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Study of the Hetero-[4+2]-Cycloaddition Reaction of Aldimines and Alkynes. Synthesis of 1,5-Naphthyridine and Isoindolone Derivatives.

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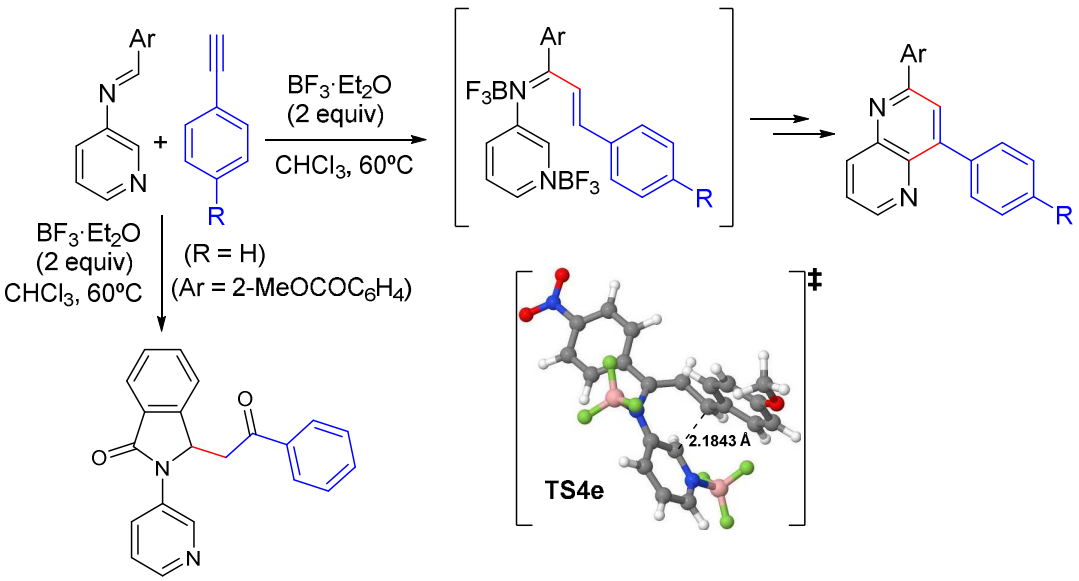


ABSTRACT

Both experimental and computational studies for the cycloaddition reaction between *N*-(3-pyridyl)aldimines and acetylenes where 1,5-naphtyridines are obtained are reported. The reaction of

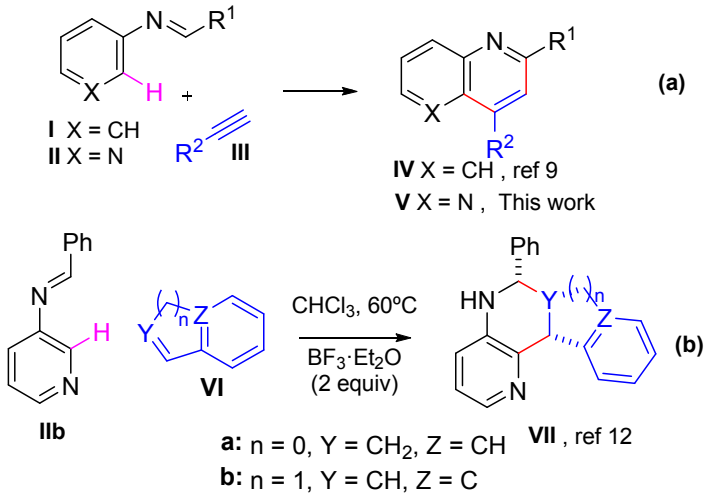
benzaldimine with a methoxycarbonyl group in position 2 with phenyl acetylene, styrene and indene afforded polycyclic isoindolone derivatives. The mechanism of reaction *N*-(3-pyridyl)aldimines with olefins can be explained by an asynchronous [4+2] cycloaddition, in the case of acetylenes the obtained results suggest a stepwise mechanism through a 3-azatriene.

INTRODUCTION

A wide range of applications in biochemistry, pharmacology and material science have been observed for nitrogenated heterocycles.[1] Various strategies for the preparation of nitrogen heterocycles are described in the literature, among which one of the most straightforward is the hetero-Diels-Alder reaction (HDAr). By this reaction the formation of the carbon-carbon bond[2] is effectively achieved from an atom economic point of view, allowing the preparation of six-membered rings with a high molecular diversity[3] which may have applications in industry.[4] An example of HDAr is the Povarov reaction,[5,6] and this process is an tool for the preparation of nitrogen-containing heterocyclic compounds. The Povarov reaction has been applied in total synthesis of interesting biologically active compounds, such as (±)–martinelline, (±)-martinellic acid, luotonin A, and camptothecin.[7] This methodology also represents a direct route to the naphthyridine core structure of interesting biologically active compounds as Topoisomerase I inhibitors and with antiproliferative activity against several cancer cell lines[8] as reported in our research group.

As Povarov initially described, electron rich olefins are usually used as dienophiles in the reaction with aromatic aldimines **I** (X = CH, Scheme 1a) derived from aniline,[5] while only scarce examples have been reported with acetylenic compounds **III** (Scheme 1a) acting as dienophiles[9] and very few examples with imines **II** (X = N, Scheme 1a) derived from heterocyclic amines have been reported.[10] Moreover, if pyridyl amines are used instead of anilines, a new entry to nitrogenated derivatives such as 1,5-naphthyridine derivatives **V** could be prepared by this strategy. Furthermore, pyridyl substitution instead of phenyl ring in polycyclic systems may be expected to afford more water-soluble compounds which

show better cytotoxic properties.[11] By a combined theoretical and experimental study we previously reported that the Povarov type cycloaddition reaction between pyridylaldimines **IIb** and olefins such as styrene **VIa** (n = 0, Y = CH_2, Z = CH, Scheme 1b) and indene **VIb** (n = 1, Y = CH, Z = C, Scheme 1b) suggested an asynchronous concerted process favoured by double Lewis acid activation with $BF_3{\cdot}Et_2O$ and formation of *endo*-cycloadducts **VIIa** or **VIIb**.[12]



Scheme 1. Reactions of aldimines and alkynes and/or olefins.

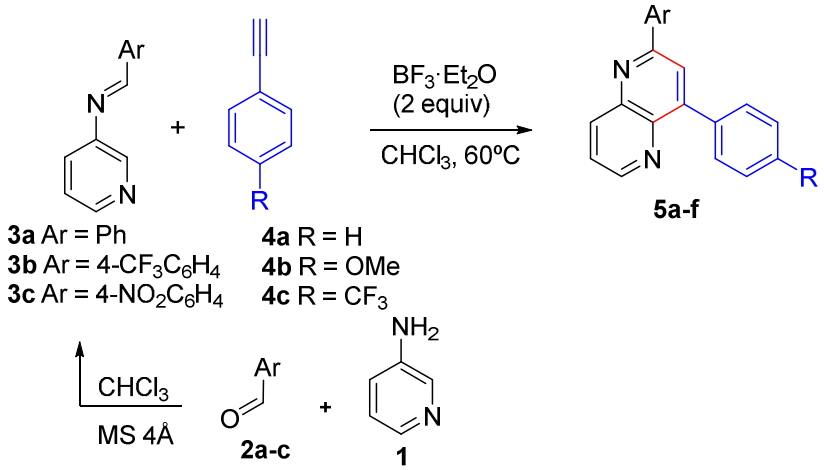
In this sense, if acetylenes are used as dienophiles instead of olefins, the electronic and structural properties of starting materials and compounds obtained may represent an interesting challenge for their theoretical and experimentally study, and from a preparative point of view 1,5-naphtiridines may be directly obtained. It must be taken into account that pyridine, a π-electron deficient aromatic, is less reactive than benzene due to the electronegativity of the nitrogen atom, which would greatly affect the reactivity of *N*-(3-pyridyl)aldimines in a Lewis acid activated aza-[4+2]-cycloaddition reaction.

We report herein both experimental (synthetic and NMR) and computational studies of the cycloaddition reaction between *N*-(3-pyridyl)aldimines and alkynes. By means of these studies carried out in parallel, we were able to get useful information regarding the plausible mechanism for the synthesis of heterocyclic products according to the dienophile.

RESULTS AND DISCUSSION

Experimental study

We started with the preparation of the corresponding *N*-(3-pyridyl)aldimines **3** by means of a solution of 3-aminopyridine **1** and aromatic aldehydes **2** in chloroform in the presence of molecular sieves (Scheme 2). Afterwards, the obtained aldimines **3** were reacted with acetylenes **4**. In the absence of catalyst no product formation was observed and starting material recovered. However, when trifluorboroetherate as Lewis acid catalyst was used good results were observed: the optimal ones were when 2 equivalents of Lewis acid were used. The crude mixture was treated with NaOH 2N and water in order to remove easily all inorganic salts and subsequently extracted with CH_2Cl_2 affording only 2,4-disubstituted 1,5-naphthyridines **5** regioselectively (Table 1), while the formation of the other regioisomers, namely 2,3-disubstituted 1,5-naphthyridines was not observed. The multicomponent reaction of 3-aminopyridine **1**, aromatic aldehydes **2** and acetylenes **4** was also explored. However, a complex mixture of reaction products was obtained.



Scheme 2. Reactions of aldimines **3** and acetylenes **4** with Lewis acid.

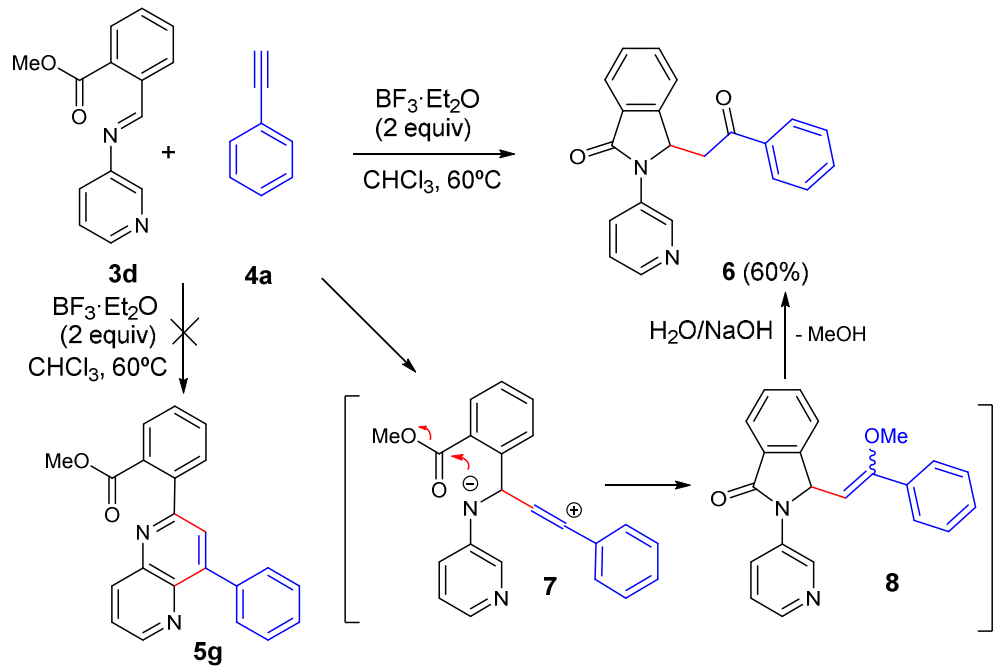
The structure of aromatic 1,5-naphthyridines **5** was assigned on basis of NMR spectra and mass spectrometry. For example, when aldimine **3b** (Ar = 4-$CF_3C_6H_4$) and 4-methoxyphenyl acetylene **4b** (R = OMe) were used the 1,5-naphthyridine **5d** (Table 1, entry 4) was obtained. Its structure was assigned by means of NMR experiments and confirmed by HRMS. For instance, in the ^{19}F-NMR spectrum of compound **5d** one signal was observed at δ_F = - 63.1 ppm and in the ^{1}H-NMR spectrum the corresponding two signals at low field corresponding to two protons of the naphthyridine ring, one double doublet at δ_H = 8.49 ppm with coupling constants $^3J_{HH}$ = 8.5 Hz, $^4J_{HH}$ = 1.8 Hz and another double doublet at δ_H = 9.01 with coupling constants $^3J_{HH}$ = 4.3 Hz and $^4J_{HH}$ = 1.8 Hz. Moreover, its structure has been unequivocally confirmed by X-ray analysis (see the Supporting Information). Formation of naphthyridines **5** could be explained by a formal [4+2] process of imines **3** with alkynes **4** and subsequent aromatization under the reaction conditions to afford corresponding naphthyridines **5** (Scheme 2).

Table 1. Naphthyridines **5** obtained.

entry	Product	Ar	R	Reaction time (h)	Yield (%)
1	**5a**	Ph	H	24	75
2	**5b**	4-$CF_3C_6H_4$	H	18	60
3	**5c**	4-$NO_2C_6H_4$	H	48	50
4	**5d**	4-$CF_3C_6H_4$	MeO	36	60
5	**5e**	4-$NO_2C_6H_4$	MeO	18	60
6	**5f**	4-$CF_3C_6H_4$	CF_3	36	60

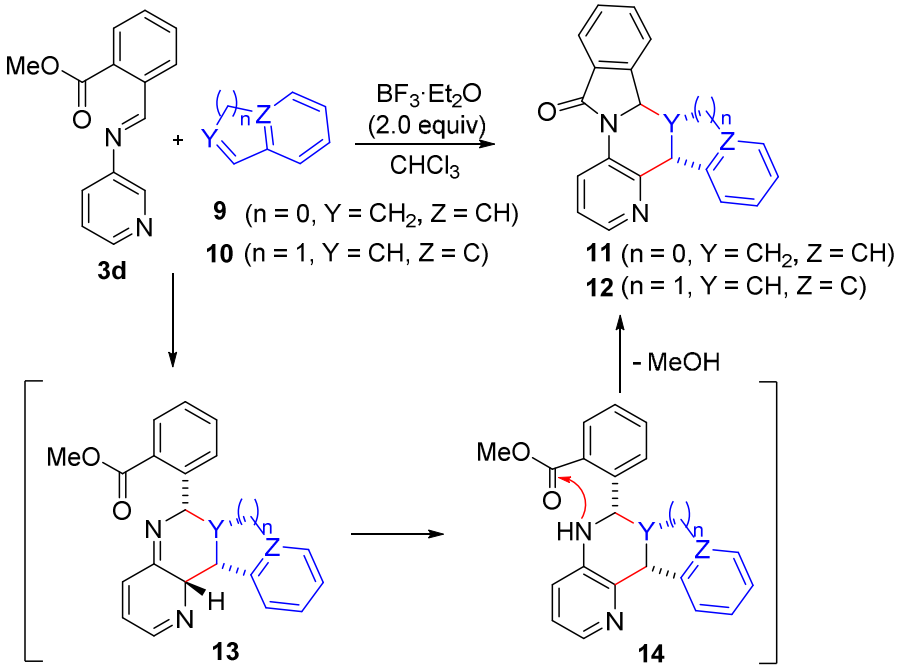
In order to explore the scope of the process, the same synthetic protocol was applied to aldimine **3d** (Scheme 3), prepared as before from commercially available 3-pyridylamine **1** and methyl 2-formylbenzoate **2d**, and used *in situ*. Subsequent treatment of aldimine **3d** with acetylene **4a** (R = H) was performed in chloroform at reflux by using 2 equivalents of $BF_3{\cdot}Et_2O$ as Lewis acid. However, in this case, the corresponding naphthyridine **5g** was not detected, while the *N*-3-pyridyl isoindolinone **6** was obtained in a 60 % yield (Scheme 3). Isoindolinones are ubiquitous in complex natural products and pharmaceutical active ingredients.[13,14]

1D and 2D NMR experiments and mass spectrometry were used for the characterization of isoindolone **6**. The ^{1}H NMR spectroscopy shows signals of two methylenic protons at δ = 3.25 ppm and at δ = 3.50 ppm, with coupling constants $^{2}J_{HH}$ = 17.4 Hz and $^{3}J_{HH}$ = 9.4 Hz for the first methylenic proton and $^{2}J_{HH}$ = 17.4 Hz and $^{3}J_{HH}$ = 2.8 Hz for the second one. Moreover, in ^{13}C NMR spectrum a signal at δ = 197.1 ppm which corresponds to a carbonyl carbon was observed. COSY experiment results (see Supporting Information) are consistent with this structure **6** showing coupling relationship between methylenic protons and the adjacent proton at three bond distance. The formation of the isoindolinone **6** may be explained by an initial nucleophilic addition of terminal acetylene **4a** over the iminic double bond to give the intermediate **7**, whose intramolecular cyclization would yield **8** followed by loss of methanol affording derivative **6**. As far as we know, this process represents the first example for the synthesis of *N*-3-pyridylisoindolin-1-one containing an alkylcarbonyl substituent at position 6. Taking these observations into account we wondered if a stepwise mechanism might be implied in the reaction of aldimines with acetylenes, rather than an asynchronous concerted process via *endo* transition states as in the case of alkenes.[12]



Scheme 3. Reaction of aldimine **3d** and phenylacetylene **4a** with Lewis acid.

So as to check if the mechanism and the behaviour involved in the reaction of aldimines with acetylenes may be different to the use of olefins, we performed the process with olefins. In this case, the reaction of aldimine **3d** with styrene **9** (n = 0, Y = CH_2, Z = CH, Scheme 4) or indene **10** (n = 1, Y = CH, Z = C, Scheme 4) in the presence of 2.0 equivalents of $BF_3{\cdot}Et_2O$ and chloroform as solvent yielded corresponding isoindolones fused with an *endo*-dihydro-[1,5]-naphthyridine **11** (n = 0, Y = CH_2, Z = CH) and an *endo*-tetrahydroindeno[1,5]-naphthyridine **12** (n = 1, Y = CH, Z = C) moiety in good yields (80% and 85% respectively, see Supporting Information for characterization data). As far as we know, this process represents the first example of the synthesis of these polycyclic heterocycles **11** and **12** containing an isoindolone moiety.

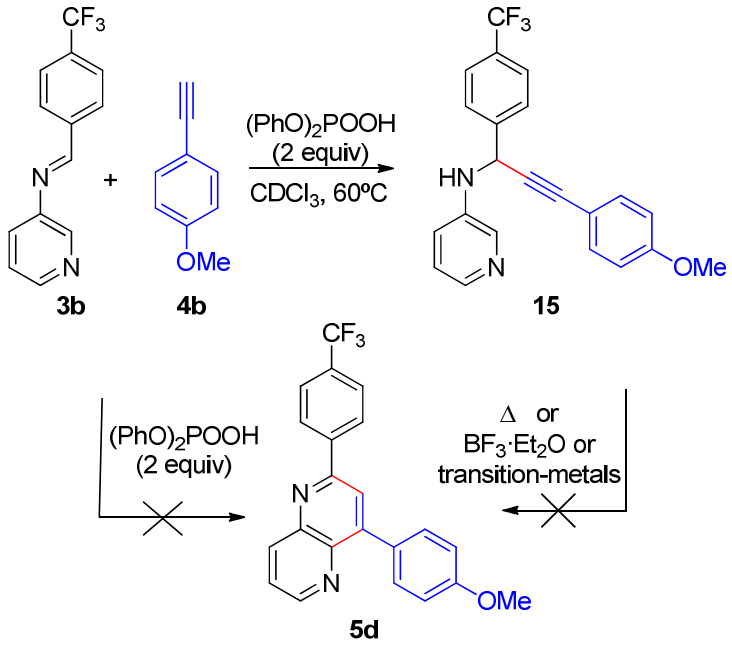


Scheme 4. Reactions of aldimine **3d** and olefins **9** and **10** with Lewis acid.

These experimental results obtained with olefins, which are in accordance with our previously reported computational studies,[12] suggest that the [4+2]-cycloaddition reactions between the aldimine **3d** and olefins **9** and **10** occur through an asynchronous concerted process via *endo* transition states to give

polycyclic isoindolinone derivatives **13** (Scheme 4), subsequent prototropic tautomerization, posterior intramolecular cyclization of **14** and subsequent loss of methanol would lead to the formation of polycyclic indolinones **11** and **12** with regio- and stereoselective control of the two or three stereocenters, respectively.

In order to gain insight into what happened in the case of acetylenes **4** we decided to monitor the reaction by NMR spectroscopy. As an inhomogeneous solution was observed when the reaction was performed in the presence of $BF_3 \cdot Et_2O$ as Lewis acid, we decided to study the reaction by using 2 equivalents of a Brönsted acid such as phosphoric acid diphenyl ester [$(PhO)_2P(O)OH$]. The use of a Brönsted acid instead of a Lewis acid might avoid the heterogeneity complications when performing the reaction in a NMR tube.



Scheme 5. Reaction of aldimine **3b** and acetylene **4b** with a Brönsted acid.

In this sense, the reaction between aldimine **3b** and acetylene **4b** promoted by two equivalents of Brönsted acid was monitored by NMR spectroscopy (Scheme 5). Phosphonic acid was added to a solution of aldimine **3b** in deuterated chloroform (see Figures S3 and S4 the Supporting Information) Afterwards, an stoichiometric amount of acetylenic compound **4b** was added to the solution and the

mixture heated under reflux until the disappearance of signal corresponding to the iminic proton (δ = 8.21 ppm) was observed in the ^{1}H NMR spectrum. Subsequent treatment with NaOH 2N and extraction afforded a crude mixture whose ^{13}C NMR spectrum (Figure S4d in the Supporting Information) showed signals at δ = 85.1 and 86.1 ppm corresponding to an internal alkyne. Purification of the crude mixture allowed the isolation of propargylamine **15** as major compound (Scheme 5) which was characterized by means of NMR spectroscopy and HRMS. The formation of *N*-pyridylpropargylamine **15** could be explained by alkynylation of aldimines **3** with alkynes **4**. Often called A3-coupling, this requires the presence of a transition-metal that catalyzes the reaction, resulting in a convenient and general approach towards propargylamines.[15] In our case propargylamines **15** were obtained in the presence of Brönsted acid, in the absence of transition-metal catalysts.

In previous reports, the electrocyclic ring closure of aromatic propargylamines in the presence of transition metal catalysts[16] had been described. However, in our case, all attempts for the electrocyclic ring closure of aromatic propargylamines **15**, such as thermal treatment and/or in presence of copper or zinc transition metal catalysts (using CuCl or AgOTf) or $BF_3{\cdot}Et_2O$ did not give the corresponding naphthyridines **5d** and the starting materials were recovered (Scheme 5). Probably the presence of nitrogen in the pyridine ring not only deactivates the intramolecular cyclization with respect to the benzene, but also creates a different reactivity pattern, the α and γ carbons being the most deactivated ones respect to the nitrogen atom in the pyridine ring. For these reasons the formation of the corresponding naphthyridine **5d** by an intramolecular cyclization of *N*-pyridylpropargylamine **15** even when phosphoric acid diphenyl ester [$(PhO)_2P(O)OH$] is used as a Brönsted acid would not be favoured. Therefore, these experimental results observed by the monitoring of the reaction of aldimines and alkynes in NMR and the formation of heterocyclic naphthyridines **5** via reaction of pyridylimines **3** with acetylenic dienophiles **4** in the presence of 2 equivalents of $BF_3{\cdot}Et_2O$ suggest that the reaction could be initially explained by a stepwise [4+2] process followed by aromatization under the reaction conditions.

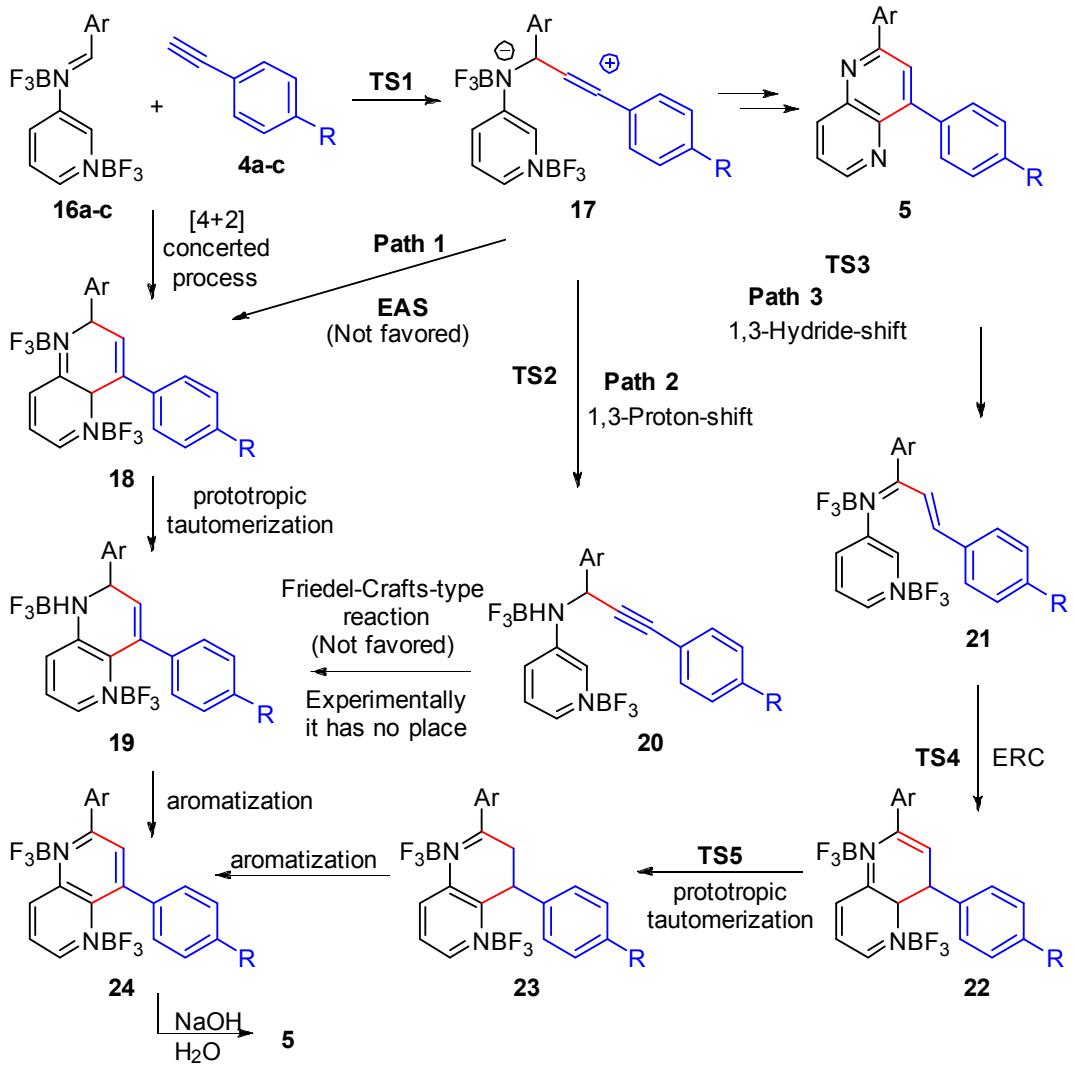
Computational study

To confirm our experimental results and to predict a computational model consistent with the reaction between *N*-(3-pyridyl)aldimines **3** and acetylenes **4** (see Scheme 2, *vide supra*), we then focused our attention on the theoretical study of these reactions. As far as we know, this would be the first study carried out to elucidate the mechanism of the Povarov reaction of imines and acetylenes. We analyzed the putative reaction mechanisms employing Gaussian 09[17] program within the density functional theory (DFT) framework[18] using B3LYP[19] and also performing single-point energy calculations with M06-2X,[20] hybrid functional were used along with the 6-311G** basis set.[21] The accuracy of both methods has been extensively tested for stable molecules and pericyclic reactions[22] (see Supporting Information).

So, after treatment of aldimines **3** with two equivalents of $BF_3 \cdot Et_2O$ as Lewis acid, a double coordination of the two nitrogen atoms[12] may afford the activated *N*-(3-pyridyl)aldimines **16** and may undergo nucleophilic addition of acetylene **4** giving a resonance stabilized zwitterionic intermediate **17** through a transition structure **TS1** (see Scheme 6 and Supporting Information). Based on the experimental results described in Schemes 2 and 3, the first question to determine theoretically would be whether the formation of 1,5-naphthyridines **5** involves a concerted [4+2] cycloaddition through a cyclic intermediate **18** or a stepwise process involving an zwitterionic intermediate **17** (Scheme 6). All our theoretical attempts to locate transition structures corresponding to the [4+2]-cycloaddition reaction that would afford intermediate **18** precursor of naphthyridines **5** by means of a concerted process met with no success. All the starting geometries converged to a transition structure with the *C*-iminic—*C1*-acetylene bond formed while the distance between *C2*-pyridine—*C2*-acetylene was higher than 3Å upon the optimization at the B3LYP/6-311G** + ZPVE level, which may support initially the stepwise pattern.

At this point, three pathways may be conceivable for the formation of **24**, precursors of naphthyridines **5**. First, intermediate **17** could cyclise to give the corresponding dihydronaphthyridine **18** prior to **19** and

finally **24** (path 1, Scheme 6). A second pathway is possible where the zwitterionic intermediate **17** by a 1,3-proton-shift may give the propargylamine **20,** whose subsequent ring closure could afford **19** (path 2, Scheme 6). And a third pathway could be the transformation of the zwitterionic intermediate **17** into a 3-azatriene **21** formed by a 1,3-hydride-shift followed by a 6π-electron electrocyclic ring closure (ERC),[23] whose subsequent prototropic tautomerization and aromatization would result in the formation of **24** (path 3, Scheme 6) and naphthyridines **5**.



Scheme 6. Reactions of doubly activated aldimines **16** and acetylenes **4**.

With respect to path 1, if a stepwise [4+2]-cycloaddition takes place an electrophilic aromatic substitution (EAS) of the pyridine ring at 2 position should occur for the formation of a new *C2*-pyridine—*C2*-acetylene bond to give cycloadducts **19** which is hard to understand since the pyridine ring is disabled and mainly at the α and γ positions respect to the nitrogen atom.[24] Regarding the second pathway, the formation of propargylamines by direct addition of alkynes to imines derived from aniline in the presence of a metal catalyst and that these compounds cyclise to give the corresponding quinoline derivatives in a copper[16a,b] or gold[16c] catalyzed Friedel-Crafts-type process has been previously described.[15] However, in our case, cyclization of propargylamines **15** derived from 3-pyridylamines (Scheme 5) is not favoured because of the previously mentioned electronic restrictions of the pyridine ring respect to the phenyl ring. This behaviour has been experimentally confirmed since all attempts for the cyclization of experimentally obtained propargylamine **15** did not occur (*vide supra* Scheme 5). Therefore, a plausible mechanism for the formation of naphthyridines **5** may be indicated by pathway 3 (Scheme 6) which implies a transformation of intermediates **17** into 3-azatrienes **21** whose electrocyclic ring closure (ERC)[23] may give intermediates **22** followed by prototropic tautomerization to lead **23** and subsequent aromatization to afford compounds **24** and the corresponding naphthyridines **5**.

Therefore, we studied whether the formation of propargylamines **20** or 3-azatrienes **21** is favoured theoretically. In this sense, we have located both a transition structure **TS2** connecting zwitterionic intermediates **17** with propargylamines **20** as well as transition structures **TS3** connecting zwitterionic intermediates **17** with 3-azatrienes **21** (Scheme 6). In gas phase and in the presence of chloroform (solvent effect), computed results indicate that the activation barriers associated to the formation of azatrienes **21** through transition structures **TS3** are lower than the activation barriers corresponding to the formation of propargylamines **20** (about 6 to 9 kcal/mol, see Table 3 and Figures S7 and S8 of Supporting Information). Although, formation of both **20** and **21** are very exothermic either in the gas phase or in the presence of chloroform, the formation of azatriene **21** is almost twice as exothermic as the formation of propargylamine **20**, and at all calculation levels of theory.

Next, we investigated whether the electrocyclic closure of the intermediates **21** could lead to the formation of the compounds **22** and finally to **24** (Scheme 6). In this sense, we located in all cases transition structures **TS4** (Figure 1) connecting the azatrienes **21** with compounds **22** through a disrotatory electrocyclization mode (6π-ERC) and also transition structures **TS5** corresponding to the [1,3]-proton shift for the transformation of **22** into theirs tautomeric compounds **23** (Scheme 6 and Supporting Information), both in gas phase and in the presence of solvent and at all calculation levels.

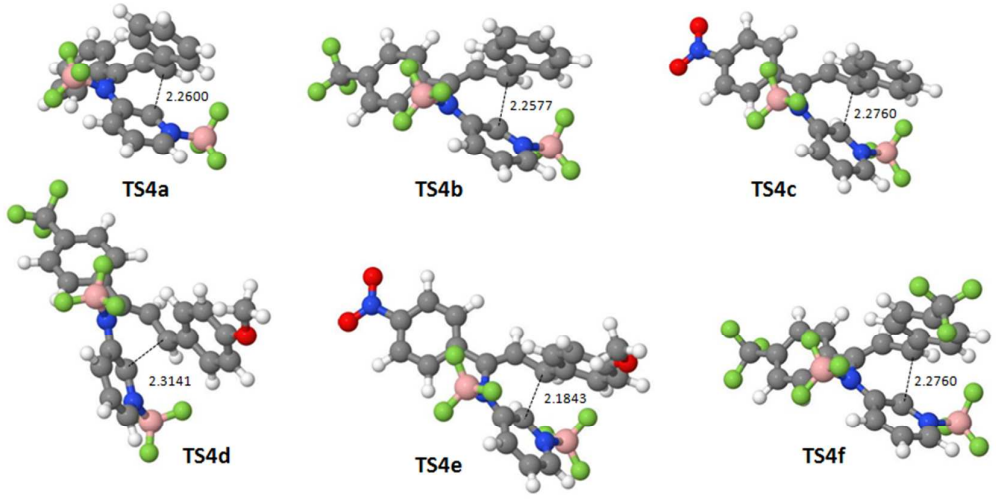


Figure 1. Fully optimized transition structures **TS4a-f** (B3LYP/6-311G** level) found into the conversion of azatrienes **21a-f** into dihydronaphthyridines **22a-f** through a disrotatory electrocyclization mode (6π-ERC). Selected bond lengths are given in Å.

Therefore, computational calculations suggest that 3-azatrienes **21** undergo an electrocyclic ring closure (ERC), prototropic tautomerization and aromatization to finally afford compounds **24**. As experimentally observed, the treatment of the crude reaction would give naphthyridines **5**. The activation barriers for the ERC through **TS4** are higher (more than 10 kcal/mol, see Table 4, entries 1, 3, 5, 7, 9 and 11 in the Supporting Information) than the activation barriers corresponding to this step of the process through **TS5** (See Table 4 entries 2, 4, 6, 8, 10 and 12 in the Supporting Information). At all levels of calculation, both in gas phase and in the presence of chloroform, computational results indicate

that the formation of **22** is slightly endothermic but its tautomerization into compounds **23**, where aromatic pyridine ring is regenerated, is strongly exothermic (-30 kcal/mol aprox, see Table S4 in the Supporting Information). To sum up, this second stage of the reaction as a whole turns out to be thermodynamically favoured. Moreover, taking into account that the formation of 3-azatrienes **21** is a highly exothermic process we might think that the formation of **23** is favoured kinetically and thermodynamically. As an example, the energy profile ΔE in kcal/mol of the reaction between the acetylene **4a** (R = H) and the double activated aldimine **16b** (Ar = 4-$CF_3C_6H_4$, see Scheme 6) computed at the M06-2X(PCM)/6-311G**//B3LYP/6-311G* + ZPVE level using chloroform as solvent is showed (Figure 2).

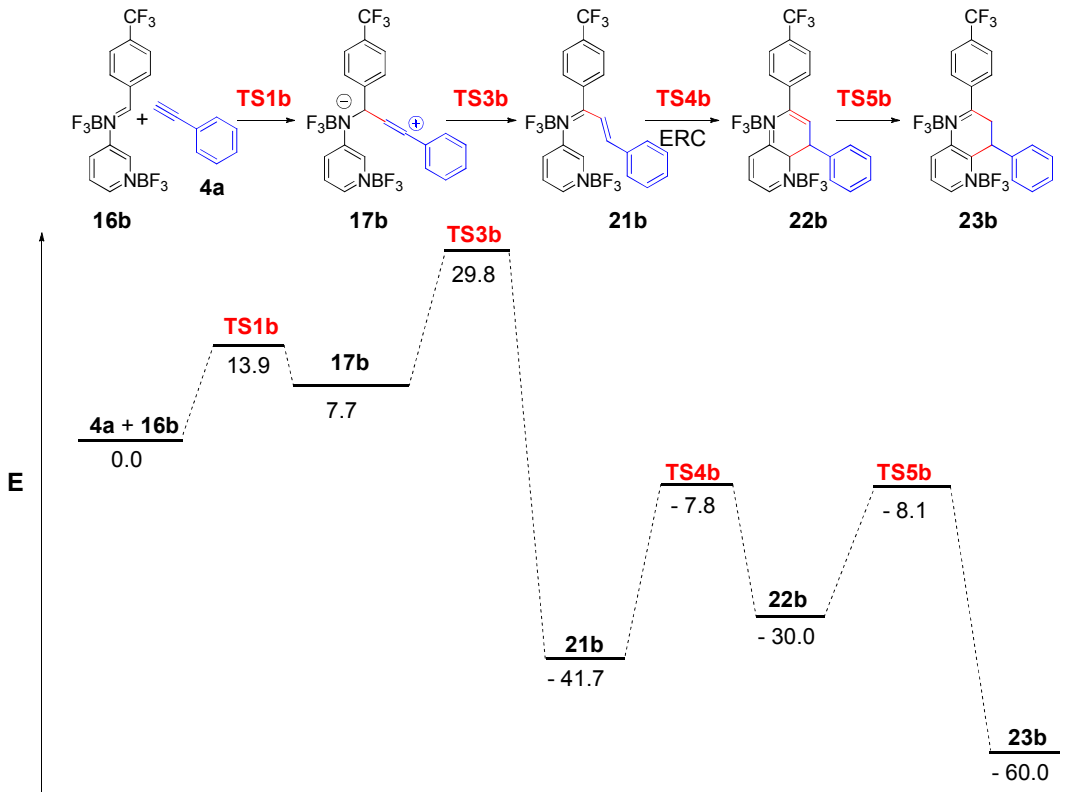


Figure 2. Energy profile for the catalysed Povarov reaction between **4a** (R = H) and **16b** (Ar = 4-$CF_3C_6H_4$) at M06-2X(PCM)/6-311G**//B3LYP/6-311G** + ΔZPVE level (unit: kcal/mol) using chloroform as solvent.

CONCLUSIONS

In summary, experimental results show different behaviours for the reaction of aldimines derived from 3-aminopyridine and alkynes depending on the promoter. Thus, when the reaction was performed in the presence of a Lewis acid, such as $BF_3 \cdot Et_2O$, the corresponding naphthyridine and isoindolinone compounds were isolated. Alternatively, in the presence of Brönsted acid, such as phosphoric acid diphenyl ester [$(PhO)_2P(O)OH$], propargylamines were obtained. Moreover, our combined experimental and computational investigations of the Povarov reaction between *N*-(3-pyridyl)aldimines and acetylenes with a Lewis acid suggest a stepwise [4+2]-cycloaddition mechanism. The presence of nitrogen in the pyridine ring deactivates the SE with respect to the benzene, yielding the formation of a 3-azatriene whose electrocyclic ring closure (ERC) may give the corresponding heterocyclic intermediates followed by prototropic tautomerization and subsequent aromatization to afford naphthyridines.

EXPERIMENTAL SECTION

General Methods. All reagents from commercial suppliers were used without further purification. All solvents were freshly distilled before use from appropriate drying agents. All other reagents were recrystallized or distilled when necessary. Reactions were performed under a dry nitrogen atmosphere. Analytical TLCs were performed with silica gel 60 F_{254} plates. Visualization was accomplished by UV light. Column chromatography was carried out using silica gel 60 (230-400 mesh ASTM). Melting points were determined with a digital melting point apparatus without correction. NMR spectra were obtained on a 300 MHz and on a 400 MHz spectrometers and recorded at 25 ºC. Chemical shifts for ^1H NMR spectra are reported in ppm downfield from TMS, chemical shifts for ^{13}C NMR spectra are recorded in ppm relative to internal chloroform (δ = 77.2 ppm for ^{13}C), chemical shifts for ^{19}F NMR are reported in ppm downfield from fluorotrichloromethane ($CFCl_3$). Coupling constants (*J*) are reported in

Hertz. The terms m, s, d, t, q refer to multiplet, singlet, doublet, triplet, quartet. ^{13}C NMR, and ^{19}F NMR were broadband decoupled from hydrogen nuclei. High resolution mass spectra (HRMS) was measured by positive-ion electrospray ionization (EI) method using a mass spectrometer Q-TOF. Aldimines **3a-c** were prepared as previously described.[8a]

Methyl-2-pyridin-3-yliminomethylbenzoate **(3d).** 3-Aminopyridine **1** (10 mmol, 0.941 g) was solved in $CHCl_3$ (30 mL) and methyl-2-formylbenzoate **2d** (10 mmol, 1.390 mL) was added. The mixture was stirred under nitrogen at refluxing chloroform for 12 h. The reaction product is unstable during distillation and/or chromatography and was used *in situ* for further reactions. ^1H RMN of crude reaction mixture (300 MHz, $CDCl_3$) δ: 3.93 (s, 3H), 7.28-7.39 (m, 1H), 7.56-7.69 (m, 3H), 8.02 (d, $^3J_{HH}$ = 7.7 Hz, 1H), 8.25 (d, $^3J_{HH}$ = 7.7 Hz, 1H), 8.48-8.59 (m, 2H), 9.27 (s, 1H) ppm; ^{13}C {^1H} NMR of crude reaction mixture (75 MHz, $CDCl_3$) δ: 52.5, 123.7, 127.9, 128.5, 130.5, 130.9, 132.5, 134.7, 136.7, 143.2, 147.4, 147.7, 161.8, 167.1 ppm.

General procedure for Povarov reaction. **Synthesis of naphthyridines 5 and isoindolinone 6.** To a solution of of the *in situ* prepared aldimine **3** (5 mmol) in chloroform the corresponding acetylenes **4** (7 mmol) and $BF_3{\cdot}Et_2O$ (10 mmol, 1.230 mL) were added and the mixture was stirred at the opportune temperature until TLC and ^1H NMR spectroscopy indicated the disappearance of aldimine. The reaction mixture was washed with 2M aqueous solution of NaOH (25 mL) and water (25 mL), extracted with dichloromethane (2 x 25 mL), and dried over anhydrous $MgSO_4$. The removal of the solvent under vacuum afforded and oil that was purified by silica gel flash column chromatography using a gradient elution of 10-40% ethyl acetate in hexane to afford products **5a-f** and when imine **3d** was used compound **6**.

2,4-Diphenyl-1,5-naphthyridine **(5a).** The general procedure was followed using imine **3a** prepared *in situ* and phenylacetylene **4a** (7 mmol, 0.768 mL) and the reaction mixture was stirred at refluxing chloroform for 24 h. Compound **5a** (1.057 g, 75 %)was obtained as a white solid; mp 122-124 ºC (ethyl

acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.48-7.60 (m, 6H), 7.66 (dd, $^{3}J_{HH}$ = 8.4 Hz, $^{3}J_{HH}$ = 4.0 Hz, 1H), 7.86 (d, $^{3}J_{HH}$ = 7.6 Hz, 2H), 8.12 (s, 1H), 8.22 (d, $^{3}J_{HH}$ = 7.8 Hz, 2H), 8.52 (d, $^{3}J_{HH}$ = 7.9 Hz, 1H), 8.99 (d, $^{3}J_{HH}$ = 4.0 Hz, 1H) ppm; ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ: 122.5, 124.5, 127.8, 128.5, 128.9, 129.1, 129.9, 130.6, 137.3, 137.9, 139.2,141.5, 144.6, 149.2, 150.6, 157.9 ppm. HRMS (EI) calculated for $C_{20}H_{14}N_2$ $[M]^+$ 282.1157; found 282.1165.

4-Phenyl-2-(4-(trifluoromethyl)phenyl)-1,5-naphthyridine **(5b).** The general procedure was followed using imine **3b** prepared *in situ* and phenylacetylene **4a** (7 mmol, 0.768 mL) and the reaction mixture was stirred at refluxing chloroform for 18 h. Compound **5b** (1.050 g, 60 %)was obtained as a yellowish solid; mp 173-174 ºC (ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.42-7.50 (m, 3H), 7.57 (dd, $^{3}J_{HH}$ = 8.5 Hz, $^{3}J_{HH}$ = 4.1 Hz, 1H), 7.68-7.74 (m, 4H), 8.00 (s, 1H), 8.22 (d, $^{3}J_{HH}$ = 8.5 Hz, 2H), 8.41 (dd, $^{3}J_{HH}$ = 8.5 Hz, $^{4}J_{HH}$ = 1.7 Hz, 1H), 8.91 (dd, $^{3}J_{HH}$ = 4.1 Hz, $^{4}J_{HH}$ = 1.7 Hz, 1H) ppm; ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ: 122.3, 124.5 (q, $^{1}J_{CF}$ = 270.1 Hz), 124.9, 126.1 (q, $^{3}J_{CF}$ = 4.5 Hz), 128.2, 128.6, 129.2, 130.7, 131.6 (q, $^{2}J_{CF}$ = 32.5 Hz), 137.1, 138.1, 141.6, 142.5, 144.7, 149.7, 151.2, 156.3 ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ: - 63.0 ppm. HRMS (EI): calculated for $C_{21}H_{13}N_2F_3$ $[M]^+$ 350.1031; found 350.1037.

2-(4-Nitrophenyl)-4-phenyl-1,5-naphthyridine (**5c**). The general procedure was followed using imine **3c** prepared *in situ* and phenylacetylene **4a** (7 mmol, 0.768 mL) and the reaction mixture was stirred at refluxing chloroform for 48 h. Compound **5c** (0.817 g, 50 %)was obtained as a yellow solid; mp 178-179 ºC (ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.56-7.86 (m, 6H), 8.16 (s, 1H), 8.34-8.57 (m, 5H), 9.06 (s, 1H) ppm; ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ: 122.2, 124.2, 124.9, 128.6, 129.2, 130.6, 136.7, 138.1, 141.5, , 144.9, 148.7, 149,8, 151.6, 155.1 ppm. HRMS (EI): calculated for $C_{20}H_{13}N_3O_2$ $[M]^+$ 327.1008; found 327.1013.

4-(4-Methoxyphenyl)-2-(4-(trifluoromethyl)phenyl)-1,5-naphthyridine (**5d**). The general procedure was followed using imine **3b** prepared *in situ* and 4-methoxyphenylacetylene **4b** (7 mmol, 0.908 mL) and the reaction mixture was stirred at refluxing chloroform for 36 h. Compound **5d** (1.140 g, 60 %) was obtained as a white solid; mp 165-166 ºC (ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.91 (s, 3H), 7.09-7.13 (m, 2H), 7.66 (dd, $^{3}J_{HH}$ = 8.5 Hz, $^{3}J_{HH}$ = 4.3 Hz, 1H), 7.69-7.77 (m, 4H), 8.10 (s, 1H), 8.31 (d, $^{3}J_{HH}$ = 8.5 Hz, 2H), 8.49 (dd, $^{3}J_{HH}$ = 8.5 Hz, $^{4}J_{HH}$ = 1.8 Hz, 1H), 9.01 (dd, $^{3}J_{HH}$ = 4.3 Hz, $^{4}J_{HH}$ = 1.8 Hz, 1H, H_{arom}) ppm; ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ: 55.6, 114.2, 121.8, 124.5 (q, $^{1}J_{CF}$ = 274.5 Hz), 124.7, 126.0 (q, $^{3}J_{CF}$ = 4.1 Hz), 128.1, 129.2, 131.6 (q, $^{2}J_{CF}$ = 33.5 Hz), 132.1, 138.1, 141.7, 142.6, 144.7, 149.2, 151.0, 156.3, 160.6 ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ: - 63.1 ppm. HRMS (EI): calculated for $C_{22}H_{15}F_3N_2O$ $[M]^+$ 380.1136; found 380.1138.

4-(4-Methoxyphenyl)-2-(4-nitrophenyl)-1,5-naphthyridine (**5e**). The general procedure was followed using imine **3c** prepared *in situ* and 4-methoxyphenylacetylene **4b** (7 mmol, 0.908 mL) and the reaction mixture was stirred at refluxing chloroform for 18 h. Compound **5e** (1.071 g, 60 %) was obtained as a white solid; mp 134-135 ºC (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.92 (s, 3H), 7.11 (d, $^{3}J_{HH}$ = 8.7 Hz, 2H),7.70 (dd, $^{3}J_{HH}$ = 8.5 Hz, $^{3}J_{HH}$ = 4.0 Hz, 1H), 7.83 (d, $^{3}J_{HH}$ = 8.7 Hz, 2H), 8.13 (s, 1H), 8.40 (s, 4H), 8.52 (dd, $^{3}J_{HH}$ = 8.5 Hz, $^{4}J_{HH}$ = 2.0 Hz, 1H), 9.54 (dd, $^{3}J_{HH}$ = 4.0 Hz, $^{4}J_{HH}$ = 2.0 Hz, 1H) ppm; ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ: 55.6, 114.2, 121.8, 124.3, 124.9, 128.6, 129,0, 132.2, 138.2, 143.3, 144.7, 145.1, 149.4, 151.4, 151.5, 155.2, 160.7 ppm. HRMS (EI): calculated for $C_{21}H_{15}N_3O_3$ $[M]^+$ 357.1112; found 357.1117.

2,4-bis(4-(Trifluoromethyl)phenyl)-1,5-naphthyridine (**5f**). The general procedure was followed using imine **3b** prepared *in situ* and 4-trifluoromethylphenylacetylene **4c** (7 mmol, 1.190 g) and the reaction mixture was stirred at refluxing chloroform for 36 h. Compound **5f** (1.251 g, 60 %) was obtained as a white solid; mp 191-192 ºC (ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.73 (dd, $^{3}J_{HH}$ = 8.5 Hz, $^{3}J_{HH}$ = 4.1 Hz, 1H), 7.75-7.85 (m, 4H), 7.95 (d, $^{3}J_{HH}$ = 8.0 Hz, 2H), 8.13 (s, 1H), 8.34 (d, $^{3}J_{HH}$ = 8.6

Hz, 2H), 8.56 (dd, $^{3}J_{HH}$ = 8.5 Hz, $^{4}J_{HH}$ = 1.7 Hz, 1H), 9.02 (dd, $^{3}J_{HH}$ = 4.1 Hz, $^{4}J_{HH}$ = 1.7 Hz, 1H) ppm; ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ: 122.2, 122.4 (q, $^{3}J_{CF}$ = 272.8 Hz), 122.8 (q, $^{3}J_{CF}$ = 272.3 Hz), 125.1, 125.5, 126.1, 128.1, 131.1-132.4 (m), 138.2, 140.6, 141.1, 142.1, 144.6, 148.2, 151.5, 156.4 ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ: - 63.1, - 63.6 ppm. HRMS (EI): calculated for $C_{22}H_{12}F_6N_2$ $[M]^+$ 418.0905; found 418.0908.

3-(2-Oxo-2-phenylethyl)-2-(pyridin-3-yl)isoindolin-1-one (**6**). The general procedure was followed using imine **3d** prepared *in situ* and phenylacetylene **4a** (7 mmol, 0.768 mL) and the reaction mixture was stirred at refluxing chloroform for 48 h. Compound **6** (0.984 g, 60 %).was obtained as a white solid; mp 152-153 ºC (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.25 (dd, $^{2}J_{HH}$ = 17.4 Hz, $^{3}J_{HH}$ = 9.4 Hz, 1H), 3.50 (dd, $^{2}J_{HH}$ = 17.4 Hz, $^{3}J_{HH}$ = 2.8 Hz, 1H), 6.0 (dd, $^{3}J_{HH}$ =9.4 Hz, $^{3}J_{HH}$ = 2.8 Hz, 1H), 7.33-7.42 (m, 3H), 7.47-7.55 (m, 4H), 7.81-7.84 (m, 2H), 7.89-7.91 (m, 1H), 8.09 (ddd, $^{4}J_{HH}$ = 1.5 Hz, $^{4}J_{HH}$ = 2.7 Hz, $^{3}J_{HH}$ = 9.3 Hz, 1H, H_{arom}), 8.42 (dd, $^{3}J_{HH}$ = 4.8 Hz, $^{4}J_{HH}$ = 1.5 Hz, 1H, H_{arom}), 8.85 (d, $^{4}J_{HH}$ = 2.7 Hz, 1H, H_{arom}) ppm; ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ: 41.8, 56.3, 123.3, 123.9, 124.3, 128.1, 128.8, 129.0, 130.1, 131.1, 132.9, 133.6, 134.0, 136.1, 143.8, 145.2, 146.3, 167.2, 197.1 ppm. HRMS (EI): calculated for $C_{21}H_{16}N_2O_2$ $[M]^+$ 328.1212; found 328.1215.

Synthesis of tetrahydroisoindolonaphthyridinones 11 and 12. General procedure.

Styrene **9** (7.5 mmol, 0.862 ml) or indene **10** (7.5 mmol, 0.868 ml) and $BF_3 \cdot Et_2O$ (10 mmol, 1.230 ml) were added to a solution of the previously prepared aldimine **3d** (5 mmol) in $CHCl_3$ (10 ml). The mixture was stirred at the appropriate temperature until TLC and ^{1}H NMR spectroscopy indicated the disappearance of imine **3d**. The reaction mixture was washed with 2M aqueous solution of NaOH (20 ml) and water (20 ml), extracted with dichloromethane (20 ml), and dried over anhydrous $MgSO_4$. The removal of the solvent under vacuum afforded an oil or solid that was purified by silica gel flash column chromatography using a gradient elution of 10-60% ethyl acetate in hexane to afford the desired products **11** or **12**.

5-Phenyl-6,6a-dihydroisoindolo[2,1-a][1,5]naphthyridin-11(5H)-one (**11**). The general procedure was followed using styrene **9**, and the reaction mixture was stirred at chloroform reflux for 24 h. Compound **11** (1.248 g, 80 %) was obtained as a white solid; mp 242-243 ºC (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.95 (ddd, $^{2}J_{HH}$ = 12.4 Hz, $^{3}J_{HH}$ = 12.4 Hz, $^{3}J_{HH}$ = 12.4 Hz, 1H), 2.95 (ddd, $^{2}J_{HH}$ = 12.4 Hz, $^{3}J_{HH}$ = 6.3 Hz, $^{3}J_{HH}$ = 2.5 Hz, 1H), 4.53 (dd, $^{3}J_{HH}$ = 12.4 Hz, $^{3}J_{HH}$ = 6.3 Hz, 1H), 4.98 (dd, $^{2}J_{HH}$ = 12.4 Hz, $^{3}J_{HH}$ = 2.5 Hz, 1H), 7.12-7.15 (m, 2H), 7.21-7.34 (m, 4H), 7.50-7.64 (m, 3H), 7.96 (d, $^{3}J_{HH}$ = 7.6 Hz, 1H), 8.33 (dd, $^{3}J_{HH}$ = 4.6 Hz, $^{4}J_{HH}$ = 1.6 Hz, 1H), 8.89 (dd, $^{3}J_{HH}$ = 8.3 Hz, $^{4}J_{HH}$ = 1.6 Hz, 1H), ppm; ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ: 38.4, 47.3, 58.5, 122.1, 122.3, 124.4, 126.9, 127.4, 128.6, 128.9, 129.0, 132.1, 132.7, 133.5, 143.9, 144.0, 145.2, 148.9, 166.6 ppm. (EI): calculated for $C_{21}H_{16}N_2O$ $[M]^+$ 312.1263; found 312.1265.

4b,14b,14c,15-Tetrahydro-10H-indeno[2,1-c]isoindolo[2,1-a][1,5]naphthyridin-10-one (**12**). The general procedure was followed using indene, and the reaction mixture was stirred at room temperature for 24 h. Compound **12** (1.377 g, 85 %) was obtained as a white solid; mp 223-224 ºC (ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.24-2.45 (m, 2H), 3.69-3.80 (m, 1H), 4.70 (d, $^{3}J_{HH}$ = 8.4 Hz, 1H), 5.11 (s, 1H), 6.88-6.90 (m, 1H), 7.00-7.18 (m, 3H), 7.46-7.62 (m, 3H), 7.73 (d, $^{3}J_{HH}$ = 7.4 Hz, 1H), 7.88 (dd, $^{3}J_{HH}$ = 7.4 Hz, $^{3}J_{HH}$ = 1.4 Hz, 1H), 8.28-8.30 (m, 1H), 8.56 (d, $^{3}J_{HH}$ = 8.3 Hz, 1H) ppm; ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ: 31.2, 42.1, 48.4, 59.0, 121.9, 122.2, 124.5, 126.8, 127.5, 127.7, 128.9, 132.2, 132.7, 132.8, 141.2, 143.1, 143.8, 145.7, 149.0, 166.9 ppm. (EI): calculated for $C_{22}H_{16}N_2O$ $[M]^+$ 324.1263; found 324.1265.

Synthesis of propargylamine 15. To a solution of the previously prepared imine **3c** (5 mmol, 1.250 g) in chloroform, 4-methoxyphenylacetylene **4b** (7 mmol, 0.908 ml) and diphenylphosphonic acid (10 mmol, 2.5 ml) were added and the mixture was stirred in chloroform for 24 h. The reaction mixture was washed with 2M aqueous solution of NaOH (20 ml) and water (20 ml), extracted with dichloromethane (20 ml), and dried over anhydrous $MgSO_4$. Purification by silica gel flash column chromatography using

a gradient elution of 10-50% ethyl acetate in hexane to afford the desired products **15** as an orange oil (0.955 g, 50%). Rf: 0.54 (50:50 ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.80 (s, 3H), 4.32 (d, $^{3}J_{HH}$ = 7.2 Hz, 1H), 5.54 (d, $^{3}J_{HH}$ = 7.2 Hz, 1H), 6.82 (d, $^{3}J_{HH}$ = 9.0 Hz, 2H), 7.00-7.15 (m, 2H,), 7.34 (d, $^{3}J_{HH}$ = 9.0 Hz, 2H), 7.67 (d, $^{3}J_{HH}$ = 8.6 Hz, 2H), 7.77 (d, $^{3}J_{HH}$ = 8.6 Hz, 2H), 8.05-8.07 (m, 1H), 8.16-8.17 (m, 1H) ppm; ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ: 50.3, 55.5, 85.3, 86.5, 114.1, 118.9 120.4, 123.8, 125.9 (q, $^{1}J_{CF}$ = 247.1 Hz), 126.0 (q, $^{3}J_{CF}$ = 3.9 Hz), 127.8, 130.6 (q, $^{2}J_{CF}$ = 33.1 Hz), 133.4, 137.4, 140.4, 142.3, 143.3, 160.1 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: - 63.0 ppm. HRMS (EI): calculated for $C_{22}H_{17}F_3N_2O$ $[M]^+$ 382.1293; found 382.1297.

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SUPPORTING INFORMATION AVAILABLE

Copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **3d**, **5a-f, 6, 11, 12** and **15** and COSY experiment of compound **6**. X-ray structure and crystallographic data for **5d**. Study by 1D-NOESY of structure for compound **11.** ^{1}H and ^{13}C NMR study of the reaction between aldimine **3b** and acetylene **4b** promoted by Brönsted acid. Computational Studies: Cartesian coordinates, harmonic analysis data, and energies for all the stationary points discussed. This material is available free of charge via the Internet at http://pubs.acs.org.

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