HETEROCYCLES, Vol. 96, No. 1, 2018, pp. 43 - 49. © 2018 The Japan Institute of Heterocyclic Chemistry
Received, 8th September, 2017, Accepted, 14th December, 2017, Published online, 21st December, 2017
DOI: 10.3987/COM-17-13810

EFFICIENT ONE POT SYNTHESIS OF CHROMENONAPHTHYRIDINE DERIVATIVES BY CuI/$InCl_3$ CATALYZED AZA DIELS-ALDER REACTION

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Abstract – A mild and efficient method for the synthesis of chromenonaphthyridine derivatives *via* domino reaction of aminopyridine and different *O*-propargylated salicylaldehydes using CuI/$InCl_3$ as an efficient catalyst, refluxed in acetonitrile is reported. Mild reaction condition, operational simplicity, good to excellent yield and easy isolation of product is the silent feature of this reaction.

INTRODUCTION

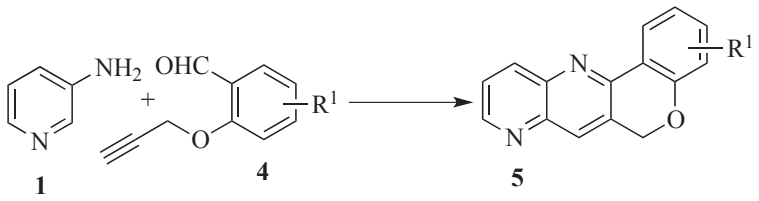
Heterocycles are omnipresent in nature and possess important biological and pharmacological activities. They represent many core structures of pharmaceutically important molecules. Naphthyridine derivatives are one of the most important classes of such compounds. Recently synthesis of different heterocyclic compounds including naphthyridine moiety has been reported, as they have potent pharmaceutical as well as excellent biological activity.[1] Several naphthyridines derivatives display antibacterial activity,[2] medicinal use in cardiac insufficiencies and infarction,[3] anticonvulsant activity,[4] anti-human cytomegalovirus (HCMV) inhibitors,[5] and anticancer activity.[6]

The development of eco-friendly process in terms of sustainable chemistry has become a focal point in chemical research in recent years. The hetero Diels-Alder reaction is one of the most efficient and powerful synthetic tool for the synthesis of heterocycles.[7] Recently various transition metal salts[8] is used as catalyst in hetero Diels-Alder reaction among which copper and indium trichloride have been extensively used in organic synthesis. Both copper and indium chloride have gained a considerable attention in organic synthesis due to their commercial availability, stable in air, inexpensive and non-toxic nature. Moreover copper can easily activate the terminal alkyne[9] bond and indium trichloride coordinate with imine double bond and facilitate in cyclization through hetero Diels-Alder reaction. So many reports are available in the literature of indium trichloride as a green and potentially Lewis acid catalyst to

construct carbon-carbon bond or carbon-heteroatom bonds such as hetero Diels-Alder reaction.[10] Some of them suffer from several disadvantages such as long reaction time, low yield and harsh reaction condition. Very recently Alonso *et al.* reported the experimental and theoretical study of cyclo-addition reaction of 3-pyridylaldimine and alkene or alkyne for the synthesis of 1,5-naphthyridine[11] using $BF_3 \cdot OEt_2$ as Lewis acid catalyst from 3-aminopyridine, aldehyde and alkyne or alkene. In view of the immense biological and pharmaceutical utility of naphthyridine and its derivatives, and wide applicability of transition metal in hetero Diels-Alder reaction motivate us to synthesize the chromenonaphthyridine derivatives *via* domino reaction of aminopyridine and differents *O*-propargylated salicylaldehydes using CuI/$InCl_3$ as a catalyst in the refluxed condition. To the best of our knowledge there is no such report about the synthesis of chromenonaphthyridine derivatives by aza Diels-Alder reaction. Herein, we report our present investigation.

RESULTS AND DISCUSSION

In this aza Diels-Alder reaction 3-aminopyrdine (**1**) and *O*-propargylated salicylaldehyde(**4a**) were allowed to react in the presence of 5 mol% of $InCl_3$ and 10 mol% of CuI in acetonitrile at refluxing condition, afforded the corresponding 1,5-chromenonaphthyridine derivative (**5a**) in good yield (**Scheme 1**). Initially, this reaction was performed with 3-aminopyridne and propargylated salicylaldehyde in the presence of 5 mol% CuI in acetonitrile at refluxed condition. But the product obtained with very low yield.

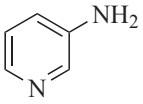
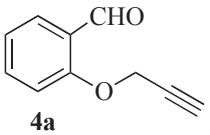
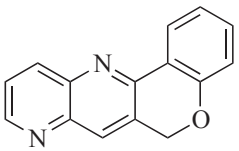
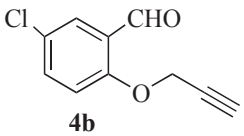
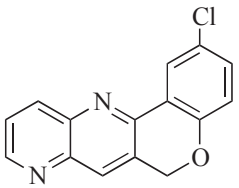
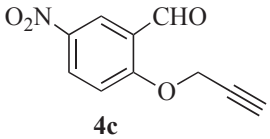
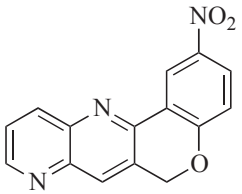
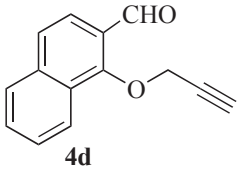
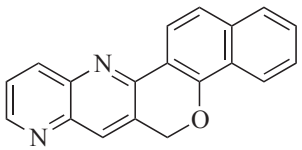
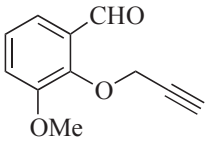
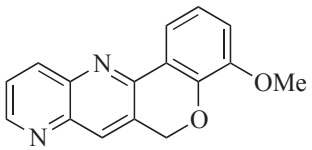
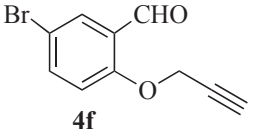
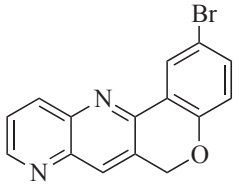


Scheme 1. Reagent and conditions: $InCl_3$ (5 mol%), CuI (10 mol%), MeCN, reflux, 2-3 h

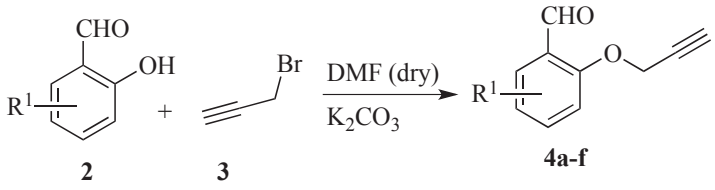
But when this similar reaction was carried out in the presence of 20, or 10 mol% of CuI at reflux in acetonitrile, it took long time to complete the reaction. Increasing the % of catalyst loading had no significant effect on the yield of product. Hence to find out the optimum reaction condition we used indium trichloride as Lewis acids along with CuI under the same reaction condition as indium chloride effectively activate the imine double bond by co-ordinating the imine nitrogen and facilitate the hetero Diels-Alder reaction. It was also found that 5 mol% indium trichloride efficiently increased the yield of the product and also reduced the reaction time. A test reaction was performed using *O*-propargylated salicylaldehyde (1 mmol) and 3-aminopyridine (1 mmol) refluxed in acetonitrile in order to establish the

catalytic activity of indium trichloride (5 mol%) and CuI (10 mol%) and better result was obtained. To explore the generality of this aza Diels-Alder reaction, we extended this reaction of 3-aminopyridine with different *O*-propargylated salicylaldehyde under similar conditions afforded respective chromenonaphthyridine derivatives in high yields. Differents *O*-propargylated salicylaldehyde containing electron-withdrawing and electron-donating substituent at *meta* or *para*-position exhibited equal activity towards the formation of product in good to excellent yields. The results are summarized in **Table 1**.

Table 1. Synthesis of chromenonaphthyridine derivatives

Entry	Amine	Aldehydes	Products	Yields
1.	 **1**	 **4a**	 **5a**	92%
2.	**1**	 **4b**	 **5b**	95%
3.	**1**	 **4c**	 **5c**	89%
4.	**1**	 **4d**	 **5d**	91%
5.	**1**	 **4e**	 **5e**	85%
6.	**1**	 **4f**	 **5f**	92%

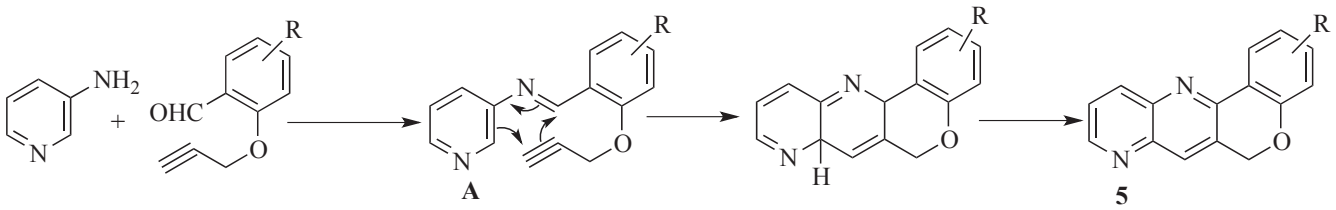
The requisite starting materials (**4a-f**) required for this present study were synthesized[12] by the reaction of various substituted salicyaldehyde (**2a-f**) with propargyl bromide (**3**) in dry DMF, stirring at room temperature in the presence of potassium carbonate (**Scheme 2**) and utilized without further purification.



4a. R^1 = H
4b. R^1 = 5-Cl
4c. R^1 = 5-NO_2
4d. R^1 = 3,4-benzo
4e. R^1 = 3-OMe
4f. R^1 = 5-Br

Scheme 2. Preparation of *O*-propargylated aldehyde

Plausible mechanistic rationalization for the formation of chromenonaphthyridine derivatives is depicted in **Scheme 3**. Initially, imine (**A**) is formed which contained the aza-heterodiene moiety. This aza-heterodiene undergoes intramolecular aza Diels-Alder reaction with the propargyl triple bond which is activated by indium chloride followed by aromatization to give the desire products.



Scheme 3. Plausible mechanism

All the synthesized compounds are characterized by the elemental analysis and spectroscopic data.

In summary, we have described a novel, mild and efficient strategy for the synthesis of potentially biologically active 1,5-naphthyridine derivatives by domino aza Diels-Alder reaction of aminopyridine and *O*-propargylated salicylaldehydes. The methodology is simple, rapid, and inexpensive affording good to high yields. In addition to its operational simplicity this procedure has the advantage of easy availability and flexibility of starting materials, and short reaction times.

EXPERIMENTAL

Melting points were determined in an open capillary and are uncorrected. IR spectra were recorded on a Perkin-Elmer spectrum II spectrometer on KBr disks. ^{1}H and ^{13}C NMR spectra were recorded at 300, 500 and 125 MHz respectively in $CDCl_3$ (chemical shift in δ) with TMS as internal standard. Mass spectra were recorded on a TOF MASS ES+ instrument respectively. Silica gel [(60-120 mesh), Spectrochem,

India] was used for chromatographic separation. Silica gel G [E-Merck (India)] was used for TLC. Petroleum ether refers to the fraction boiling between 60-80 °C.

General Procedure:

A mixture of 3-aminopyridine (**1a**, 1.0 mmol), *O*-propargylated salicylaldehyde (**4a**, 1.0 mmol) were taken in a round-bottom flask equipped with a stirring magnetic bar and allowed to stir in MeCN (15 mL) at room temperature for 5 min. To this reaction mixture $InCl_3$ (5 mol%) and CuI (10 mol%) were added and the reaction mixture was refluxed for 2 h. After completion of the reaction, as indicated by TLC, MeCN was evaporated, cooled to room temperature and ice cold water (10 mL) was added to the crude reaction mass. Then aqueous layer was extracted with EtOAc (3 × 20 mL), and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The product was purified by column chromatography on silica gel (60-120 mesh) using petroleum ether-EtOAc mixture (4:1) as eluent to afford the compounds **5a** in good yield.

6*H*-Chromeno[4,3-*b*][1,5]naphthyridine (5a). Yield: 92%, mp 120 °C, IR (KBr): 1617, 1512, 1482 cm^{-1}, ^1H NMR (500 MHz, DMSO-d_6): δ_H = 4.97 (s, 2H); 7.14 (m, 3H); 7.46 (m, 1H); 7.69 (m, 1H); 8.37 (s, 2H); 8.47 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C = 67.49, 108.24, 109.61, 111.61, 113.82, 116.98, 119.17, 122.80, 126.60, 130.93, 132.27, 133.71, 135.80, 164.51. MS *m/z*: 235 (M^+ + H), Anal. Calcd for $C_{15}H_{10}N_2O$: C, 76.91; H, 4.30; N, 11.96; Found: C, 76.94; H, 4.37; N, 11.99.

2-Chloro-6*H*-chromeno[4,3-*b*][1,5]naphthyridine (5b). Yield: 95%, mp 181 °C, IR (KBr): 1615, 1566, 1467 cm^{-1}, ^1H NMR (300 MHz, DMSO-d_6): δ_H = 5.07 (s, 2H); 7.32 (d, *J* = 9 Hz, 1H); 7.64 (d, *J* = 9 Hz, 2H); 7.70 (s, 2H); 7.99 (s, 1H); 8.80 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 67.66, 107.46, 116.63, 123.98, 124.46, 124.70, 124.96, 125.89, 126.71, 127.78, 128.17, 128.29, 130.95, 135.37, 152.30. MS *m/z*: 269 (M^+ + H), Anal. Calcd for $C_{15}H_9ClN_2O$: C, 67.05; H, 3.38; N, 10.43; Found: C, 67.16; H, 3.42; N, 10.37.

2-Nitro-6*H*-chromeno[4,3-*b*][1,5]naphthyridine (5c). Yield: 89%, mp 200 °C, IR (KBr): 1617, 1512, 1480 cm^{-1}, ^1H NMR (300 MHz, DMSO-d_6): δ_H = 5.27 (s, 2H); 7.32 (m, 1H); 7.47 (s, 1H); 8.29 (m, 2H); 8.43 (s, 2H); 9.1 (s, 1H); MS *m/z*: 280 (M^+ + H), Anal. Calcd for $C_{15}H_9N_3O_3$: C, 64.52; H, 3.25; N, 15.05; Found: C, 64.65; H, 3.32; N, 14.97.

6*H*-Benzo[7,8]chromeno[4,3-*b*][1,5]naphthyridine (5d). Yield: 91%, mp 230 °C, IR (KBr): 1617, 1512, 1437 cm^{-1}, ^1H NMR (300 MHz, DMSO-d_6): δ_H = 5.49 (s, 2H); 7.34 (d, *J* = 9 Hz, 2H); 7.51 (t, *J* = 6 Hz, 2H); 7.69 (t, *J* = 6 Hz, 2H); 7.96 (d, *J* = 6 Hz, 1H), 8.07 (d, *J* = 9 Hz, 1H); 8.54 (d, *J* = 9 Hz, 1H) 9.90 (d, *J* = 9 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 67.75, 114.71, 118.34, 124.51, 126.61, 127.95, 128.52, 130.07, 130.27, 130.58, 132.42, 133.79, 136.55, 142.39, 150.82, 157.88. MS *m/z*: 285 (M^+ + H), Anal. Calcd for $C_{19}H_{12}N_2O$: C, 80.27; H, 4.25; N, 9.85; Found: C, 80.31; H, 4.19; N, 9.79.

4-Methoxy-6*H*-chromeno[4,3-*b*][1,5]naphthyridine (5e). Yield: 85%, mp 205 °C, IR(KBr): 1617, 1583,

1481 cm^{-1}, ^1H NMR (300 MHz, DMSO-d_6): δ_H = 3.83 (s, 3H); 5.48 (s, 2H); 6.91 (t, J = 9 Hz, 2H); 7.18 (q, J = 9 Hz, 2H); 7.80 (s, 1H); 7.93 (d, J = 6 Hz, 1H); 8.47 (d, J = 6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 55.50, 67.36, 114.88, 116.60, 120.01, 122.02, 122.62, 124.37, 128.97, 132.84, 137.07, 143.50, 146.88, 148.67, 149.19, 152.41. MS *m/z*: 265 (M^+ + H), Anal. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60; Found: C, 72.79; H, 4.65; N, 10.64.

2-Bromo-6*H*-chromeno[4,3-*b*][1,5]naphthyridine (5f). Yield: 92%, mp 190 ºC, IR (KBr): 1615, 1524, 1477 cm^{-1}, ^1H NMR (300 MHz, DMSO-d_6): δ_H = 4.97 (s, 2H); 7.08 (m, 5H); 8.08 (s, 1H); 8.42 (s, 1H); MS *m/z*: 312 (M^+ + H), Anal. Calcd for $C_{15}H_9BrN_2O$: C, 57.53; H, 2.90; N, 8.95; Found: C, 57.59; H, 2.98; N, 8.97.

ACKNOWLEDGEMENTS

Author is grateful to the Department of Science and Technology (DST, New Delhi) for financial support under DST fast track project (No: SB/FT/CS-184/2012 dt-16-06-2014). Author is also sincerely acknowledged IICB Kolkata and SAIF Nehu, Assam for spectral data.

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