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One-Pot Sequential Synthesis of Fused Isoquinolines via Intramolecular Cyclization/Annulation and their Photophysical Investigation

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Abstract. One of the cyano group of γ-keto malononitrile gets hydrolyzed selectively to an amide in the presence of copper(II) acetate monohydrate. The *in situ* generated amide undergo an intramolecular dehydrative cyclization to a 1,2-dihydropyridone intermediate. Further annulation of the 1,2-dihydropyridone with an internal alkyne in the same pot produce a fused isoquinolone, 4-oxo-2,6,7-triaryl-4*H*-pyrido[2,1-*a*]isoquinoline-3-carbonitrile. This one-pot process is associated with the formation of one C–C, two C–N, two C=C and a C=O bonds. The final synthesis is a four-step process consisting of selective hydrolysis of a cyano group to an amide, dehydrative cyclization of the amide to a cyclic amide, aromatization of the cyclic amide (2-oxo-1,2,3,4-tetrahydropyridine moiety) to a 2-oxo-1,2-dihydropyridine and finally, the C–H/N–H annulation with an alkyne. Density functional theory calculation reveals that the highest occupied molecular orbital (HOMO) is localized at the central core extending to the nitrile group and a negligible contribution from the two phenyl rings of the diphenylacetylene. On the other hand, the lowest unoccupied molecular orbital (LUMO) is also localized at the identical central core and extended up to the other phenyl ring. The calculated $\Delta E_{(LUMO-HOMO)}$ is in the range of 2.88 to 3.45 eV and the compounds display emission in the green region (502–560) nm and absorption (λ_{max}) in the range of (454–490) nm. Therefore, these molecules may find application in bio-imaging, theranostics and various applications in material science.

Keywords: Isoquinoline; Ru; C–H activation; C–H/N–H annulation; DFT; photoluminescence.

Introduction

Various heterocyclic compounds having potential biological activities have been synthesized *via* Michael adduct with numerous carbon nucleophiles.[1] Malononitrile is one of the useful and convenient precursors for the synthesis of a wide range of fused *N*- and *O*- heterocyclic skeletons.[2] Over the years, many publications have appeared for nitrogen-containing six-membered heterocyclic systems highlighting their biological importance as well as photophysical properties. In the midst of fused-ring nitrogen heterocycles, isoquinolines and isoquinolones are special class possessing comprehensive biological activities (Figure 1) and exists in many synthetic drugs and natural products.[3–5] Further, organic fluorescent molecules, used in organic light emitting diodes (OLEDs),[6] liquid crystal displays (LCDs)[7] and fluorescent dyes[8] are important in bridging between the synthetic organic chemistry and material science.[9] Due to fascinating luminescent[10a,b,c] properties substituted fused isoquinolines[10d] play a significant role in material science (Figure 1). Moreover, numerous organic transformations use isoquinolones as one of the key intermediate.[11] Therefore, it is desirable to develop synthetic protocols for these potentially active heterocycles as target structures for biological evaluation and application in material science. Recently, Jeganmohan group have reported a cobalt catalyzed annulation of benzamides with alkynes to synthesize isoquinolines [Scheme 1, (i)].[12] Van der Eycken, *et al*. described a microwave-assisted Ru(II)-catalyzed highly efficient intermolecular C–H functionalization sequence to access substituted isoquinolones using α-amino esters as the directing group [Scheme 1, (ii)].[13] Of late, transition-metal-catalyzed C–H bond activation[14,15] has gained great attention for the synthesis of bioactive complex nitrogen-containing fused heterocycles, especially, isoquinolines and isoquinolones. In this context Rh(III), Pd(II), Ni(II) and Ru(II) catalysts are most common and have been used extensively to obtain isoquinolones[16] via the oxidative coupling between an internal alkyne and an amide. Recently a two-step protocol has been achieved utilizing two different catalytic systems for the synthesis of highly functionalized molecules.[17]

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The development of one-pot strategies is often ineffective because each step provides several by-products along with unreacted starting materials.

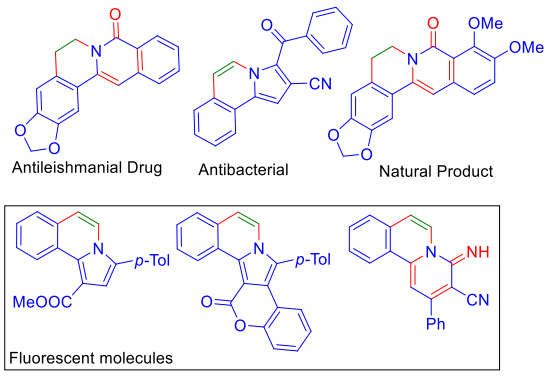
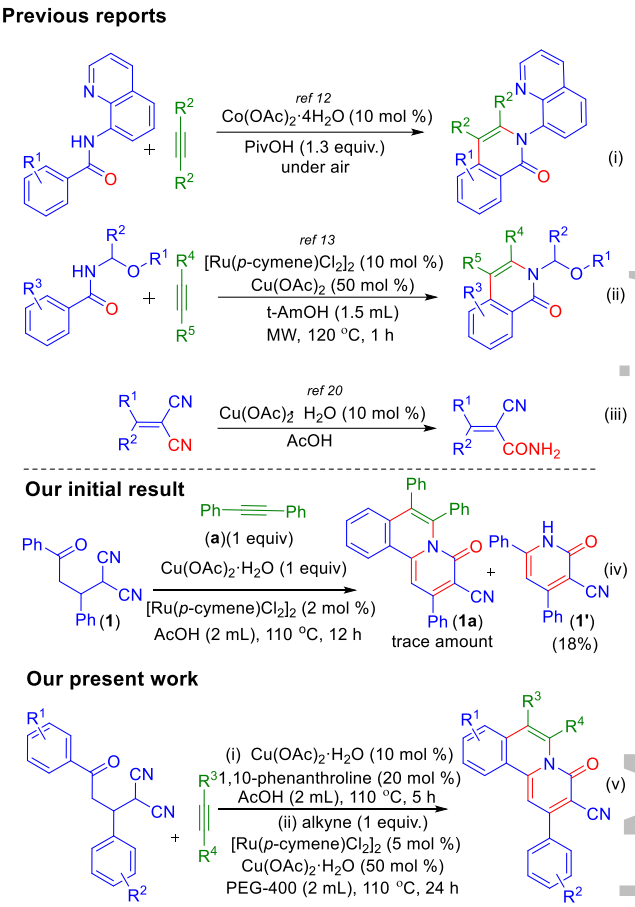


Figure 1. Representative biologically active, natural product and highly fluorescent fused isoquinoline/isoquinolones.

Inspired by transition-metal-catalyzed direct annulation of C–H bonds[18] and the advantage of two-step protocol we envisaged the synthesis of 4-oxo-2,6,7-triphenyl-4*H*-pyrido[2,1-*a*]isoquinoline-3-carbonitrile (**1a**) from a Michael-adduct,[19] 2-(3-oxo-1,3-diphenylpropyl)malononitrile (**1**). The selective hydrolysis of one of the cyano group in γ-keto dicyano compound (**1**) would led to an amide similar to hydrolysis of methylenemalononitrile [Scheme 1, (iii)].[20] The *in situ* generated monoamide may undergo an intermolecular dehydrative cyclization followed by aromatization/oxidation to form a cyclic amide, 1,2-dihydropyridone which has potential C–H/N–H sites for annulation with an alkyne to afford 4-oxo-2,6,7-triphenyl-4*H*-pyrido[2,1-*a*]isoquinoline-3-carbonitrile (**1a**). This reaction involves an intramolecular dehydrative cyclization followed by an intermolecular annulation with an alkyne to obtained a fused isoquinolone framework [Scheme 1, (v)].

Results and Discussion

Our initial investigation started using 2-(3-oxo-1,3-diphenylpropyl)malononitrile (**1**) (0.2 mmol), diphenylacetylene (**a**) (1 equiv.), $Cu(OAc)_2{\cdot}H_2O$ (1 equiv.), and $[Ru(p\text{-cymene})Cl_2]_2$ (2 mol %) in glacial AcOH at 110 °C. Interestingly, the reaction resulted in the formation of a new yellow fluorescent spot (viewed under 365 nm UV lamp) as observed by TLC. Unfortunately, the compound could not be separated for characterization as it was associated with several other side products. However, a decent amount (18%) of expected cyclic 1,2-dihydropyridone intermediate *viz.* 2-oxo-4,6-diphenyl-1,2-dihydropyridine-3-carbonitrile (**1´**) could be isolated [Scheme 1, (iv)]. Encourage by the success of our anticipated strategy we adopted a two-step protocol. In the first step the 2-(3-oxo-1,3-diphenylpropyl)malononitrile (0.2 mmol) (**1**) was treated with $Cu(OAc)_2{\cdot}H_2O$ (1 equiv.) in AcOH (2 mL) at 110 °C and the reaction was continued for 5 h, during this period all the starting materials got consumed giving 1,2-dihydropyridone intermediate (**1´**) as the major product along with significant amounts of other uncharacterized by-products.



Scheme 1. Strategies for the synthesis of fused isoquinolones.

To this crude reaction mixture, diphenylacetylene (**a**) (1 equiv.) and $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol %) were added and the reaction was allowed to proceed for 12 h. The reaction was found to be much cleaner and the product (**1a**) was isolated in 30% yield. The product was separated and characterized by spectroscopic analysis (IR, ^{1}HNMR, ^{13}CNMR, and HRMS) and the structure was found to be 4-oxo-2,6,7-triphenyl-4*H*-pyrido[2,1-*a*]isoquinoline-3-carbonitrile (**1a**). Finally, the structure of the product (**1a**) was reconfirmed by single crystal X-ray diffraction study (Figure 2). This one-pot transformation of 2-(3-oxo-1,3-diphenylpropyl)malononitrile (**1**) to a 4-oxo-2,6,7-triphenyl-4*H*-pyrido[2,1-*a*]isoquinoline-3-carbonitrile (**1a**) is accompanied by the formation of new C–C, C–N, C=C and C=O bonds. Observing the structure of the product it is evident that the amidic carbonyl group in the product (**1a**) is not the original carbonyl group of the starting material (**1**). Thus, it may possibly be originating by the selective hydrolysis of one of the cyano group. An ^{18}O incorporated product was detected when the typical reaction was carried

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out in the presence of $H_2{}^{18}O$, thereby confirming water to be the source of oxygen in the product (**1a**). Although, synthetic strategies of some of the isoquinolone involve C–H bond activation and annulation of various amides with internal alkynes employing transition metal catalysts[12-14] we feel our report exploring the alternative pattern would be useful to the synthetic community.

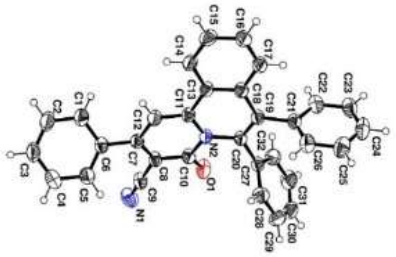
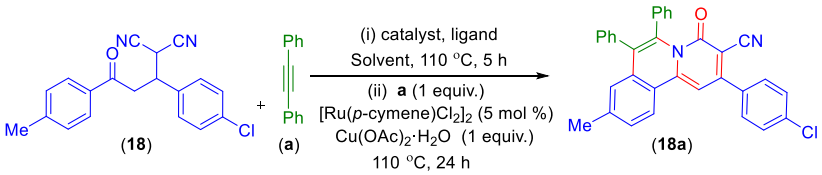


Figure 2. ORTEP diagram of compound (1a) with 40% ellipsoid probability. [21a]

Encouraged by the above one-pot two-fold sequential synthesis of fused isoquinoline, further optimizations were carried out by varying various reaction parameters using 2-(1-(4-chlorophenyl)-3-oxo-3-(*p*-tolyl)propyl)malononitrile (**18**) as the model substrate and diphenylacetylene (**a**) as the annulating partner in the presence of $Cu(OAc)_2{\cdot}H_2O$ and [Ru(*p*-cymene)$Cl_2]_2$. Fixing the conditions [*i.e.* diphenyl acetylene (**a**) (1 equiv.), $Cu(OAc)_2{\cdot}H_2O$ (1 equiv.) and [Ru(*p*-cymene)$Cl_2]_2$ (5 mol %)] of the second step (*i.e.* annulating step), reaction parameters for the first steps (*i.e.* hydrolytic-dehydrative cyclization) were varied. Among various solvents such as *p*-xylene (00%), toluene (00%), DMF (00%) and DMSO (00%) were tested (Table 1, entries 2–5) all were found to be ineffective compared to AcOH (45%) (Table 1, entry 1). When the reaction was carried out in the absence of Cu(II)-catalyst very poor yield (<10%) of (**18a**) was detected (Table 1, entry 6), suggesting the involvement of copper salt in facilitating the reaction, possibly via the coordination with the cyano (–CN) group. The selective hydrolysis of one of the cyano group in the presence of Cu(II) catalyst is in agreement with earlier report.[20] An improvement in the yield (55%) was observed when the ligand 1,10-phenanthroline (10 mol %) was used (Table 1, entry 7). Keeping the catalyst loading constant (10 mol %), an increase in the ligand loading to 15 and 20 mol % improved the yield to 60 and 65% respectively (Table 1, entry 8–9).

Table 1. Optimization of the reaction conditions for the first step.[a-e]



Entry	Catalyst (mol %)	Ligand (mol %)	Solvent	Yield (%)[b]
1	$Cu(OAc)_2{\cdot}H_2O$ (10)		AcOH	45
2	$Cu(OAc)_2{\cdot}H_2O$ (10)		*p*-xylene	00
3	$Cu(OAc)_2{\cdot}H_2O$ (10)		Toluene	00
4	$Cu(OAc)_2{\cdot}H_2O$ (10)		DMF	00
5	$Cu(OAc)_2{\cdot}H_2O$ (10)		DMSO	00
6			AcOH	<10
7	$Cu(OAc)_2{\cdot}H_2O$ (10)	1,10-phenanthroline (10)	AcOH	55
8	$Cu(OAc)_2{\cdot}H_2O$ (10)	1,10-phenanthroline (15)	AcOH	60
9	**$Cu(OAc)_2{\cdot}H_2O$ (10)**	**1,10-phenanthroline (20)**	**AcOH**	**65**
10	$Cu(OAc)_2{\cdot}H_2O$ (20)	1,10-phenanthroline (20)	AcOH	65
11	$Cu(OAc)_2{\cdot}H_2O$ (10)	2,2'-bipyridyl (20)	AcOH	55
12	$Cu(OAc)_2{\cdot}H_2O$ (10)	L-proline (20)	AcOH	48
13	$Cu(OAc)_2{\cdot}H_2O$ (10)	Jhon Phos (20)	AcOH	28
14	$Cu(OAc)_2{\cdot}H_2O$ (10)	PPh_3 (20)	AcOH	27
15	$Cu(OAc)_2{\cdot}H_2O$ (10)	1,10-phenanthroline (20)	AcOH	26[c]
16	$Cu(OAc)_2{\cdot}H_2O$ (10)	1,10-phenanthroline (20)	AcOH	42[d]
17	$Cu(OAc)_2{\cdot}H_2O$ (10)	1,10-phenanthroline (20)	AcOH	67[e]

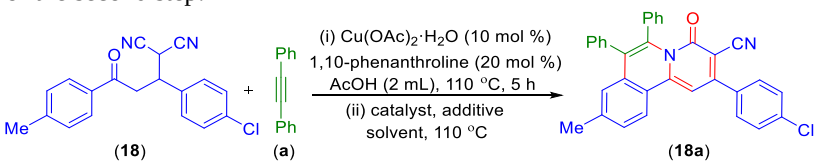
a) Reaction condition: 2-(1-(4-chlorophenyl)-3-oxo-3-(p-tolyl)propyl)malononitrile (18) (0.2 mmol), catalyst (mol %), ligand (mol %) at 110 °C for 5 h. b) Isolated yields. c) Temperature 90 °C. d) Temperature 130 °C. e) Yield after 12 h.

Maintaining the ligand loading to 20 mol % and increasing the catalyst loading up to 20 mol % did not alter the product yield (65%) any further (Table 1, entry 10). With $Cu(OAc)_2{\cdot}H_2O$ (10 mol %) as the suitable catalyst and AcOH as the solvent the use of other ligands such as 2,2´-bipyridyl (52%), L-proline

(48%), JhonPhos (28%), PPh_3 (27%) were screened (Table 1, entries 11–14). All the ligands tested gave lower yields compared to 1,10-phenanthroline (65%) (Table 1, entry 9). Reaction carried out both at higher 130 °C (42%) or lower 90 °C (26%) temperature was detrimental to the product formation (Table 1, entries 15 and 16). No significant improvement in the overall yield (67%) was observed when the hydrolytic dehydrative-cyclization step of the reaction mixture was maintained up to 12 h. After screening of various reaction parameters, the optimized condition for this transformation in the first step is the use of 2-(1-(4-chlorophenyl)-3-oxo-3-(*p*-tolyl)propyl)malononitrile (**18**) (0.2 mmol), $Cu(OAc)_2·H_2O$ (10 mol %), and 1,10-phenanthroline (20 mol %), at 110 °C in AcOH (2 mL) (Table 1, entry 9).

Maintaining the optimized condition for the hydrolytic-dehydrative cyclization step (Table 1, entry 9), further optimization was carried out for the annulation step using $[Ru(p\text{-cymene})Cl_2]_2$ as the catalyst in AcOH at 110 °C. Increasing the amount of catalyst loading (from 2 to 5 mol %) marginally enhanced the yield of the desired product (27 to 38%, Table 2, entries 1–2). No significant improvement in the product yield (40%) was observed even when the catalyst loading was increased to 10 mol % (Table 2, entry 3). Among the additives such as, $AgSbF_6$ (31%), AgOTf (33%), $Cu(OAc)_2$ (36%) and $Cu(OAc)_2·H_2O$ (38%) (Table 2, entries 4–7), the later proved to be the best choice (Table 2, entry 7). The yield progressively improved from 38 to 52% as the additive $Cu(OAc)_2·H_2O$ loading increased from 10 to 50 mol % (Table 2, entries 7–10). No significant improvement in the product yield (53%) was observed even when the additive loading was increased up to 1 equiv. (Table 2, entry 11). Since the intermediate dihydropyridone (**18´**) form in the first step precipitated in AcOH medium, thus, it was felt necessary to have additional co-solvent in the second step to make the medium homogeneous. Among few representative solvents tested such as ^{t}AmOH (18%), MeOH (12%), iso-propanol (16%) (Table 2, entries 12–15), PEG-400 proved to be the best choice, affording the annulated product (**18a**) in 72% yield (Table 2, entry 15). No major improvement in the yield was observed even when the quantity of diphenylacetylene (**a**) was increased to 1.5 equiv. (74%) and 2 equiv. (75%) (Table 2, entries 16 and 17). Both decrease (80 °C) or increase (130 °C) in the reaction temperature resulted lowering in the product yields (36% and 42% respectively) (Table 2, entries 18 and 19). When the reaction was stopped after 12 h the product (**18a**) was isolated in lower yield (59%) as substantial amount of intermediate 1,2-dihydropyridone remain unconsumed (Table 2, entry 20). To see the efficacy in a step wise process, the intermediate **1'** was isolated in 82% yield that was subsequently subjected to the annulation step which provided 64% yield of the product (**1a**), thus giving an overall yield of 52%. Although this two-step yield (52%) is slightly better than the one step process (45%) for convenience we preferred the later.

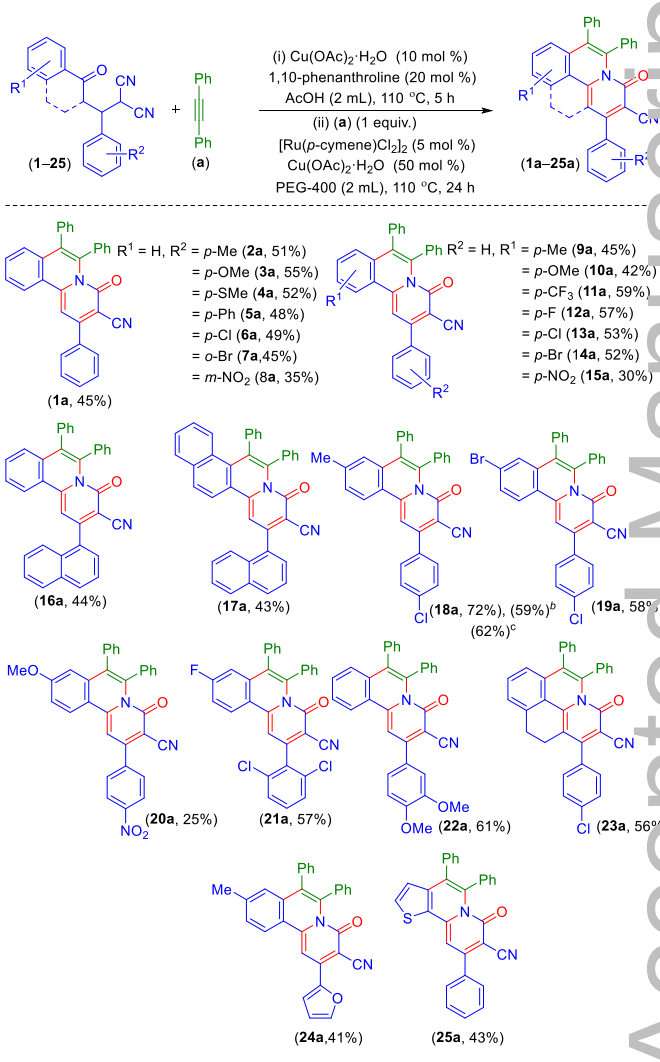
Table 2. Optimization for the second step.[a-h]



Entry	Catalyst (mol %)	Additive (mol %)	Solvent	Yield (%)[b]
1	$[Ru(p\text{-cymene})Cl_2]_2$ (2)		AcOH	27
2	$[Ru(p\text{-cymene})Cl_2]_2$ (5)		AcOH	38
3	$[Ru(p\text{-cymene})Cl_2]_2$ (10)		AcOH	40
4	$[Ru(p\text{-cymene})Cl_2]_2$ (5)	$AgSbF_6$ (10)	AcOH	31
5	$[Ru(p\text{-cymene})Cl_2]_2$ (5)	AgOTf (10)	AcOH	33
6	$[Ru(p\text{-cymene})Cl_2]_2$ (5)	$Cu(OAc)_2$ (10)	AcOH	36
7	$[Ru(p\text{-cymene})Cl_2]_2$ (5)	$Cu(OAc)_2·H_2O$ (10)	AcOH	38
8	$[Ru(p\text{-cymene})Cl_2]_2$ (5)	$Cu(OAc)_2·H_2O$ (20)	AcOH	42
9	$[Ru(p\text{-cymene})Cl_2]_2$ (5)	$Cu(OAc)_2·H_2O$ (30)	AcOH	46
10	$[Ru(p\text{-cymene})Cl_2]_2$ (5)	$Cu(OAc)_2·H_2O$ (50)	AcOH	52
11	$[Ru(p\text{-cymene})Cl_2]_2$ (5)	$Cu(OAc)_2·H_2O$ (100)	AcOH	53[c]
12	$[Ru(p\text{-cymene})Cl_2]_2$ (5)	$Cu(OAc)_2·H_2O$ (50)	^{t}AmOH	18
13	$[Ru(p\text{-cymene})Cl_2]_2$ (5)	$Cu(OAc)_2·H_2O$ (50)	MeOH	12
14	$[Ru(p\text{-cymene})Cl_2]_2$ (5)	$Cu(OAc)_2·H_2O$ (50)	iso-propanol	16
15	**$[Ru(p\text{-cymene})Cl_2]_2$ (5)**	$Cu(OAc)_2·H_2O$ (50)	**PEG-400**	**72**
16	$[Ru(p\text{-cymene})Cl_2]_2$ (5)	$Cu(OAc)_2·H_2O$ (50)	PEG-400	74[d]
17	$[Ru(p\text{-cymene})Cl_2]_2$ (5)	$Cu(OAc)_2·H_2O$ (50)	PEG-400	75[e]
18	$[Ru(p\text{-cymene})Cl_2]_2$ (5)	$Cu(OAc)_2·H_2O$ (50)	PEG-400	36[f]
19	$[Ru(p\text{-cymene})Cl_2]_2$ (5)	$Cu(OAc)_2·H_2O$ (50)	PEG-400	42[g]
20	$[Ru(p\text{-cymene})Cl_2]_2$ (5)	$Cu(OAc)_2·H_2O$ (50)	PEG-400	59[h]

[a)] Reaction condition: 2-(1-(4-chlorophenyl)-3-oxo-3-(*p*-tolyl)propyl)malononitrile (**18**) (0.2 mmol), diphenylacetylene (**a**) (0.2 mmol), catalyst (mol %) additive (mol %.) at 110 °C for 24 h. [b)] Isolated yields. [c)] 1 equiv. additive was used. [d)] 1.5 equiv. of (**a**) was used. [e)] 2 equiv. of (**a**) was used. [f)] Temperature 80 °C. [g)] Temperature 130 °C. [h)] Yield after 12 h

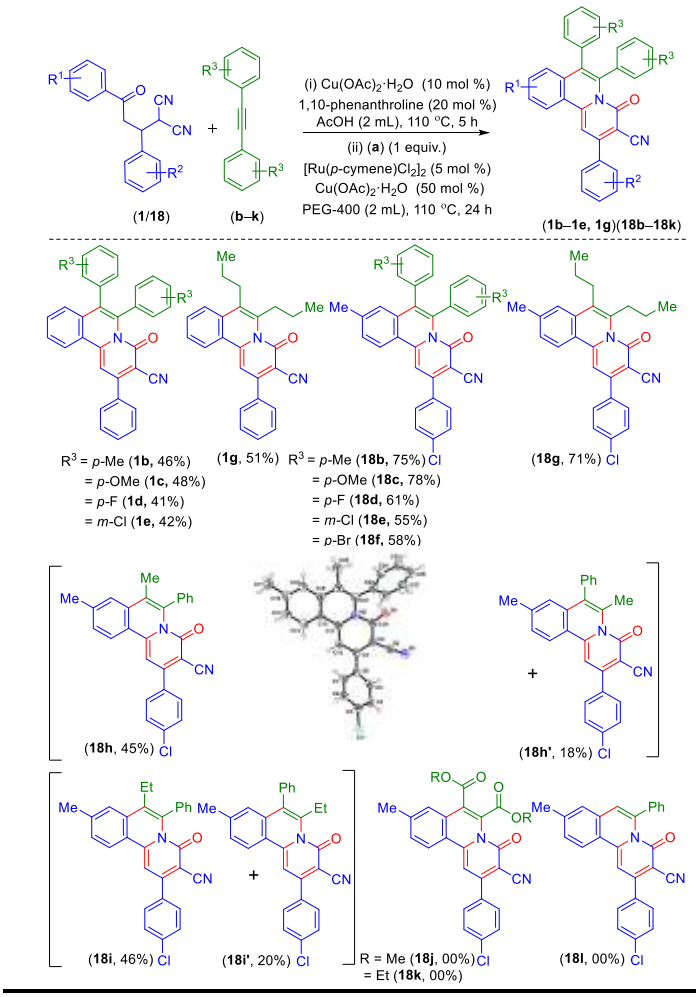
This one-pot two-step synthesis of 4-oxo-2,6,7-triaryl-4*H*-pyrido[2,1-*a*]isoquinoline-3-carbonitrile was then explored with various other γ-keto-malononitriles with diphenylacetylene (**a**) under the optimized reaction condition (Scheme 2). A substrate (1), having both unsubstituted phenyl rings coupled with diphenylacetylene (a), yielding its fused isoquinoline (**1a**, 45%) in moderate yield (Scheme 2). Reactants having an electron-neutral substituent (-H) in the phenyl ring attached towards keto group and electron-donating substituents such as *p*-Me (**2**), *p*-OMe (**3**), *p*-SMe (**4**), and *p*-Ph (**5**) in the other phenyl ring reacted successfully with diphenylacetylene (**a**), yielding their fused isoquinolines (**2a**), (**3a**), (**4a**) and (**5a**) in 51%, 55%, 52% and 48% yields respectively (Scheme 2). When the phenyl ring α- to the malononitrile is substituted with electron-withdrawing substituents such as *p*-Cl (**6**), *o*-Br (**7**), and *m*-NO_2 (**8**) all provided their respective products (**6a**, 49%), (**7a**, 45%) and (**8a**, 35%) (Scheme 2). This methodology was equally successful when the phenyl ring α- to the malononitrile is unsubstituted and the aroyl phenyl ring is substituted with either electron-donating *p*-Me (**9**), and *p*-OMe (**10**) or electron-withdrawing groups such as *p*-CF_3 (**11**), *p*-F (12), *p*-Cl (**13**), *p*-Br (**14**) and *p*-NO_2 (**15**) all yielded their respective fused isoquinolines (**9a**, 45%), (**10a**, 42%), (**11a**, 59%), (**12a**, 57%), (**13a**, 53%), (**14a**, 52%), and (**15a**, 30%). Although, the yields obtained here is not high but considering the number of steps involved in the process, such as selective hydrolysis of a cyano group to an amide, followed by a dehydrative cyclization of an unreactive amide, aromatization and finally, the C–H/N–H annulation with an alkyne, these yields are very well acceptable. This protocol was explored to a substrate (**16**), having a naphthyl ring instead of a phenyl ring and to another substrate (**17**) having a 1-naphthyl ring towards the malononitrile and a 2-naphthyl ring towards the keto side, both provided their respective products (**16a**) and (**17a**) in 44% and 43% yields (Scheme 2). Similarly, the presence of various other substituents either electron-donating groups (EDGs) or electron-withdrawing groups (EWGs) in any or both the phenyl rings all provided their anticipated products. As demonstrated earlier, the substrate (**18**) having EDG *p*-Me and EWG *p*-Cl gave good yield (72%) of the product (**18a**). Other Michael adducts bearing EWG *p*-Br/EWG *p*-Cl (**19**) and EDG *p*-OMe/EWG *p*-NO_2 (**20**) both provided their resultant products (**19a**, 58%) and (**20a**, 25%) respectively. Observing the trends in the yield obtained in Scheme 2, there is no correlation between the nature of the substituents present in either of the phenyl rings. Besides mono-substituted phenyl rings, di-substituted aryl rings α-to malononitrile side such as 2,6-dichloro (**21**) and 3,4-diOMe (**22**) reacted efficiently giving good yields of their products (**21a**, 57%) and (**22a**, 61%) respectively. Besides flexible keto substrates in (Scheme 2), a cyclic γ-keto substrate (**23**) underwent efficient transformation to its fused isoquinoline product (**23a**) in 56% yield. Further, a furan (**24**) or a thiophene (**25**) bearing substrates were quite compatible and yielded their resultant products (**24a**, 41%) and (**25a**, 43%) respectively. To evaluate the potential of this two-step process and to expand the scope of this reaction, (**18**) and (**a**) were reacted on a 1 mmol scale which provided isoquinolone (**18a**) in 62% yield (Scheme 2).



[a] Reaction conditions: (i) **1**–**25** (0.2 mmol), $Cu(OAc)_2·H_2O$ (0.02 mmol), 1,10-phenanthroline (0.04 mmol), and glacial AcOH (2 mL) at 110 °C for 5 h. (ii) diphenylacetelene (**a**) (0.2 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (0.01 mmol), $Cu(OAc)_2·H_2O$ (0.1 mmol) and PEG-400 (2 mL) at 110 °C for 24 h. [b)] Yield after 12 h, [c)] Yield reported for 1 mmol scale.

Scheme 2. Substrate scope for the synthesis of 4-Oxo-2,6,7-triphenyl-4*H*-pyrido[2,1-a]isoquinoline-3-carbonitriles.[a-c]

In order to further expand the scope of this methodology, the compatibility of various alkynes was tested with two selected γ-keto malononitriles namely, (**1**) and (**18**) (Scheme 3). The reaction proceeded smoothly with different symmetrical 1,2-diarylacetylenes (**b**–**e**), possessing either electron-donating groups such as *p*-Me (**b**), *p*-OMe (**c**) or electron-withdrawing groups such as *p*-F (**d**), and *m*-Cl (**e**) irrespective of their position of attachments. All underwent efficient annulation when reacted with γ-keto malononitrile (**1**) providing their expected fused isoquinolines (**1b**, 46%), (**1c**, 48%), (**1d**, 41%), and (**1e**, 42%) respectively. Besides symmetrical 1,2-diarylacetylenes (**b**–**e**), an aliphatic symmetrical alkyne, 4-octyne (**g**), upon reaction with (**1**) provided 51% yield of the product (**1g**) (Scheme 3). All these symmetrical internal alkynes (**b**–**g**) reacted competently with another γ-keto malononitrile (**18**), providing their corresponding annulated products (**18b**, 75%), (**18c**, 78%), (**18d**, 61%), (**18e**, 55%), (**18f**, 58%), and (**18g**, 71%) respectively (Scheme 3). Observing the trend in the yields for substrates (**1**) and (**18**) with various substituted aryl alkynes (**b**–**f**), it was found that aryl alkynes possessing electron-donating substituents (*p*-Me, *p*-OMe) provided better yields than the aryl alkynes having electron-withdrawing substituents (*p*-F, *m*-Cl, and *p*-Br) (Scheme 3).



[a] Reaction conditions: (i) **1**/**18** (0.2 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.02 mmol), 1,10-phenanthroline (0.04 mmol), and glacial AcOH (2 mL).at 110 °C for 5 h. (ii) **b**–**k** (0.2 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (0.01 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.1 mmol) and PEG-400 (2 mL) at 110 °C for 24 h.

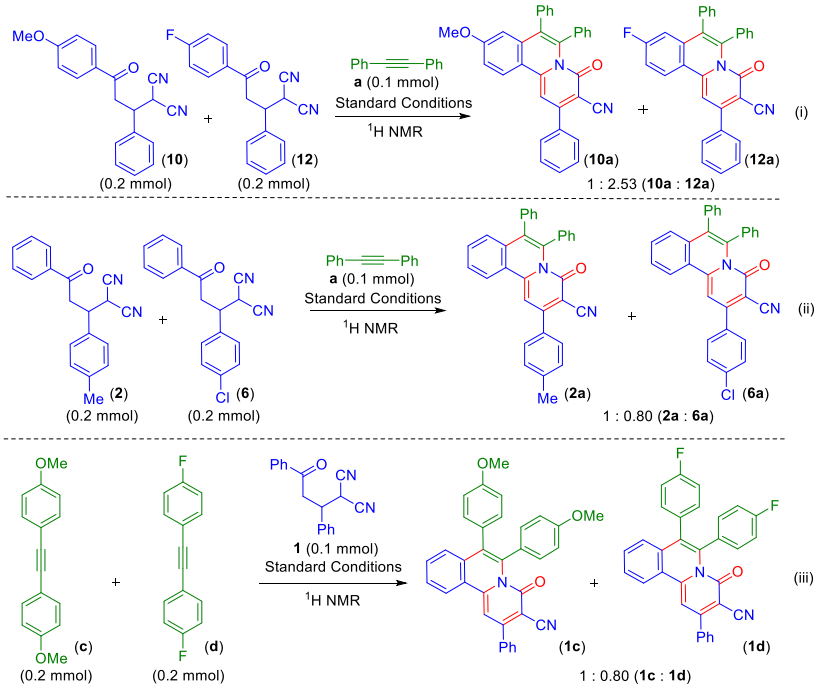
Scheme 3. Substrate scope for alkynes.[a]

To check the regioselectivity of this C–H/N–H annulation, in an unsymmetrical alkyne, 1-phenyl-1-propyne (**h**), whether it is taking place towards the phenyl side or the alkyl side, it was reacted with (**18**) under an identical condition. The reaction provided a regio-isomeric mixture of (**18h**) and (**18h´**) in 2.4 : 1 ratio in a combined yield of 63%, suggesting the attachment of the benzylic carbon to the N atom of the *in situ* generated 2-pyridone intermediate. The structure of the major regioisomer (**18h**) was confirmed by X-ray crystallography analysis (Scheme 3).[21b] Further, another unsymmetrical alkyne, 1-phenyl-1-butyne (**i**) also afforded a regio isomeric mixture of products (**18i**) and (**18i´**) in the ratio of 2.3 : 1 in a combined yield of 65% which is almost identical to that of product obtained from alkyne (**h**). This preferential reactivity of the N atom at the benzylic carbon of an unsymmetrical internal alkynes[16] (**h**) and (**i**) leading to regioselective C–H/N–H annulation is similar to other (C–H/O–H and C–H/S–H) hetero annulation reactions.[22] Highly electron-deficient symmetrical aliphatic alkynes, such as dimethylacetylenedicarboxylate (**j**) and diethylacetylenedicarboxylate (**k**) both failed to react with substrate (**18**) giving no traces of the annulated products (**18j**) and (**18k**). It should be mentioned here that these electron-deficient alkynes (**j** and **k**) reacts efficiently during C–H/S–H annulation process[22b] demonstrating the lower propensity for C–H/N–H annulation. This method is however unsuccessful for terminal alkynes such as phenyl acetylene (**l**) giving no annulated product (**18l**).

Whether the electronic effect of the substituents (R^1) on the aroyl phenyl ring have any influence on the reaction, an equimolar mixture of substrates having an electron-donating *p*-OMe (**10**) and an electron-withdrawing *p*-F (**12**) were reacted with diphenylacetylene (**a**) (Scheme 4 (i)). The ratio of the products (**10a**) : (**12a**) obtained was 1 : 2.53, suggesting a slightly higher reactivity of electron-withdrawing substrate *p*-F (**12**) compared to electron-donating substrate *p*-OMe (**10**) [(Scheme 4 (i)]. Further, to see the effect of substituents, either an EDG *p*-Me (**2**) or an EWG *p*-Cl (**6**) present on the phenyl rings (R^2 *i.e.* α-to malononitrile) were reacted with diphenylacetylene (**a**). The ratio of the products **2a** : **6a** obtained was 1 : 0.80 [Scheme 4 (ii)] suggesting the preferential reactivity of electron-donating substituents (R^2) in this annulation reaction. Next, the nature of the substituents present on the phenyl rings of the alkynes was investigated. In an intermolecular competition reaction between an electron-rich alkyne *p*-OMe (**c**) and a relatively electron-deficient alkyne *p*-F (**d**), both yielded their annulated products (**1c**) and (**1d**) in the ratio of 1 :

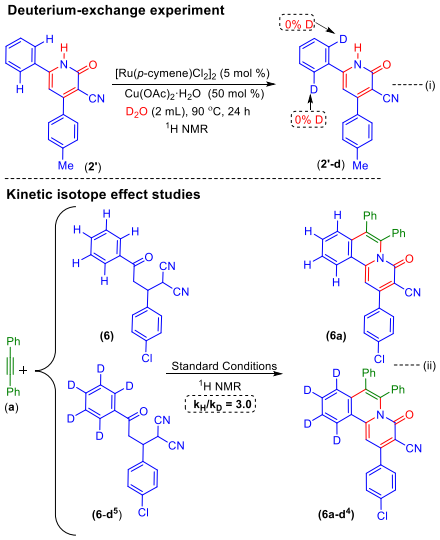
0.80 suggesting a slight preferential reactivity of the electron-rich alkyne (**c**) over the electron-deficient alkyne *p*-F (**d**) [Scheme 4 (iii)].

Next, to understand the mechanism and nature of the C–H bond activation, whether the C–H metalation step is reversible or irreversible a deuterium-scrambling experiment was performed. The deuterium exchange experiment on the isolated intermediate (**2´**) in the absence of an alkyne under the standard reaction



Scheme 4. Intermolecular competition experiments.

condition in D_2O did not afford any deuterium exchange at the ortho-C–H of the annulating phenyl ring, suggesting an irreversible C–Ru bond formation[23a] [Scheme 5, (i)]. Further, in an intermolecular competition experiment between (**6**) and its deuterated analogue (**6-d$_5$**) with (**a**), an observed k_H/k_D = 3.00 signifies the irreversible C–H bond cleavage to be the rate-limiting step [Scheme 5, (ii)].[23b,c]



Scheme 5. Experiments with isotopically labelled compounds.

Mechanism

Based on the above isotopic experiments and from previous reports,[13,24,25] a plausible mechanism is depicted in Scheme 6. In the first step, one of the nitrile (–CN) group of the substrate (**1**) is hydrolyzed selectively to a mono amidic intermediate (**I**). The NH_2 of the amide then attacks at the carbonyl group and undergoes a dehydrative-cyclization to produce a six-membered cyclic intermediate (**II**). The intermediate (**II**) is oxidized/aromatized under the reaction conditions to an aromatic pyridone intermediate (**III**). Formation of intermediate (**I**), (**II**) and (**III**) has been detected by the HRMS analysis of the reaction aliquots at various time intervals [see Supporting Information (SI)]. In the second step the catalyst $[RuCl_2(p\text{-cymene})]_2$ undergoes ligand exchange with $Cu(OAc)_2{\cdot}H_2O$ to generate the active catalytic species, which coordinates with the nitrogen atom of the intermediate (**III**) via NH deprotonation. This is then followed by ortho C–H bond activation through the elimination of AcOH, forming a five-membered ruthenacycle (**V**). Further coordination of the alkyne (**a**), followed by an alkyne insertion and reductive elimination afforded the final product (**1a**) via the intermediate (**VI**). The active catalyst species is then regenerated by the oxidant $Cu(OAc)_2{\cdot}H_2O$ and air for the next catalytic cycle (Scheme 6).

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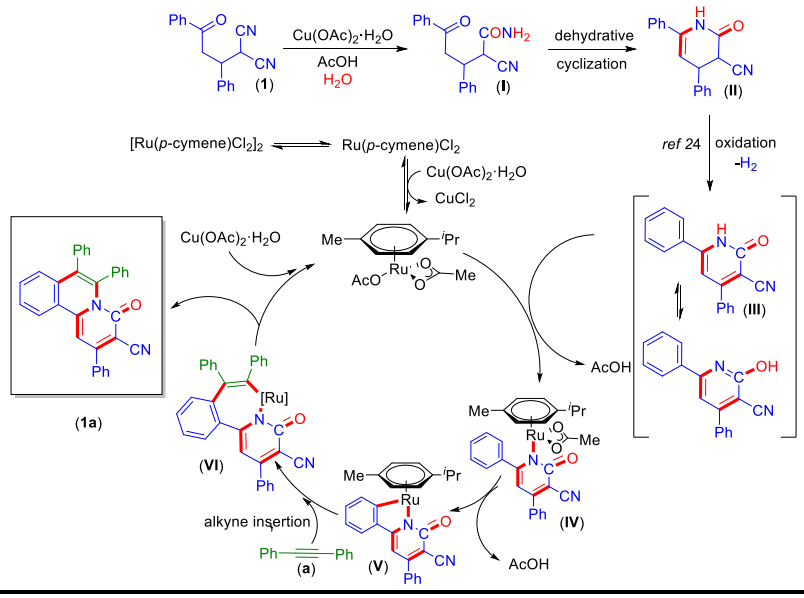

Scheme 6. Plausible reaction mechanism.

Theoretical Investigation

The crystal structure of (**1a**) reveals the presence of a slightly twisted 4*H*-pyrido[2,1-*a*]isoquinoline-3-one core and the three phenyl rings are out of the molecular plane. While the aroyl ring is part of the 4*H*-pyrido[2,1-*a*]isoquinoline-3-one core, the phenyl ring α- to the malononitrile is twisted out of the planar core with a dihedral angle of 42.58°. The two phenyl rings originating from the diphenylacetylene moiety are also twisted out of the molecular plane with a dihedral angle of 78.16° and 85.24° respectively. To further ascertain the geometry and electronic structure of the annulated fused isoquinoline, density functional theory (DFT) calculations were performed with a B3LYP/6-31G (d, p) basis set level in acetonitrile solvent modeled by the PCM approach (the Gaussian 09 programme).[26] The density functional theory (DFT) calculation of (**1a**) reveals that the electron density in the highest occupied molecular orbital (HOMO) is localized at the central core extending to the nitrile and minor contributions from the two phenyl rings originating from the diphenylacetylene. Whereas the lowest unoccupied molecular orbital (LUMO) is again localized at the central core and extended up to the phenyl ring originating from the α to the malononitrile (Figure 3).

In a donor-π-acceptor (D-π-A) type system the $\Delta E_{(LUMO-HOMO)}$ energy can be directly correlated with the presence of either electron-donating or electron-withdrawing groups on the donor (HOMO) or the acceptor (LUMO) part of the molecule.[27] Here, since both the HOMO and LUMO are localized on the central molecular core with very insignificant contributions from the three phenyl rings, no proper correlation between the HOMO-LUMO energy gap could be found due the presence of EDG or EWG groups. The calculated $\Delta E_{(LUMO-HOMO)}$ energy gap for unsubstituted (**1a**), *p*-Me substituted (**1b**), *p*-OMe substituted (**1c**) and *p*-F substituted (**1d**) isoquinolines respectively are 3.42, 3.41, 3.34 and 3.43 eV (Figure 4). When a 1,2-dialkylacetylene, namely, 4-octyne (**g**) was replaced with the diphenylacetylene (**a**) in the fused isoquinolines moiety (**1g**), the energy gap was found to be 3.39 eV (Figure 4). The calculated $\Delta E_{(LUMO-HOMO)}$ energy of various other substituents either in the acceptor (LUMO) or in the donor (HOMO) are summarized in Figure S13, Figure S14 and Figure S15 (SI).

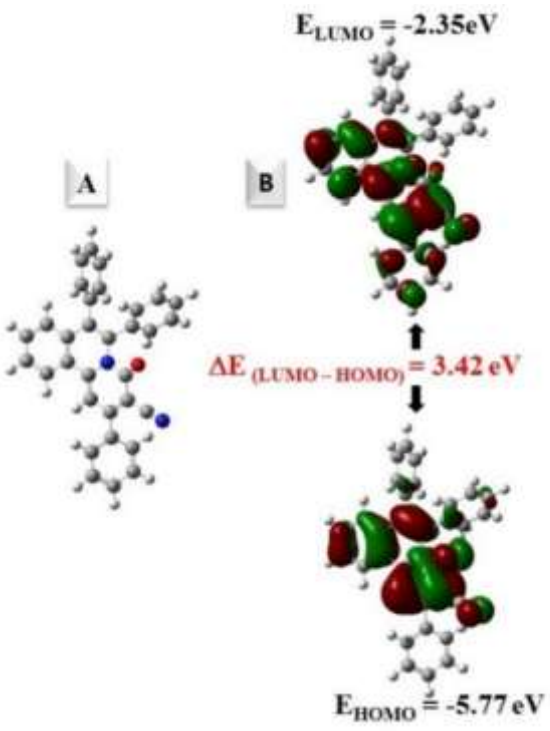

Figure 3. a) Optimized structure of **1a;** b) Molecular orbitals amplitude plots of HOMO and LUMO of **1a** using density functional theory calculation at the B3LYP/6-31G (d, p) basis set level in acetonitrile solvent modelled by the PCM approach.

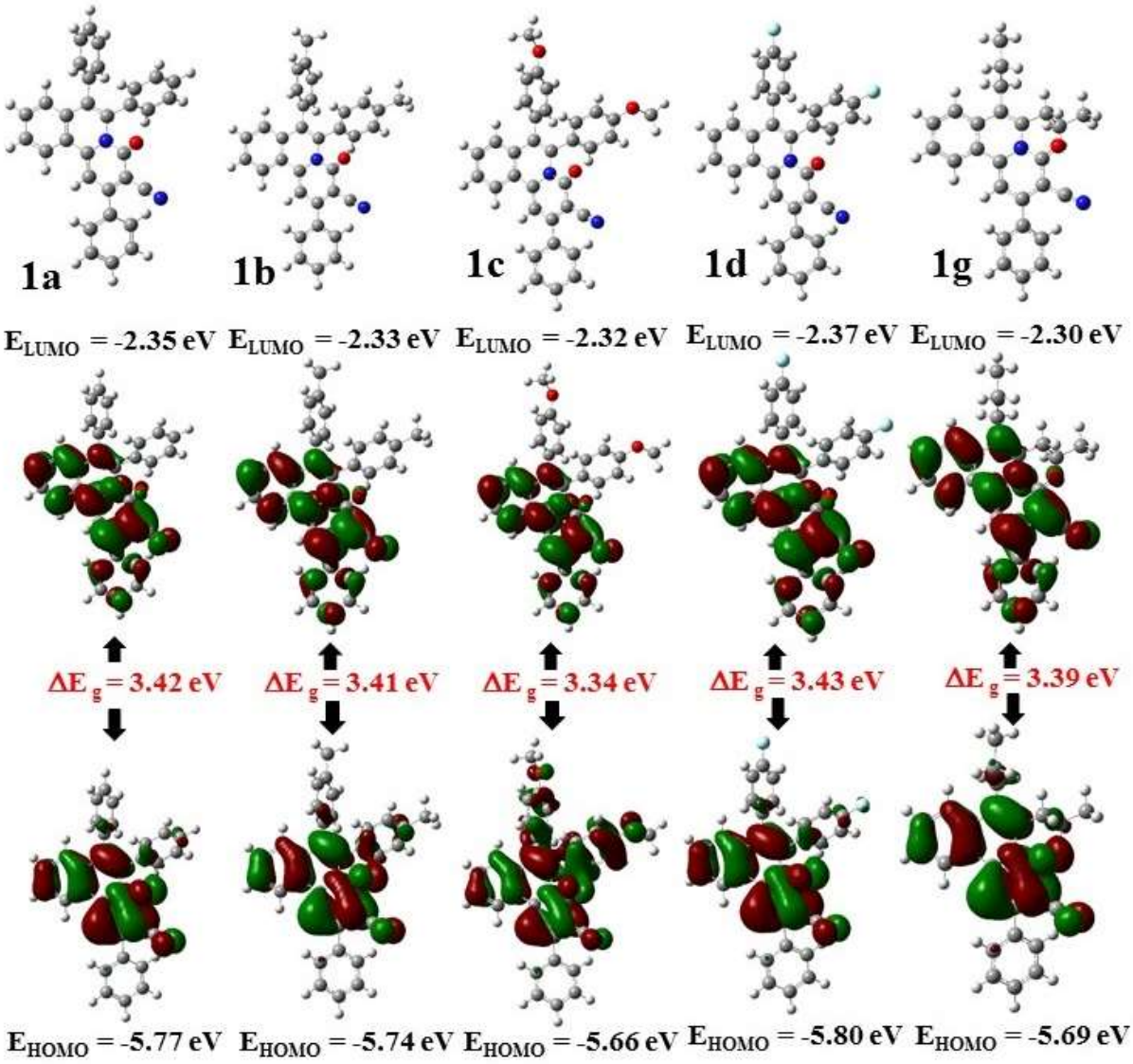

Figure 4. DFT optimized structures and HOMO-LUMO energy level diagrams of synthesized compounds (1a), (1b), (1c), (1d), and (1g) respectively using the B3LYP/6-31G (d, p) basis set level in acetonitrile solvent modelled by PCM approach.

Photophysical Properties

As stated earlier in the result and discussion section that the newly synthesized compounds having highly conjugated fused isoquinoline core display yellow fluorescent when viewed under 365 nm UV lamp. In solution, these class of fused conjugated heterocycles exhibits an intense yellowish green color. Therefore, their photophysical properties such as UV visible and photoluminescence were investigated. The absorption spectra (λ_{abs}) and emission spectra (λ_{em}) were measured for a few selected compounds in CH_2Cl_2. The UV-Vis spectra of compounds (**1a**, **2a**, **3a**, **6a**, **8a**) are shown in Figure 5(a) and for (**10a**, **12a**, **13a**, **15a**, **18a**, **20a**, **1b**, **1c**, **1d**, **1g**, **18c**, **18d**, and **18h**) in Figure S16 and the results are summarized in Table S1 (SI). All these synthesized compounds showed strong absorptions, with the positions of maximum ranging from 454–490 nm. The compounds exhibit three distinct absorption maxima, a band in the region of 313–321 nm, a band in the region of 428–467 nm and another in the region of 454–490 nm. In dichloromethane solution (10^{-5} M) one of fused isoquinoline derivative (**1a**) showed absorption peaks at 318, 431, and 458 nm with high extinction coefficients (ε) of 27000, 26000 and 35000 L mol^{-1} cm^{-1}, respectively (Table S1, SI).

The fluorescence emissions of some selected fused isoquinoline compounds were also recorded, which are summarized in Table S1 (SI). The emission spectra of (**1a**, **2a**, **3a**, **6a**, **8a**), in dichloromethane solution (10^{-5} M) is shown in Figure 5(b), and for compounds (**10a**, **12a**, **13a**, **15a**, **18a**, **20a**, **1b**, **1c**, **1d**, **1g**, **18c**, **18d**, and **18h**) in Figure S17 (SI). All exhibiting strong fluorescence emission in the range of 502–560 nm which belongs to the green region of the visible light spectrum.

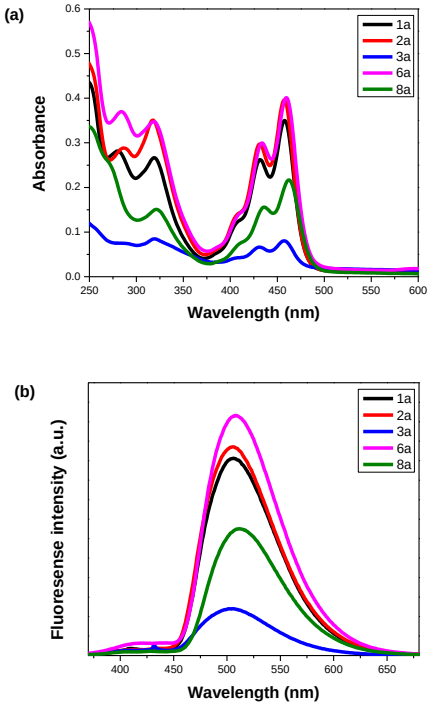

Figure 5. a) UV-VIS spectra, b) Photoluminescence spectra of (**1a**, **2a**, **3a**, **6a**, and **8a**) in CH_2Cl_2 (1 x 10^{-5} M)

Conclusion

In conclusion, we have utilized a Michael-adduct γ-keto malononitrile, obtained from the reaction between α,β-unsaturated aromatic ketone and malononitrile as the substrate for the C–H/N–H annulation with an alkyne. In this one-pot sequential two component synthesis of π-conjugated fused ring *N*-containing heterocycle 4-oxo-2,6,7-triaryl-4*H*-pyrido[2,1-*a*]isoquinoline-3-carbonitrile is accomplished via the formation of six new bonds namely a C–C, two C–N, two C=C and a C=O bonds. The success of the strategies lies in the selective hydrolysis of one of the cyano group of γ-keto malononitrile to an aromatic cyclic amide and finally C–H/N–H annulation with disubstituted alkynes in the presence of Ru(II) catalyst. This process is compatible to a range of substituents present in various coupling partners. On the basis of DFT calculation the positions and electronic nature of MO levels were investigated but no significant correlation of the substituents effects with the HOMO-LUMO energy levels could be correlated since both the HOMO and LUMO are localized at the same central part of the molecule. These synthesized heterocyclic compounds having several phenyl rings are emissive under 365 nm UV lamp, so beyond synthesis the UV-Vis and fluorescence spectra of some selected compounds were also examined. These molecules may therefore find application in fluorescent probes, optoelectronics applications in organic light emitting diode (OLEDs) and various other applications in material science.

Experimental Section

General information:

All the reagents and solvents used were purchased from commercial available sources and used without further purification. HPLC grade solvents were purchase from commercial sources. Organic extracts were dried over anhydrous sodium sulphate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60-120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F_{254} (0.25mm). All NMR spectra were recorded in $CDCl_3$ with tetramethylsilane (TMS) as the internal standard and few were taken in DMSO-d^6 in 600 and 400 MHz NMR. The ^{1}H spectra were referenced to the residual $CDCl_3$ (7.26 ppm) whereas for DMSO-d^6 it is 2.50 ppm. The ^{13}C spectra were referenced to the residual $CDCl_3$ (77.230 ppm) and for DMSO-d^6 it is 39.50 ppm. All ^{19}F NMR spectra were recorded in 400 MHz, and hexafluorobenzene (C_6F_6) was taken as reference. Mass spectra were recorded using ESI mode (Q-TOF MS analyzer). IR spectra were recorded in KBr or neat in FT-IR spectrometer. All UV experiments were performed at a probe concentration of 10^{-5} M in 1 mL quartz cuvettes of path length 1 cm at 25 °C in UV/VIS Spectrometer. Photoluminescence were carried out at a concentration of 10^{-5} M in 1 mL quartz cuvettes at 25 °C in Spectrofluorometer in HPLC grade dichloromethane solution.

General Procedure for the Synthesis of 2-(3-oxo-1,3-diarylpropyl)malononitrile (1-25)[19]

Compounds 1-25 were synthesized as per the following the method described in S. Lin, Y. Wei, F. Liang. *Chem. Commun*. 2012, *48*, 9879.

General Procedure for the Synthesis of 4-Oxo-2,6,7-triphenyl-4*H*-pyrido[2,1-*a*]isoquinoline-3-carbonitrile (1a) from 2-(3-Oxo-1,3-diphenylpropyl)malononitrile (1) and Diphenylacetylene (a)

To an oven-dried 10 mL round bottom flask was added 2-(3-oxo-1,3-diphenylpropyl)malononitrile (1) (55 mg, 0.2 mmol), $Cu(OAc)_2{\cdot}H_2O$ (4 mg, 0.02 mmol), 1,10-phenanthroline (7 mg, 0.04 mmol), and glacial AcOH (2 mL). The reaction mixture was heated in an oil bath at 110 °C for 5 h. Then to this reaction mixture was added

diphenylacetylene (a) (36 mg, 0.2 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (6 mg, 0.01 mmol), Cu(OAc)$_2$·H_2O (20 mg, 0.1 mmol) and PEG-400 (2 mL). The reaction mixture was further heated for 24 h. Then the reaction mixture was cooled to room temperature, admixed with ethyl acetate (25 mL) and the organic layer was washed with saturated sodium bicarbonate solution (1 x 5 mL). The organic layer was dried over anhydrous sodium sulfate (Na_2SO_4), and solvent was evaporated under reduced pressure. The crude product so obtained was purified over a column of silica gel (hexane / ethyl acetate, 9:1) to give pure 4-oxo-2,6,7-triphenyl-4*H*-pyrido[2,1-*a*]isoquinoline-3-carbonitrile (1a) (40 mg, yield 45%). The identity and purity of the product was confirmed by spectroscopic analysis.

Acknowledgements

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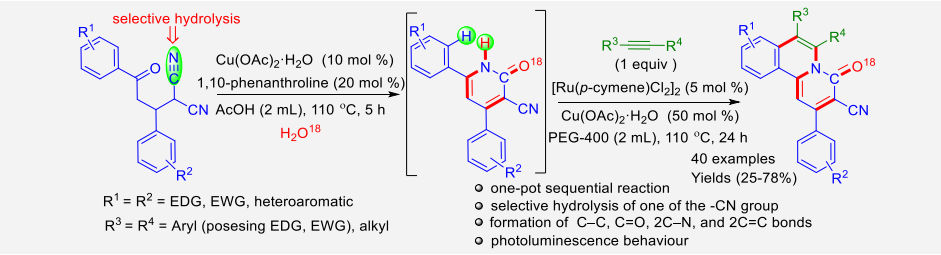
Graphical Abstract



Intramolecular Cyclization, C–H Activation and Annulation

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One-Pot Sequential Synthesis of Fused Isoquinolines via Intramolecular Cyclization/ Annulation and their Photophysical Investigation

Keywords: Isoquinoline; Ru; C–H activation; C–H/N–H annulation; DFT; photoluminescence.