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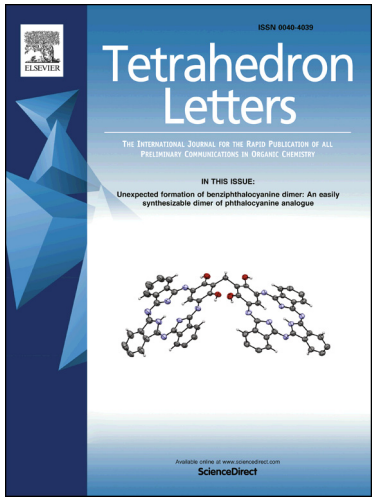

CuI-$Zn(OAc)_2$ catalyzed $C(sp^2)$-H activation for the synthesis of pyridocoumarins through an uncommon Cu^{I}-Cu^{III} switching mechanism: A fast, solvent-free, combo-catalytic, ball milling approach

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Graphical Abstract

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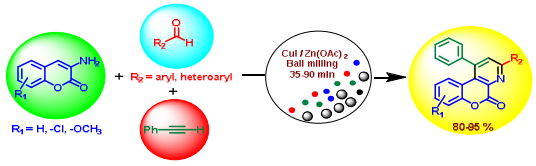

- A solvent-free, oxidant-free, fast and mild synthetic protocol
- Oxidative C-C and C-N coupling *via* C(sp^2)-H activation assisted by Cu^{I}
- A combo-catalytic method involving Cu^{I}-Cu^{III} switching
- Zn(OAc)$_2$ may act as Lewis Acid catalyst to polarise C=O during C-C and C-N coupling
- Wide substrate scope with good to excellent yield
- Control Experiments, ESI-MS, UV-Vis and XPS study

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ABSTRACT

CuI-Zn(OAc)$_2$ catalyzed, a fast, solvent-free synthetic protocol has been developed for the oxidative C-C and C-N coupling *via* C(sp^2)-H activation. In this work, an aldehyde, terminal alkyne and 3-aminocoumarin were coupled together to form pyridocoumarin framework through a greener ball milling process under very mild condition. In contrast to the frequently used imine-alkyne cyclization reactions, this uncommon mild Cu^I-Cu^{III}switching combo-catalysis is expected to proceed through the formation of a flexible propargylic amine intermediate, which leads to a rapid C(sp^2)-H activation for cyclization involving transient Cu^{III} species. The in-situ formation of transient Cu^{III} species was confirmed through ultraviolet-visible spectroscopy (UV−Vis), electrospray ionization mass spectrometry (ESI-MS), and X-ray photoelectron spectroscopy (XPS) analyses of the reaction mixture.

1. Introduction

Metal catalyzed activation of the carbon–hydrogen (C–H) bond for the formation of carbon–carbon (C–C) bond is a fast and economic approach for the development of biologically significant compounds and natural products[1]. It is a useful strategy of synthetic organic chemistry because it can be used for efficient functionalization of arenes without the use of hazardous precursors [2]. On the other hand, 'combo-catalysis' is an emerging area in modern organic synthesis for diverse cyclization reaction through C(sp^2)-H activation[3]; for example, CuBr–ZnI$_2$-catalyzed N–N/C–N coupling for oxidative cyclization reactions,[3d]Pd(I)–Ru(I)-mediated Suzuki cross-coupling reactions[3e] and [IrCuCl$_2$]$_2$–AgNTf$_2$-promoted amination reaction[3h]. The combo-catalytic strategy is also found to be an efficient tool for direct N-C and C-C coupling of amine with aldehyde and terminal alkyne[4]. Taking the advantages of the combo-catalysis, we targeted to synthesize a wide range of pyridocoumarin derivatives through the oxidative C-C and C-N coupling employing 3-aminocoumarin, aldehyde and terminal alkyne.

3-aminocoumarin and its derivatives are one of the most active classes of compounds possessing a wide range of biological activity.[5]Due to their wide spectrum of biological activities, various research groups have put their efforts to synthesize compounds containing 3-aminocoumarin structural core[6].

Among the various 3-aminocoumarin scaffold containing molecules, pyridocoumarin derivatives are an important class of naturally occurring molecules and they exhibit a wide range of pharmacological activities such as CNS depressant,[7] anti-inflammatory,[8] anti-tumor[9]and antimicrobial activities.[10] They also exhibit interesting photochemical properties and have been used as laser dye stuffs,[11] luminescence intensifiers,[12] and spasmolytics.[13] From the literature it is found that only a few methods are reported for the synthesis of pyrido[2,3-*c*] coumarin derivatives. Majumdar et al. devised a synthetic protocol for the synthesis of pyrido[2,3-*c*]coumarins[14] through the palladium catalyzed Heck reaction followed by dehydrogenation with palladium charcoal. Bodwell and co-workers reported the synthesis of pyrido[2,3-*c*]coumarin derivatives using Yb(OTf)$_3$ catalyst through the Povarov reaction followed by oxidation with Br$_2$.[15]Later on, the same group devised a synthetic protocol (Scheme 1, c) for the synthesis of pyrido[2,3-*c*]coumarins involving the intramolecular Povarov reaction of 3-aminocoumarin and 2-(propargyloxy)benzaldehyde. This synthetic protocol afforded the product in 45% yield after 9 days.[16]Recently, similar Povarov-type 3-component reaction was reported by McNulty[17a] and co-workers. In that work, a Bronsted acid catalyst, TFA (trifluoroacetic acid) in dichloromethane was used to accomplish the desired transformation. Khan et al[17b] described a three-component reaction to access pyrido[2,3-*c*]coumarins using molecular iodine in acetonitrile solvent under refluxing condition. The main disadvantages of the above mentioned protocols are low yield, requirement of expensive

metal catalysts, prolonged reaction time, use of higher thermal energy, hazardous solvent and low substrate scope. Thus, a mild and competent strategy to access pyrido[2,3-*c*]coumarins is still challenging and highly desirable.

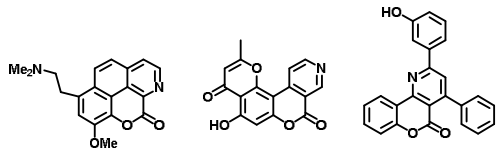
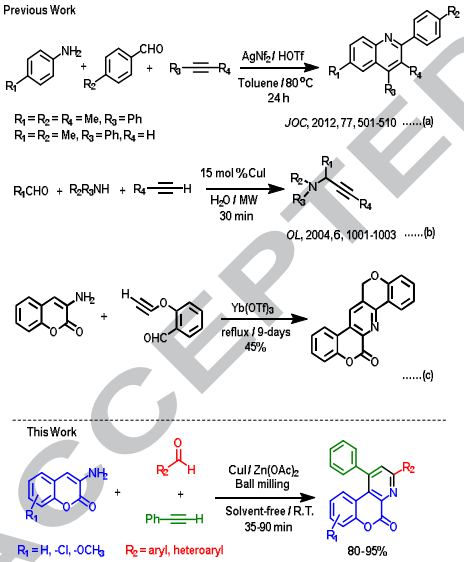


Figure. 1 Bioactive and naturally occurring molecules containing pyridocoumarin moiety

In recent years, solvent-free, ball-milling process has been emerged as a powerful tool for greener reactions.[18]High Speed Ball-Milling (HSBM) is a sustainable mechanochemical technique, which is used in synthetic organic chemistry to promote reactions under solvent-free conditions.[18a,19]This technique has been applied to a variety of organic reactions such as Knoevenagel condensation reactions,[20]Heck-type cross-couplings,[21]Baylis Hillman reactions,[22]Michael additions,[20] functionalization of fullerenes[23]and Sonogashira coupling[24]. Analyzing the literature reports, we have opted this ball milling technique and planned to materialize the oxidative C-C and C-N bond formation through C(sp^2)-H activation. In continuation of our recent effort to synthesize biologically relevant heterocycles,[25] we wish to report a solvent-free, greener ball milling synthetic protocol for the synthesis of a wide range of pyridocoumarin derivatives starting from 3-aminocoumarin, aldehyde and phenyl acetylene, catalyzed by CuI-$Zn(OAc)_2$ involving a propargylic amine intermediate and Cu^{I} -Cu^{III} switching mechanism.

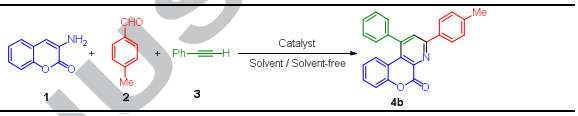


Scheme 1: Various synthetic strategies involving amine/3-aminocoumarin, aldehyde and terminal alkyne

2. Results and Discussion

To study the possibility of our hypothesis for the synthesis of pyridocoumarin derivatives, 3-aminocoumarin(**1**),4-methylbenzaldehyde (**2**) and phenyl acetylene (**3**) were chosen as the model substrate. Initially, 3-aminocoumarin (**1**),4-methylbenzaldehyde (**2**) and phenyl acetylene (**3**) were taken in CH_3CN solvent and treated with 10 mol % of CuI at 70 °C but reaction did not proceed even after prolonged heating (Table 1, entry 1). After several unsuccessful attempts using $Zn(OAc)_2$, ZnI_2, $Cu(OAc)_2$ catalysts (Table 1, entries 2-4), we have designed a combo-catalyst CuBr/ZnI_2(10 mol % each) for this three-component recation in CH_3CN solvent at 70 °C. Interestingly, we got 52% yield of the product after heating for 4h (Table 1, entry 5).Then we employed another combo-catalyst, CuI/$Zn(OAc)_2$(10 mol % each) for the desired transformation.To our delight, yield of the reaction (70%) as well as the reaction rate (3h) were significantly improved under the identical reaction condition (Table 1, entry 6). It was found that the said reaction was unable to proceed at room temperature in CH_3CN medium under similar catalyst loading (CuI/$Zn(OAc)_2$, 10 mol % each). Different solvents such as PhMe, THF (tetrahydrofuran) were also screened for this reaction, but in each case compound **4b** was obtained in comparatively low yield and after a much longer period of time (Table 1, entries 8-9).Few other reactions (**4a**, **4d**) were also performed in these solvent systems (THF,PhMe) which provided relatively lower yields of the corresponding products (Table 1, entries 10-13).

Table 1.Optimization of reaction condition to synthesize pyridocoumarinderivatives[a]

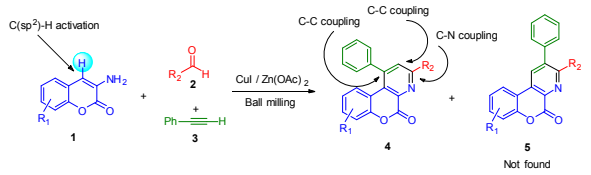


Entry	Catalyst (mol %)	Reaction condition	Temperature (° C)	time (min)	yield[b] (%)
1	CuI (10 mol%)	CH_3CN	70 °C	8 h	-
2	$Zn(OAc)_2$(10 mol%)	CH_3CN	70 °C	8 h	-
3	ZnI_2(10 mol%)	CH_3CN	70 °C	8 h	-
4	$Cu(OAc)_2$(10mol%)	CH_3CN	70 °C	8 h	-
5	CuBr-ZnI_2 (10 mol% each)	CH_3CN	70 °C	4 h	52
6	CuI-$Zn(OAc)_2$ (10 mol% each)	CH_3CN	70 °C	3 h	70
7	CuI-$Zn(OAc)_2$ (10 mol% each)	CH_3CN	r.t.	3 h	-
8	CuI-$Zn(OAc)_2$ (10 mol% each)	PhMe	70 °C	4 h	69
9	CuI-$Zn(OAc)_2$ (10 mol% each)	THF	70 °C	4 h	65
10[c]	CuI-$Zn(OAc)_2$ (10 mol% each)	THF	70 °C	4 h	49
11[d]	CuI-$Zn(OAc)_2$ (10 mol% each)	THF	70 °C	4 h	59
12[c]	CuI-$Zn(OAc)_2$ (10 mol% each)	PhMe	70 °C	4 h	60
13[d]	CuI-$Zn(OAc)_2$ (10 mol% each)	PhMe	70 °C	4 h	61
14[e]	CuBr-$Zn(OAc)_2$(10mol% each)	Solvent-free Ball-milling	r.t	1	82
15[e]	**CuI (7mol %)/$Zn(OAc)_2$(9mol %)**	**Solvent-free Ball-milling**	**r.t**	**35 min**	**89**
16[e]	CuI-$Zn(OAc)_2$(5mol% each)	Solvent-free Ball-milling	r.t	1 h	85
17[e]	CuBr-ZnI_2(10 mol% each)	Solvent-free Ball-milling	r.t	1h	77
18[e]	-	Solvent-free Ball-milling	r.t	2h	-
19[e]	TFA (10 mol%)	Solvent-free Ball-milling	r.t	1h	-
20	TFA (10 mol%)	DCM	r.t	2h	-
21	CuI (7mol %)/$Zn(OAc)_2$ (9mol%)	Solvent-free Ball-milling	r.t	50min	85

[a]In each case 3-aminocoumarin (1.0 mmol), 4-methylbenzaldehyde (1.2 mmol) and phenyl acetylene (1 mmol) and 3 mL of solvent were taken in a 25 mL rb flask. [b] Yield of the isolated product. [c]benzaldehyde (1.2 mmol) was used. [d]4-cyanobenzaldehyde (1.2 mmol) was used. [e]Reactions performed

in a stainless steel jar under solvent-free ball-milling technique, internal temperature based on friction is 65°C

Next we focused our attention to perform the reaction under solvent-free condition. In this regard, 3-aminocoumarin (**1**), 4-methylbenzaldehyde (**2**), phenyl acetylene (**3**) and ($CuI/Zn(OAc)_2$, 10 mol % each) were placed in high vibrational ball milling apparatus and grinded at 30 Hz. Surprisingly, we obtained 82 % yield of the product within 1h (Table 1, entry 14). Lowering of the catalyst loading ($CuI/Zn(OAc)_2$, 5 mol % each) under ball-milling process decreases the yield of the product (Table 1, entry 16). Finally, it was established that employment of $CuI/Zn(OAc)_2$,@ 7 mol % and 9 mol % respectively provided the desired product (**4b)** within 35 min giving 89% yield (Table 1, entry 15).It was also noticed that on continuation of the optimized reaction for a longer time (50 min) under ball-milling technique has resulted in slightly lowering of the yield (**4b**).At the end of the experiment, all the contents were taken out for column chromatographic separation directly using ethyl acetate/ petroleum ether (1:4).



Scheme 2. Combo-catalysis for $C(sp^2)$-H activation and cyclization

Achieving the optimized reaction condition for our protocol to synthesize pyridocoumarins, we have investigated the substrate scope for this chemical transformation. A wide range of aromatic aldehydes, heteroaromatic aldehydes and substituted 3-aminocoumarins were employed for this reaction.However, desired transformation became unsuccessful under imposed reaction condition when disubstituted alkyne (Diethyl acetylenedicarboxylate) was employed.

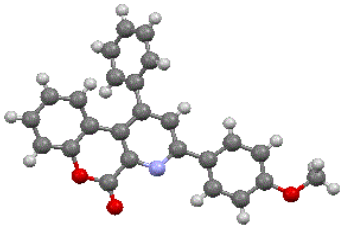
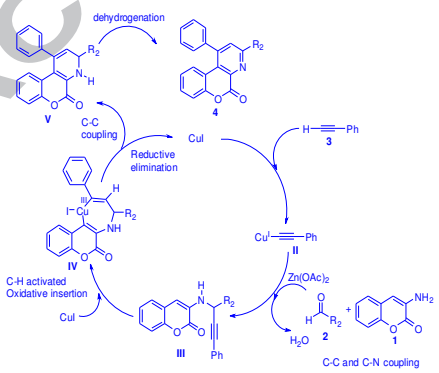
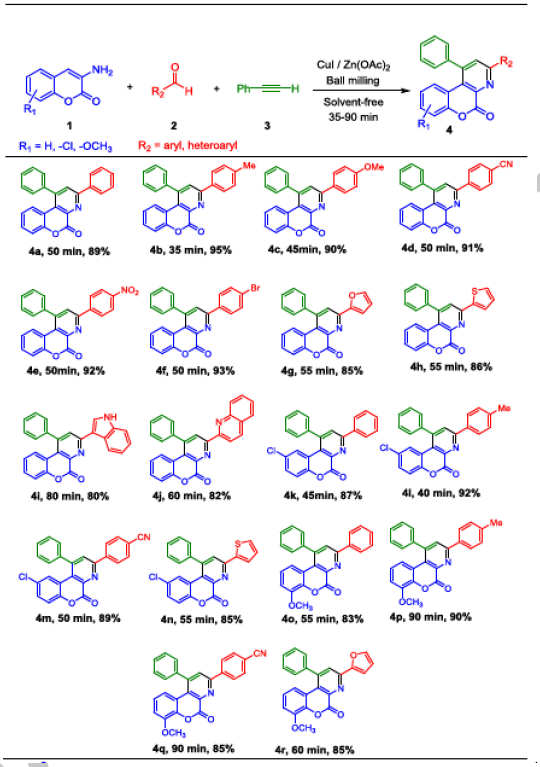


Figure 2. Single Crystal Structure of compound **4c**



Scheme 3. Combo-catalysis cycle

Table 2: Substrate scope for the synthesis of pyridocoumarins[a]



[a] In each case 3-aminocoumarin derivatives (1.0 mmol), substituted aldehyde (1.2 mmol) and phenyl acetylene (1 mmol) were taken in a stainless steel ball milling vial with two stainless steel ball (*d*= 5.0 mm). [b] Yield of the isolated product

This synthetic protocol was found to be extremely facile to access a library of pyridocoumarin derivatives under solvent-free condition (Table 2, entry **4a-4r**). It is noteworthy to mention that the reaction was very clean producing only pyridocoumarin as the sole isolable product and no other side products were detected (Scheme 2). All the synthesized pyridocoumarin derivatives have been well characterized by spectral analysis (^{1}H NMR, ^{13}C NMR, IR) and finally the structural motif of the pyridocoumarin scaffold was established through X-ray crystallographic analysis of single crystal of one representative compound **4c** (CCDC 1540607, Figure 2).

A plausible mechanism for this reaction is depicted in scheme 3. On the basis of the controlled experiments, UV–Vis data[26], XPS data[27] and literature reports[28], we proposed a plausible mechanism for this chemical transformation (scheme 3). At first, CuI activated the terminal C–H of the alkyne to produce (II, Scheme 3). The C–C and C–N bond formation between 3-aminocoumarin (**1**), aldehyde (**2**), and intermediate **II** generated propargylic amine intermediate **III**.[29] $Zn(OAc)_2$ might act as Lewis Acid catalyst to polarize C=O during C-C and C-N coupling to form **III**. The intermediate **III** containing the flexible C-C triple bond allowed CuI to activate the aromatic C–H and π-bonds for oxidative C–H insertion with C–C coupling[30] to form a seven-membered intermediate **IV**. This Cu^{III} containing seven-membered intermediate **IV** was then

transformed into a transient intermediate **V** by reductive elimination of IV. Then intermediate **V** immediately transformed into desired product **4** involving the aromatization of **V** [31](scheme 3).

To establish the reaction mechanism, we conducted several control experiments. In this regard, reaction was performed under catalyst-free condition but it was unable to proceed even after prolonged grinding (Table 1, entries 18). We also performed two separate control experiments with CuI and $Zn(OAc)_2$ (Table 1, entries 1-2) and the reaction did not proceed. Formation of copper acetylide is supported by the fact that the reaction was completely plugged when internal alkyne was employed.The cyclization reaction was ineffective upon using the imine (generated from 3-aminocoumarin and benzaldehyde) and phenylacetylene under imposed reaction condition which justifies that the reaction proceeded without the formation of an imine intermediate.Moreover, application of catalytic amount (10 mol%) of Bronsted acid catalyst[17b] (trifluoroacetic acid) could not trigger the reaction under solvent-free ball milling condition (Table 1, entry 19) and also in DCM medium (Table 1, entry 20).The formation of the transient Cu^{III}-species (**IV**) was confirmed and established by analyzingUV–Vis[26] spectra of the reaction mixture of **4p** at different time interval (15 min, 30 min, 60 min) of the reaction(Figure 3), XPS[27] (Figure 4)and electrospray ionization mass spectrometry (ESI-MS) (for **IV**; e/z 541.9675 [M + H]) of the reaction mixture (**4p**) after 15 min of the reaction.

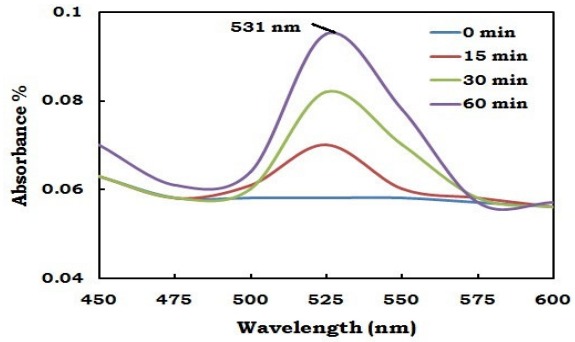


Figure 3.UV-Visible study for detection of aryl-Cu^{III} species

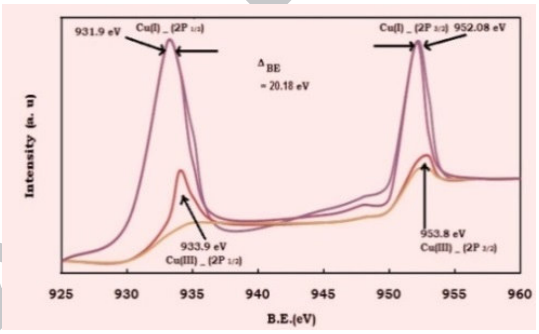


Figure 4. XPS study for detection of Cu^{I}-Cu^{III} species

3. Conclusions

In conclusion, a combo-catalytic, rapid, solvent-free, ball-milling process has been developed for the synthesis of pyridocoumarins starting from 3-aminocoumarin, aldehyde and phenyl acetylene. This method describes a proper example of Cu^{I}-catalyzed $C(sp^2)$-H activation and functionalization involving in-situgenerated aryl-Cu^{III} species. UV-Vis, XPS, ESI-MS, and control experiments were successfully carried out to establish the reaction mechanism which clearly depictsthat the reaction proceeds through a mechanistic pathway of Cu^{I}-Cu^{III} switching.

4. Acknowledgments

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5. References and notes

1. Yamaguchi J, Yamaguchi AD, Itami K. *Angew Chem Int Ed.* 2012;51:8960.

2. (a) Coperet C. *Chem Rev.* 2010;110:656-690; (b) Lyons TW, Sanford MS. *Chem Rev.* 2010;110:1147-1169; (c) Campbell AN, Stahl SS. *Acc Chem Res.*2012;45:851-863; (d) Engle KM, Mei T-S, Wasa M, Yu J-Q. *Acc Chem Res.*2012;45:788-802; (e) Li B, Dixneuf, PH. *Chem Soc Rev.*2013;42:5744-5767; (f) Ackermann L. *Acc Chem Res.*2014;47:281-295.

3.(a) Maiti DK, Halder S, Pandit P, et al.*J Org Chem.* 2009;74:8086-8097; (b) Roy D, Sarkar S, Laha RM, Pramanik N, Maiti DK. *RSC Adv.* 2015;5:73346-73351; (c) Pramanik N, Sarkar S, Roy D, et al. *RSC Adv.* 2015;5:101959-101964; (d) Ueda S, Nagasawa H. *J Am Chem Soc.* 2009;131:15080-15081; (e) Das RK, Saha B, Rahaman SMW, Bera JK. *Chem Eur J.* 2010;16:14459-14468; (f) Carreras J ,Gopakumar G, GuL, Gimeno A, et al. *J Am Chem Soc*. 2013;135:18815-18823; (g) Liu S, Motta A, Delferro M, Marks TJ. *J Am Chem Soc*.2013;135:8830-8833; (h) PiC, Cui X, Wu Y. *J Org Chem.*2015;80:7333-7339.

4. (a) Wei C, Li C-J. *J. Am Chem Soc*. 2002; 124:5638-5693; (b) Gommermann N, Koradin C, Polborn K, Knochel P. *Angew Chem Int Ed*. 2003; 42:5763-5766; (c) Aschwanden P, Stephenson CRJ ,Carreira EM. *Org Lett*. 2006;8:2437-2440; (d) Matsubara S, Okamura T, Asano K. *Synlett*.2010; 3053-3056; (e) Meyet CE ,Pierce CJ, Larsen CH. *Org. Lett*.2012;14: 964-967; (f) Cardoso FSP, Abboud KA, Aponick A. *J Am Chem Soc*.2013;135:14548-14551.

5. (a) Kumar A, Verma M, Saxena AK, Shanker K. *Indian J Chem.* 1987; 26B:378-380; (b)Burlison JA, Neckers L, Smith AB, Maxwell A, Blagg BSJ. *J Am Chem Soc.* 2006; 128:15529.

6. (a) Chen Z, Hu L, Peng F. *Synlett*. 2016; DOI: 10.1055/s-0035-1561610; (b) Kadhum AAH, Mohamad AB, Al-Amiery AA, Takriff MS. *Molecules* 2011; 16:6969-6984.

7. Kulkarni YD, Srivastava D, Bishnoi A, Dua PR. *J Indian Chem Soc*.1996;73:173.

8. Melagraki G, Afantitis A, Igglessi-MarkopoulouO, et al.*Eur J Med Chem.*2009;44:3020.

9. Marcu MG, Schulte TW, NeckersL. *J Natl Cancer Inst*. 2000;92: 242.

10. Rodighiero G,Antonello C. *Boll Chim Farm.*1958;97:592.

11. (a) Hammond PR, Atkins RL. *J Heterocycl Chem.* 1978;12:1061; (b) Atkins RL, Bliss DE. *J Org Chem.* 1978;43:1975; (c) Grandberg II, Denisov LK, Popova OA. *Khim Geterotsikl Soedin.*1987;2:147.

12. Fujimoto A, Sakurai A, Iwase E. *Bull Chem Soc Jpn*. 1976;49:809.

13. Mohanty N, Rath PC, Rout KK. *J Indian Chem Soc.* 1967;44:1001.

14. Majumdar KC, Chattopadhyay B, Taher A. *Synthesis* 2007; 3647-3652.

15. Kudale AA, Kendall J, Miller DO, Collins JL, Bodwell GJ. *J Org Chem.* 2008;73:8437-8447.

16. Kudale AA, Miller DO, Dawe LN, Bodwell GJ. *Org Biomol Chem.*2 011;9:7196.

17. (a) Brown CE, McNulty J, Bordón C, et al. *Org Biomol Chem.* 2016; 14: 5951–5955; (b) Khan AT, Das DK, Islam K, Das P. *Tetrahedron Lett.* 2012;53:6418-6422.

18. (a) Stolle A, Szuppa T, Leonhardt SES, Ondruschka B.*Chem Soc Rev.* 2011;40:2317-2329; (b) Rodríguez B, Bruckmann A, Rantanen T, Bolm C. *Adv Synth Catal.* 2007; 349:2213-2233; (c) Chauhan P, Chimni, SS. *Beilstein J Org Chem.* 2012; 8:2132-2141.

19. (a) Li Z, Jianga Z, Su W.*Green Chem.* 2015; 17:2330-2334.

20. Kaupp G, Naimi-Jamal MR, Schmeyers J. *Tetrahedron* 2003; 59: 3753-3760.

21. Tullberg E, Peters D, Frejd, T. *J Organomet Chem.* 2004; 689:3778-3781.

22. Mack J, Shumba M. *Green Chem.* 2007; 9:328-330.

23. Komatsu K. *Top Curr Chem*. 2005; 254:185-206.
24. Thorwirth R,Stolle A.Ondruschka B. *Green Chem*. 2010; 12:985-991.
25. (a) Das AR, Medda, A ,Singha R. *Tetrahedron Lett*. 2010; 51:1099-1102; (b) Bhattacharyya P, Medda A, Das AR, et al. *J Indian Chem Soc*. 2012; 89:623-629; (c) Kausar N, Mukherjee P, Das AR.*RSC Adv*. 2016; 6:88904-88910; (d) Kausar N, Masum AA, Islam MM, Das AR. *Mol Divers*. 2017; DOI: 10.1007/s11030-017-9728-9.
26. King AE, Huffman LM, Casitas A, et al. *J Am Chem Soc*. 2010; 132: 12068-12073.
27. Kim MS, Yang JB, Medvedeva J, et al. *J Phys: Condens Matter* 2008; 20:255228.
28. Deng X, Liang J, Allison BB, et al.*J Org Chem*. 2015; 80:11003-11012.
29. Rotstein BH, Zaretsky S, Rai V, Yudin AK. *Chem Rev*. 2014; 114: 8323-8359.
30. Arockiam PB, Bruneau C, Dixneuf PH. *Chem Rev*. 2012; 112:5879-5918.
31. Jana R, Paul S, Biswas A, Ray JK. *Tetrahedron Lett*.2010; 51:273-276.

General Procedure for the Synthesis of pyridocoumarins: A mixture of 3-aminocoumarin (**1**, 1 mmol), aldehyde (**2**, 1.2 mmol), phenylacetylene (**3**, 1 mmol), catalyst CuI (0.013 mg, 7 mol %) and $Zn(OAc)_2$ (0.017 mg, 9 mol %) were taken in a stainless steel ball milling vial with two stainless steel ball (*d*= 5.0 mm). Then the vial was placed in a vibrational micromill, and grinded at 30 Hz for 35-90 min. A pause was added after every 10 minutes of grinding until the vial cool down. The progress of the reaction was monitored using TLC. At the end of the experiment, all the contents were taken out for column chromatographic separation directly using ethyl acetate/ petroleum ether (1:4).*Characterization data of* **4c**:White solid (0.341g, 90%); Mp: 206-208 ^{o}C; ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si): δ 3.79 (s, 3H), 6.79-6.81 (m, 1H), 6.91-6.96 (m, 3H), 7.26-7.28 (m, 2H), 7.34-7.38 (m, 2H), 7.47-7.49 (m, 3H), 7.81 (s, 1H), 8.05 (d, J= 8.7 Hz, 2H); ^{13}C NMR (75 MHz; $CDCl_3$; Me_4Si): δ 55.28, 114,16, 117.12, 117.60, 123,51, 126.64, 127.39, 128.03, 128.11, 128.73, 128.91, 129.36, 129.59, 139.07, 139.79, 148.62, 150. 69, 157.02, 159.06, 161.37; IR (KBr): 2936, 1759, 1607cm$^{-1;}$ ESI-MS Calcd. for $C_{25}H_{17}NO_3$: $[M+Na]^+$, 402.1101; Found: m/z 402.1103 (See Supplementary Information).