 115.6 (C≡N), 118.2, 126.8, 128.4, 132.5, 140.2, 150.3, 155.3 and 162.4 (Ar-C and C=O). Anal. Calcd for $C_{19}H_{21}N_5O_2$(351.40): C, 64.94; H, 6.02; N, 19.93.

Found: C, 64.88; H, 6.05; N, 19.89.

4,6-Dimethyl-2-oxo-5-(phenyldiazenyl)-1-(piperidin-1-ylmethyl)-1,2-dihydropyridine-3-carbonitrile (11)

Orange crystals, yield 90%. mp 110-112ºC. IR (KBr, cm^{-1}): 2210 (C≡N), 1633 (C=O, amide), 1557 (N=N). ^{1}H NMR (DMSO-d_6, δ ppm): δ = 1.52-1.59 (m, 6H, 3C$\underline{H}_2$-piperidine), 2.55 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 2.68 (t, 4H, J = 5.01 Hz, 2NC$\underline{H}_2$-piperidine), 4.53 (s, 2H, N-CH_2-N), 7.50-7.81 (m, 5H, Ph-H). Anal. Calcd for $C_{20}H_{23}N_5O$ (349.43): C, 68.74; H, 6.63; N, 20.04.

Found: C, 68.77; H, 6.61; N, 20.01.

1-((dimethylamino)methyl)-4,6-dimethyl-2-oxo-5-(phenyldiazenyl)-1,2-dihydropyridine-3-carbonitrile (12)

Orange crystals, yield 89%. mp 140-142ºC. IR (KBr, cm^{-1}): 2206 (CN), 1639 (C=O, amide), 1567 (N=N). ^{1}H NMR (DMSO-d_6, δ ppm): δ = 2.29 (s, 3H, NCH_3), 2.45 (s, 3H, NCH_3), 2.55 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 4.53 (s, 2H, N-CH_2-N), 7.49-7.80 (m, 5H, Ph-H). Anal. Calcd for $C_{17}H_{19}N_5O$ (309.37): C, 66.00; H, 6.19; N, 22.64 Found: C, 65.97; H, 6.22; N, 22.69.

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