Tetrahedron Letters 52 (2011) 1641–1643

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Ni(0) catalyzed one step synthesis of benzo[*b*][1,8] naphthyridin-5-ones from silyl-α-ketoalkynes in water

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ARTICLE INFO

Article history:
Received 2 November 2010
Revised 25 January 2011
Accepted 26 January 2011
Available online 1 February 2011

Keywords:
One-step synthesis
Benzo[*b*][1,8]naphthyridones
α-Ketoalkynes
Ni(0) catalyst
Heterocyclization

ABSTRACT

One-step synthesis of new benzo[*b*][1,8]naphthyridin-5-ones using a Ni(0) catalytic system in aqueous medium with mild conditions of pressure and temperature is described. It is very interesting to note that Ni(0) catalyst increases the rate of condensation of several α-ketoalkynes with 2-amino-4(1*H*)-quinolinone obtaining benzo[*b*][1,8]naphthyridin-5-ones in very high yield. In the absence of catalyst this condensation reaction takes 24 h with a product yield of <10%.

1. Introduction

Many benzonaphthyridine derivatives presenting biological activities and fluorescent properties are reported in the literature. These derivatives have been of great interest, as part of their chemical structure is present in some compounds isolated from natural products which display a wide range of biological activities such as antibacterial, anti-inflammatory, anticancerigen and antihypertensive.[1–7]

Nevertheless, methods for the synthesis of naphthyridone heterocycles in low yields, involving several reaction steps, drastic conditions such as high pressure, temperature, and the use of organic solvents, have been mentioned.[8–10] One of the method widely used is Friedländer reaction,[8] where *o*-amino aldehydes and α-methylenic ketones is reacted in an acidic or basic medium. Ullmann condensation[10] is an another method for the synthesis of intermediates that lead to obtain benzo[*b*][1,8]naphthyridin-5-ones.

Our earlier reports mentioned the use of Ni(0) catalyst,[11] to obtain lactones, lactams, pyrones, pyridopyrimidines, napthyridines and quinolines in good yields under mild conditions.[12–18] These reactions were carried out in basic media using nickel cyanide and potassium cyanide as catalytic precursors under carbon monoxide atmosphere.

In the present work, one-step synthesis of new benzo[*b*][1,8] naphthyridin-5-ones using a Ni(0) catalytic system in aqueous medium with mild conditions of pressure and temperature is described.

2. Results and discussion

Five new benzo[*b*][1,8]naphthyridin-5-(10*H*)-ones were obtained by heterocyclized condensation of silyl-α-ketoalkynes **2a–e** (Table 1) with 2-amine-4(1*H*)-quinolinone **1**, in an aqueous medium at atmospheric pressure and room temperature using $Ni(CN)_2{\cdot}4H_2O$, CO and KCN system as a catalytic precursor, as reported earlier by our group.[11] It is to be mentioned that compound **3a** only has already been reported by Pellon et al. using Ullmann condensation but in a very low yield[10] (6% yield).

The general reaction for the synthesis of benzo[*b*][1,8]naphthyridin-5-(10*H*)-ones is shown in Eq. 2. Silyl-α-ketoalkynes (**2a–e**) were obtained as shown in Eq. 1. It is to be noted that Ni(0) catalyst increases the rate of condensation of several α-ketoalkynes with 2-amino-4(1*H*)-quinolinone obtaining benzo[*b*][1,8]naphthyridin-5-ones with a very high yield as shown in the Table 1 (∼80%).[19] In the absence of catalyst, this condensation reaction takes more than 24 h with a product yield of <5%. Higher yields were obtained in the heterocyclization reaction when aromatic ketoalkynes (**3d–e**) were used in comparison to, when alkylic ketoalkynes (**3a–c**) are employed.

A plausible mechanism for the synthesis of benzo[*b*][1,8]naphthyridin(10*H*)-5-ones is proposed, as shown in Scheme 1. A similar

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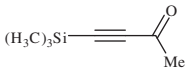
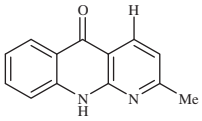
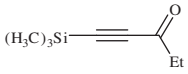
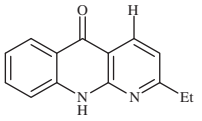
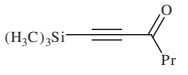
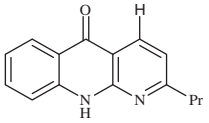
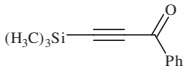
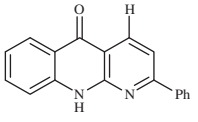
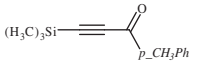
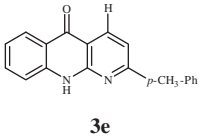
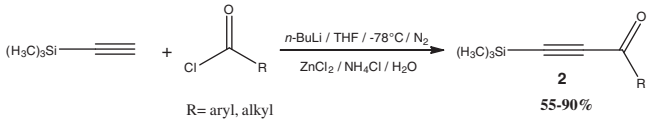
doi:10.1016/j.tetlet.2011.01.123

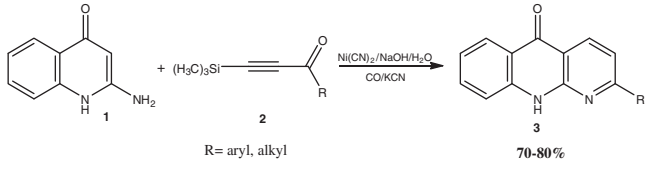
Table 1
Reaction of Silyl-α-ketoalkynes with 2-amino-4(1*H*)-quinolinone by $Ni(CN)_2$/CO/KCN system in aqueous alkaline medium

Entry	Silyl-α-ketoalkynes	Benzo[*b*][1,8]naphthyridin-5-(10H)-ones	Yield[a] (%)	Reaction time (min)
1	 **2a**	 **3a**	69	5
2	 **2b**	 **3b**	73	5
3	 **2c**	 **3c**	74	5
4	 **2d**	 **3d**	78	10
5	 **2e**	 **3e**	79	10

[a] Isolated yield

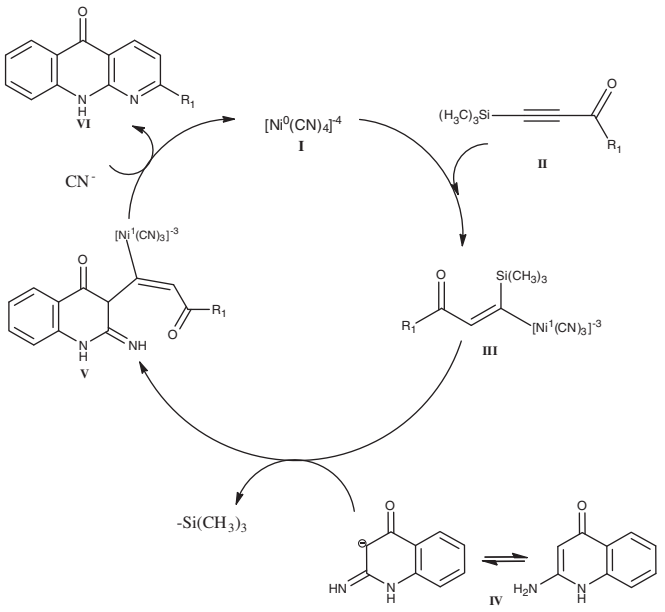


Equation 1. Synthesis of α-ketoalkynes **2**.



Equation 2. Synthesis of benzo[*b*][1,8]naphthyridin-5-(10*H*)-ones

mechanism has already been proposed earlier by our group.[15] As $(CH_3)_3Si$- is a better leaving group, higher yields and faster reaction rates are observed. As mentioned earlier, reaction starts with a nucleophilic attack of the anionic species of nickel (**I**) over the α-ketoalkyne (**II**) triple bond, thus a nucleophilic addition step occurs and provokes the conjugated bond activation (**III**). Consecutively, this is attacked by the nucleophilic carbon generated in the basic medium (**IV**) producing the imine intermediary (**V**) that attacks the carbonyllic carbon and with the consequence of dehydration benzo[*b*][1,8]naphthyridin-5-ones (**VI**) is obtained. It has been mentioned previously by our group that various nickel cyano carbonyl species are formed in situ and these species exist in equilibrium. Tetracyanonickelate $[(Ni(CN)_4]^{-4}$ ion is an active catalytic



Scheme 1. A plausible mechanism for the synthesis of benzo[*b*][1,8]naphthyridin(10*H*)-5-ones.

specie. This anion is obtained by replacement of CO ligands of $[(Ni(CO)_2(CN)_2]^{-2}$, formed in situ, by CN^- anion .[11]

All these synthesized compounds were characterized by various physicochemical methods. In MS–IE spectrum a *m*/*z* molecular ion

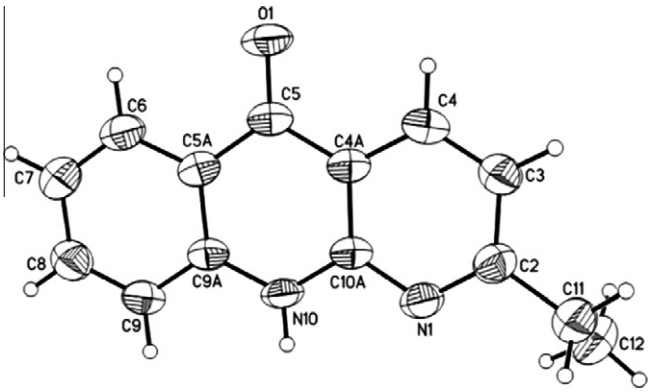


Figure 1. Molecular structure of 2-ethylbenzo[*b*][1,8]naphthyridin-5(10*H*)-one (**3b**).

peak was observed for all the compounds, followed by a peak with a loss of the carbonyl group (M^+–CO). Vibrations corresponding to the C=O group between 1596–1620 cm^{-1} and vibrations corresponding to the N–H amine group between 3208–3269 cm^{-1} were observed in the FT–IR spectra.

In all these compounds, proton signals were individually assigned based on the J_{HH} coupling constant values. All assignations were corroborated by COSY and HETCOR experiments.

X-ray crystal structure of **3b** has been determined as shown in Figure 1. The molecule is chiral. The compound show N–H···C=O intermolecular interactions in the unit cell forming a chain structure.[20]

In conclusion, the methodology shows an easy way to carry out heterocyclization reactions to obtain benzo[*b*][1,8]naphthyridin-5-ones derivatives, in a single step under very mild conditions in water. This work presents, the employment of a nickel catalyst in aqueous medium having significant advantages such as the absence of organic solvents, fast reaction and elimination of tiresome experimental methodologies. The work is in process to generalize the transformation of aminoquinolinones to benzo[*b*][1,8]naphthyridin-5-ones using this catalytic system.

Acknowledgment

Authors are grateful to DGAPA (IN-204507) for financing the work.

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19. *Synthesis of benzo[b][1,8]naphthyridin-5(10H)-one* (3).A typical experiment was performed as follows. A 2M NaOH solution (10 mL) was degassed and saturated with CO under atmospheric pressure for 30 min. To the solution was then added 0.04 mmol of $Ni(CN)_2$ $4H_2O$, the mixture was kept at room temperature overnight with stirring and slow bubbling of CO (2–3 mL/min) until a pale yellow solution was obtained. Addition of 0.25 mmol of KCN resulted in a color change to orange. To this resulting catalytic system, the corresponding Silyl-α-ketoalkynes (1 mmol) and the 2-amino-4(1*H*)quinolinone compounds were added (1 mmol). The evolution of the reaction was followed by TLC. At the end of the reaction, ether was used to extract the product. The product was concentrated and purified by column chromatography over silica gel using hexane–ethyl acetate (1:1) as the eluent to obtain pure benzo[*b*][1,8]naphthyridin-(10*H*)-5-one. The compound 3b was recrystallized from methanol:pentane mixture.
2-ethylbenzo[b][1,8]naphthyridin-5(10H)-one (**3a**) Yellow solid; yield 70%; mp: 279–281 °C; FT-IR (ν_{max} cm^{-1}): 3208 (N–H), 3137 (C–H Ar), 2998 (CH_3), 2923 (CH_3), 1606 (C=O), 1437 (C–N), 1268 (C=N Ar); MS(EI) *m*/*z* 210$[M]^+$; 182$[M-CO]^+$; ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm) 2.48 (s, 3H, -CH_3), 7.17 (d, *J* = 8.10 Hz, 1H, CH-Ar), 7.24 (td, *J* = 7.08 Hz, 1H, CH-Ar), 7.59 (d, *J* = 8.19 Hz, 1H, CH-Ar), 7.7 (td *J* = 6.96 Hz, 1H, CH-Ar), 8.16 (dd, *J* = 8.04 Hz 1H, CH-Ar), 8.4 (d, *J* = 8.07 Hz, 1H,), 12.18 (s, 1H, N–H); ^{13}C NMR (75 MHz, DMSO-d_6, δ ppm) 24.57, 113.0, 117.6, 117.9, 120.9, 121.6, 125.8, 133.7, 135.7, 140.8, 150.6, 164.2, 177.1.
2-ethylbenzo[b][1,8]naphthyridin-5(10H)-one (**3b**) Yellow solid; yield 75%; mp: 233–235 °C; FT-IR (ν_{max} cm^{-1}): 3209 (νN–H), 3135 (C–H Ar), 2936 (CH_3), 2866 (CH_3), 1620 (C-O), 1438 (C–N), 1276 (C–N Ar); MS(EI) *m*/*z* 224 $[M]^+$; 192 $[M-CO]^+$; ^{1}H NMR (300 MHz DMSO-d_6, δ ppm) 1.3 (*t*, *J* = 7.56 Hz,3H), 2.88 (q, *J* = 7.53 Hz 2H), 7.22 (d, *J* = 8.10 Hz, 1H), 7.26 (td, *J* = 6.87 Hz, 1H), 7.63 (d, *J* = 7.83 Hz, 1H), 7.7 (td *J* = 6.87 Hz, 1H), 8.18 (dd, *J* = 8.1 Hz 1H, CH-Ar), 8.47 (d, *J* = 8.1 Hz, 1H), 12.22 (s, 1H, N–H); ^{13}C NMR (DMSO-d_6, δ ppm) 13.8, 39.5, 113.9, 117.5, 118.3, 121.4, 122.2, 126.4, 134.4, 136.5, 141.4, 151.2, 169.4, 177.7.
2-propylbenzo[b][1,8]naphthyridin-5(10H)-one (3c) Yellow solid; yield 75%; mp: 214–216 °C; FT-IR (ν_{max} cm^{-1}): 3212 (N–H), 3131 (C–H Ar), 2959 (CH_3), 2930 (CH_3), 1607 (C=O), 1432 (C–N), 1260 (νC=N Ar); MS (EI) *m*/*z* 238 $[M]^+$; 181$[M-CO]^+$; ^{1}H NMR (300 MHz DMSO-d_6, δ ppm) 0.9 (*t*, *J* = 7.20 Hz,3H, -CH_3), 1.7 (m, 2H, -CH_2), 2.8 (*t*, *J* = 7.8 Hz, 2H), 7.18 (d, *J* = 8.10 Hz, 1H), 7.24 (td, *J* = 6.9 Hz, 1H), 7.61 (dd, *J* = 9.3 Hz, 1H), 7.7 (td, *J* = 6.9 Hz, 1H), 8.17 (dd, *J* = 8.1 Hz 1H), 8.4 (d, *J* = 8.1 Hz, 1H), 12.17 (s, 1H, N–H); ^{13}C NMR (75 MHz, DMSO-d_6, δ ppm) 13.7, 22.0, 39.8, 113.3, 117.4, 117.6, 120.8, 121.6, 125.8, 133.7, 135.7, 140.8, 150.6, 167.6, 177.13.
2-phenylbenzo[b][1,8]naphthyridin-5(10H)-one (**3d**) Yellow solid; yield 80%; mp: 286–288 °C; FT-IR (ν_{max} cm^{-1}): 3244 (N–H), 3149 (C–H Ar), 1596 (C=O), 1430 (C–N), 1385 (C=N Ar); MS (EI) *m*/*z* 272 $[M]^+$; 243 $[M-CO]^+$; ^{1}H NMR (300 MHz DMSO-d_6, δ ppm) 7.26 (td, *J* = 6.9 Hz, 1H), 7.5-7-6 (m, 3H), 7.67 (dd, *J* = 8.4 Hz, 1H), 7.72 (td, *J* = 6.9Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 8.19–7.24 (m, 1H), 8.6 (d, *J* = 8.4 Hz, 1H), 12.25 (s, 1H, N–H); ^{13}C NMR (75 MHz DMSO-d_6, δ ppm), 114.1, 114.7, 117.7, 121.0, 121.7, 125.9, 127.4 (2C), 128.9 (2C), 130.4, 133.9, 136.8, 137.6, 141.1, 150.8, 160.4, 177.1.
2-p-tolylbenzo[b][1,8]naphthyridin-5(10H)-one (**3e**) Yellow solid; yield 80%; mp: 338–341 °C; FT-IR (ν_{max} cm^{-1}): 3244 (N–H), 3140 (C–H Ar), 2916 CH_3),1603 (C=O), 1433 (C–N), 1282 (C–N Ar); MS (EI) *m*/*z* 286 $[M]^+$; 257[M-CHO]$^+$; ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm) 2.38 (s, 3H), 7.26 (td, *J* = 6.9 Hz, 1H) 7.35 (d, *J* = 7.8 Hz, 2H), 7.67 (d, *J* = 7.5 Hz), 7.72 (td, *J* = 6.9 Hz, 1H), 7.8 (d, *J* = 8.4 Hz, 1H), 8.12 (d, *J* = 8.1 Hz 2H), 8.19 (dd, *J* = 8.1 Hz), 8.58 (d, *J* = 8.4 Hz), 12.08 (s, 1H, N–H); ^{13}C NMR (75 MHz, DMSO-d_6, δ ppm) 20.8, 113.8, 114.3, 117.7, 121.0, 121.6, 125.8, 127.3 (2C), 129.5 (2C), 133.8, 134.8, 136.6, 140.2, 141.2, 150.8, 160.3, 177.0.
20. Supplementary Material Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre CCDC No. 791910.