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ONE POT SYNTHESES OF SUBSTITUTED NAPHTHYRIDINES AND 2*H*-PYRANO[3,2-*g*]QUINOLIN-2-ONES IN WATER

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Abstract-One pot catalytic syntheses of substituted 1,8-naphthyridines and 2*H*-pyrano[3,2-*g*]quinolin-2-ones by the reaction of α-ketoalkynes with 6-aminonicotinamide and 7-amino-4-methylcoumarin respectively in water, using a homogeneous nickel catalyst at very mild reaction conditions are described. In the absence of this catalytic system very low yields are obtained even after long reaction time.

INTRODUCTION

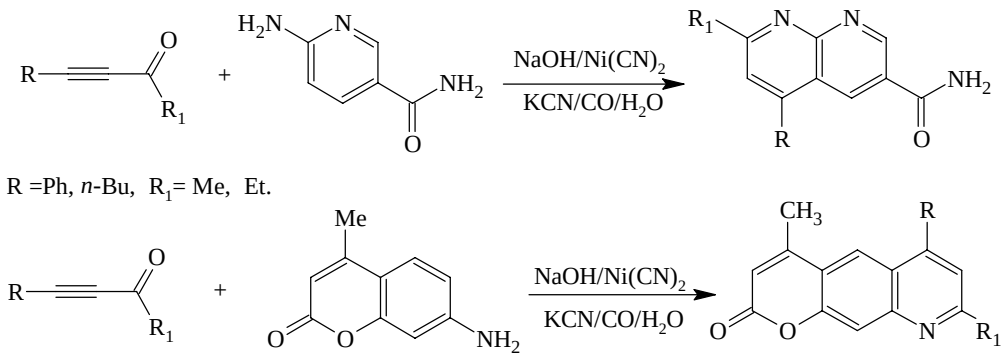
Due to the interesting biological and pharmacological activities[1-4] of 1,8-naphthyridines and 2*H*-pyrano[3,2-*g*]quinolin-2-ones derivatives, there is a growing interest in the synthesis of these heterocyclic systems. However the traditional syntheses usually involve multi step reaction sequences and/or stringent reaction conditions (*e.g.* high temperatures or long reaction times), low yields and use of organic solvents are common in these methods.[5-9]

Recently our group has reported[10] that active catalytic, an anionic specie of nickel Ni (0), induced carbonylation, hydrocyanation, heterocyclization and cyclocondensation reactions of propargylic compounds.[11-14] Here we report the simple one step syntheses of naphthyridines and quinolin-2-ones derivatives *via* the reaction of substituted α-ketoalkynes with 6-aminonicotinamide and 7- amino-4-methylcoumarin respectively using the named Ni(0) promotor.

RESULTS AND DISCUSSION

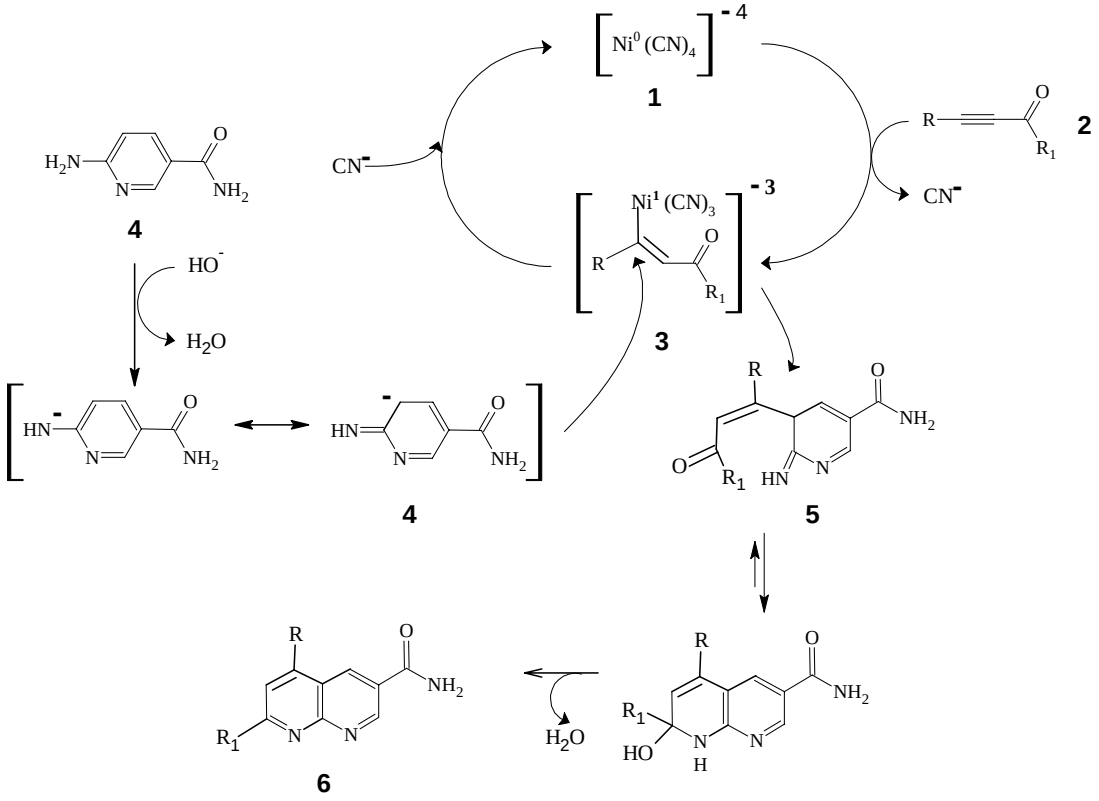
The reaction is performed in mild reaction conditions using a basic medium containing potasium cyanide under carbon monoxide atmosphere and room temperature, which provides naphthyridines and quinolinones in good yields. The general reactions are shown in Scheme I and the results obtained are shown in the Table I.

The reactions were also performed in the absence of the catalytic system and very low yields (< 10%) were obtained even after 48 h. However in the presence of the nickel catalyst, the reactions complete in less than 30



Scheme I

min with moderate to good yields (60-80%). Our group have previously reported[10] that alkaline solution of $Ni(CN)_2$ in the presence of CO, attains an equilibria which involve different carbonylic species in the solution. The addition of an excess of KCN in the media yield, an active anionic specie$[Ni(CN)]^{-4}$. In Scheme II, a tentative mechanism in case of naphthyridines can be proposed, which involves in the first step, the Michael-type attack of a nickel(0) anionic active species$[Ni(CN)]^{-4}$ (**1**) onto the triple bond of the α-ketoalkyne (**2**) according previous reports.[11,14]

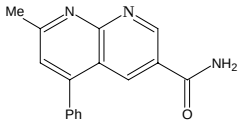
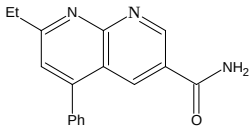
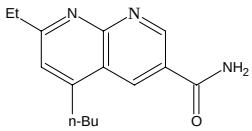
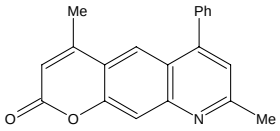
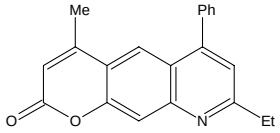
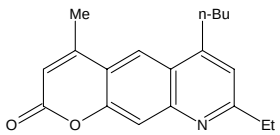


Scheme II

The resulting activated double bond species (**3**) is further attacked by the C-nucleophilic moiety generated in the basic media intermediate (**4**), *via* an addition-elimination mechanism, the sequence regenerates the catalyst,

and affords the ketoamine adduct (**5**). Finally a tautomeric equilibria followed by a dehydration step transform species (**5**) into the fused pyridine bicycle (**6**).

TABLE I: Reaction of substituted α-ketoalkynes with 6-aminonicotinamide and 7-amino-4-methylcoumarin[a]

α-ketoalkynes R	R_1	Compound	Reaction time	Yield (%)
Ph	Me		30 min	82
Ph	Et		30 min	83
n-Bu	Et		30 min	80
Ph	Me		30 min	60
Ph	Et		30 min	65
n-Bu	Et		30 min	62

a- Reaction conditions: Ketoalkyne (10 mmol), 6-aminonicotinamide and 7-amino-4-methylcoumarin (10 mmol), 5M NaOH (50 mL), KCN (15 mmol), bubling of CO 1 L/h, $Ni(CN)_2$ (2 mmol)

CONCLUSIONS

The nickel catalyzed pyridine annelation method here reported provides an easy access to synthesize substituted 1,8-naphthyridines and 2*H*-pyrano[3,2-*g*]quinolin-2-ones.The reaction is remarkably fast and gives good yields

of products. A nickel(0) anionic species seems to be the active catalytic species. The easy availability of substituted α-ketoalkynes, 6-aminonicotinamide and 7-aminocoumarin (or similar heterocycles) rends this nickel catalyzed route very attractive.

EXPERIMENTAL

6-Aminonicotinamide and 7-amino-4-methylcoumarin were purchased from Aldrich. Alkynyl ketones were prepared according to a previous published method.[15] ^{1}H and ^{13}C NMR spectra were recorded on a JEOL GX3 00 instrument, 300 MHz for ^{1}H and 75.5 MHz for ^{13}C using Me_4Si as an internal reference and $CDCl_3$ as solvent at 25°C. IR spectra were recorded in KBr pellets on a Nicolet FT 5SX spectrophotometer. MS spectra were obtained using a JEOL JMS-AX505 HA spectrometer. Elemental analyses were performed by Galbraith Laboratory at Knoxville TN. USA. The reaction products were quantified by GC in a Hewlett Packard 5890 analyzer with a HP 225 (10 m x 0.53 mm) packed column.

Preparation of the catalytic system

A stirred solution of 5 N NaOH (25 mL) was saturated with CO by slow bubbling of carbon monoxide at rt for a few min. To this solution was then added 2 mmol of $Ni(CN)_2$ and the stirring was continued under CO atmosphere for 2 h, yielding a yellowish green suspension. The addition of 15 mmol of KCN resulted in an orange colored solution.

Synthesis of naphthyridine and 2*H*-pyrano[3,2-*g*]quinolin-2-ones

A typical experiment procedure: After stirring for 0.5 h, to the orange colored solution of the catalyst prepared as mentioned above, the corresponding α-ketoalkyne (10 mmol) and the 6-aminonicotinamide or 7-amino-4-methyl-coumarin were added (10 mmol). The progress of the reaction was followed by TLC and at the end of the reaction, ethyl acetate was used to extract the product. After the usual workup, the organic solvent was remove at reduced pressure in a rotary evaporator to give the crude product which were purified by crystallization with ethyl acetate.

7-Methyl-5-phenyl-1,8-naphthyridine-3-carboxamide.

The product was obtained as described in the general procedure in a 82% as white solid, mp > 275 °C. MS EI: m/z = 263; IR (KBr, selected, cm^{-1}) 3373 (N-H), 1696 (C=O), 1625 (C=C), 1452 (C=N); ^{1}H-NMR δ_H: 7.92 (1H, s, CH), 7.69 (1H, s, CH), 7.21 (1H ,s, CH), 7.10 (5H, m, Ar), 2.88 (3H, s, CH_3); ^{13}C-NMR δ_C 205.5 (C_{11}), 170.4 (C_7), 159.1 (C_2), 149.8 (C_9), 145.3 (C_5), 137.4 (C_{12}), 133.7 (C_4), 131.7 (C_3), 128.5 (C_{14} and C_{16}), 128.2 (C_{15}), 127.4 (C_6), 123.6 (C_{13} and C_{17}), 120.9 (C_{10}), 28.5 (C_{18}). Anal. Calcd for $C_{16}H_{13}N_3O$: C, 72.99; H, 4.98; N, 15.96. Found: C, 73.20; H, 4.82; N, 15.89.

7-Ethyl-5-phenyl-1,8-naphthyridine-3-carboxamide.

Yield = 83%, pale yellow solid, mp > 275 °C. MS EI: m/z = 277; IR (KBr, selected cm^{-1}) 3356 (N-H), 1707 (C=O), 1606 (C=C), 1426 (C=N); ^{1}H-NMR δ_H: 7.85 (1H, s, CH), 7.40 (1H, s, CH), 7.33 (1H, s, CH), 7.21 (5H, m, 5H, Ar), 1.92 (2H, q, *J* = 7.25 Hz, CH_2), 1.10 (3H, t, *J* = 7.25 Hz, CH_3); ^{13}C-NMR δ_C: 205.8 (C_{11}), 170.5

(C_7), 159.0 (C_2), 149.7 (C_9), 145.0 (C_5), 137.2 (C_{12}), 134.6 (C_4), 131.2 (C_3), 128.5 (C_{14} and C_{16}), 128.0(C_{15}), 127.2 (C_6), 123.6 (C_{13} and C_{17}) 120.8 (C_{10}), 31.2 (C_{18}), 28.6 (C_{19}). Anal. Calcd for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.32; H, 5.54; N, 14.97.

5-Butyl-7-ethyl-1,8-naphthyridine-3-carboxamide.

Yield = 80%, brown solid, m.p > 275 ^oC. MS EI: m/z = 257; IR (KBr, selected cm^{-1}) 3352 (N-H), 1687 (C=O), 1612 (C=C), 1432 (C=N); ^{1}H-NMR δ_H: 7.78 (1H, s, CH), 7.67 (1H, s, CH), 7.57 (1H, s, CH), 7.10 (5H, m. Ar) 2.11 (2H, m, CH_2), 1.80 (2H, q, *J* = 7.25 Hz, CH_2), 1.61 (2H, m, CH_2), 1.42 (2H, m, CH_2), 1.21 (3H, t, *J* = 7.25 Hz, CH_3), 1.04 (3H, m, CH_3); ^{13}C-NMR δc 205.4 (C_{11}), 172.2 (C_7), 159.4 (C_2), 148.5 (C_9), 144.6 (C_5), 133.3 (C_4), 130.4 (C_3), 125.1 (C_6), 123.6 (C_{10}), 29.5 (C_{13}), 29.2 (C_{12}), 24.9 (C_{16}), 22.4 (C_{14}), 17.9 (C_{17}), 13.8 (C_{15}). Anal. Calcd for $C_{15}H_{19}N_3O$: C, 70.01; H, 7.44: N, 16.33. Found: C, 70.09; H, 7.39; N, 15.98.

4,8-Dimethyl-6-phenyl-2*H*-pyrano[3,2-*g*]quinolin-2-one.

Yield = 60 %, yellow solid, mp 120-122 ^oC. MS EI: m/z = 303; IR (selected cm^{-1}) 1730 (C=O), 1609 (C=C), 1474 (C=N); ^{1}H-NMR δ_H: 7.60 (1H, s, CH), 7.51 (1H, s, CH), 7.46 (1H, s, CH), 7.20 (5H, m, Ar), 5.76 (1H, s, CH), 2.60 (3H, s, CH_3), 2.45 (3H, s, CH_3); ^{13}C-NMR δc: 160.6 (C_2), 155.4 (C_8), 153.5 (C_4), 152.9 (C_{11}), 130.5 (C_{14}), 130.2 (C_6), 129.4 (C_{17}), 129.0 (C_{19} and C_{21}), 128.7 (C_{20}), 128.5 (C_{18} and C_{22}), 127.0 (C_5), 126.8 (C_7), 111.3 (C_{12}), 108.8(C_{13}), 107.4(C_{10}), 98.5 (C_3), 29.8 (C_{15}), 17.9 (C_{16}). Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62. Found: C, 79.32; H, 5.78; N, 4.70.

8-Ethyl-4-methyl-6-phenyl-2*H*-pyrano[3,2-*g*]quinolin-2-one.

Yield = 65 %, yellow solid, mp 129-131 ^oC. MS EI: m/z = 317; IR (selected cm^{-1}) 1725 (C=O), 1607(C=C), 1479 (C=N); ^{1}H-NMR δ_H: 7.56 (1H, s, CH), 7.46 (1H, s, CH), 7.36 (1H, s, CH), 7.12 (5H, m, Ar), 5.81 (1H, s, CH), 2.62 (3H, s, CH_3), 1.71 (2H, q, *J* = 7.20 Hz, CH_2), 1.10 (3H, t, *J* = 7.20 Hz, CH_3). ^{13}C-NMR δc: 160.5 (C_2), 155.5 (C_8), 153.5 (C_6), 152.7 (C_{13}), 131.1 (C_{14}), 130.3 (C_{12}), 129.2 (C_{18}), 128.1 (C_{20} and C_{22}), 128.7 (C_{21}), 128.5 (C_4), 127.1(C_{19} and C_{23}), 126.7 (C_5), 111.4 (C_{10}), 108.5 (C_7), 107.1 (C_{11}), 98.2 (C_3), 31.0 (C_{16}), 28.0 (C_{15}), 18.0 (C_{17}). Anal. Calcd for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.07; N, 4.41.Found: C, 79.40; H, 5.80; N, 4.31.

6-Butyl-8-ethyl-4-methyl-2*H*-pyrano[3,2-*g*]quinolin-2-one.

Yield = 62 %, yellow solid, mp 113-116 ^oC. MS EI: m/z = 297; IR (selected cm^{-1}) 1714(C=O), 1613(C=C), 1461 (C=N); ^{1}H-NMR δ_H: 7.42 (1H, s, CH), 7.35 (1H, s, CH), 6.91 (1H, s, CH), 5.78 (1H, s, CH), 3.01 (3H, s, CH_3), 2.10 (2H, m, CH_2), 1.80 (2H, q, J = 7.25 Hz, CH_2), 1.61 (2H,m, CH_2), 1.42 (2H, m, CH_2), 1.20 (3H, t, *J* = 7.25 Hz, CH_3), 1.02 (3H, m , CH_3); ^{13}C-NMR δc: 160.6 (C_2), 155.4 (C_8), 153.5 (C_4), 152.9 (C_{11}), 130.5 (C_{14}), 130.2 (C_6), 129.4 (C_{12}), 126.9 (C_5), 111.2 (C_7), 108.8 (C_{13}), 107.4 (C_{10}), 98.2 (C_3), 29.5 (C_{16}), 29.2 (C_{18}), 24.9 (C_{19}), 22.4 (C_{15}), 18.7 (C_{20}), 17.9 (C_{17}), 13.8(C_{21}). Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80, N 4.71. Found: C, 76.67; H, 7.71; N, 4.69.

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