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Copper-catalyzed one-pot synthesis of 3-(*N*-heteroarenyl)acrylonitriles through radical conjugated addition of β-nitrostyrene to methylazaarenes

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Abstract

A simple procedure for the copper-catalyzed synthesis of 3-(*N*-heteroaryl)acrylonitriles was developed. Using a combination of Lewis and Brønsted acids, this one-pot procedure undergoes via a radical conjugated addition and dehydration processes, without isolation of any intermediate, affording the acrylonitriles. This diastereoselective approach allowed the synthesis of a broad scope of quinazoline derivatives (22 examples) with moderate to good yields and good functional-group tolerance and could be extended to other *N*-heterocyles such as quinolines and isoquinolines. Based on control experiments, a mechanistic proposal for this new transformation is also presented.

Introduction

Aromatic nitrogen heterocycles are well known for their biological and pharmacological properties and among this class of compounds, the quinazolines are of great interest.[1] This scaffold is present in several compounds with anticancer,[2] anti-inflammatory,[3] antiparasitary[4] and antibacterial[5] activities. Furthermore, this heterocycle is present in commercial drugs, such as gefitinib, used in the treatment of certain types of cancer,[6] or prazosin, indicated to control blood pressure.[7] Examples of bioactive quinazoline derivatives are depicted in Figure 1. Due to the important role of quinazoline derivatives, there is a need for robust, versatile, green and scalable chemistry for the synthesis of this scaffold.

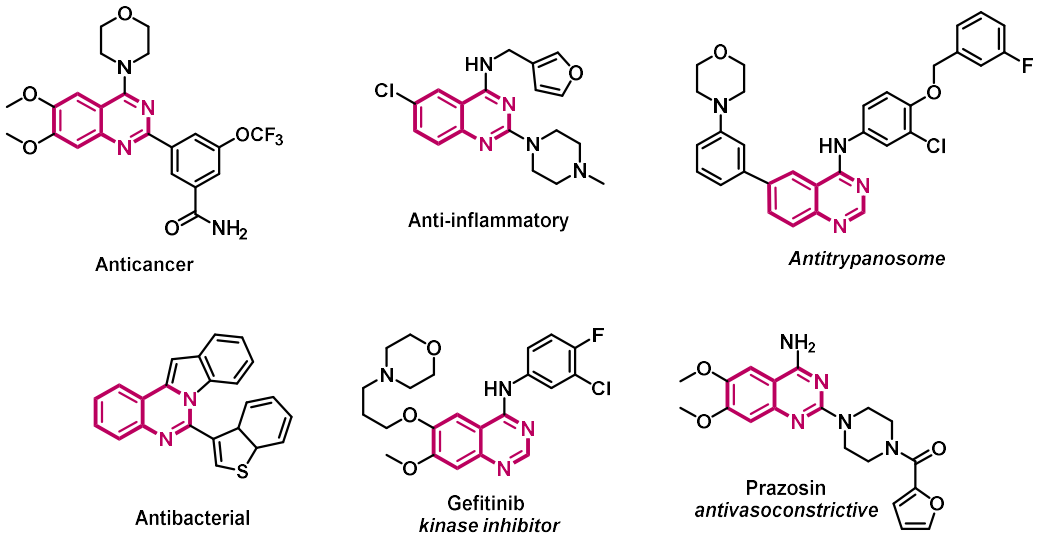
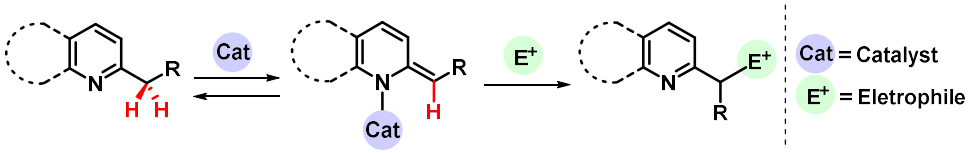


Figure 1. Selected bioactive compounds containing quinazoline moiety.

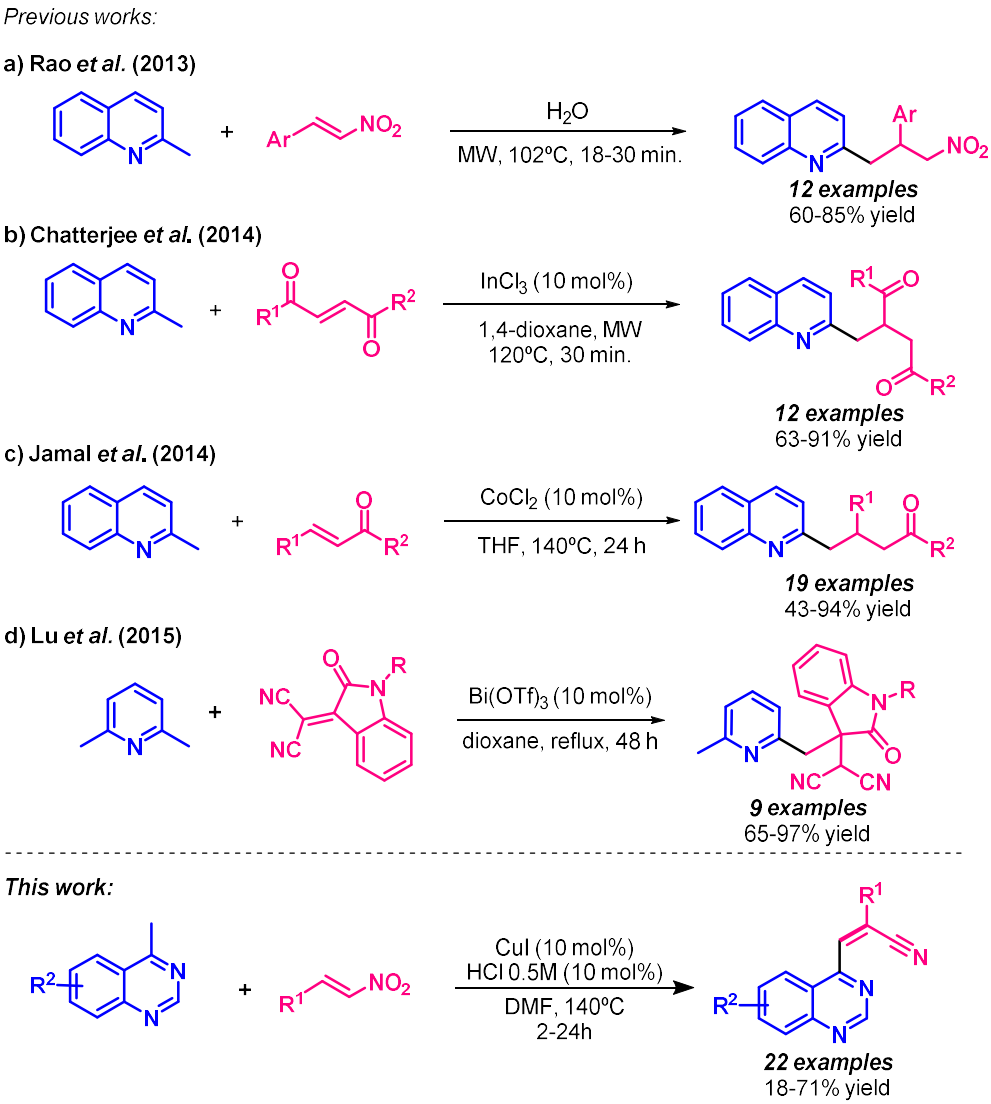
The functionalization of activated alkyl azaarenes has been extensively reported in the last years, especially for 2-methylazaarenes.[8] For example, there are reports of functionalization of benzylic bonds in azaarenes using transition metals,[9] alkaline-earth metals,[10] Brønsted acids[11] or bases.[12] These scaffolds have a privileged reactivity once the acidic nature of benzylic hydrogens allows the facile deprotonation and tautomerization to the corresponding enamine form. This tautomerization gives to the azaarene a nucleophilic character, which allows the reaction with a variety of electrophiles (Scheme 1).[13]



Scheme 1. General representation of functionalization of 2-alkyl azaarenes.

1,4-Addition reactions of 2-methylquinoline has also been explored. For example, the Michael addition to β-nitrostyrene using PEG-400 as a recyclable reaction medium without the need of any additive or acid catalyst was described by Yeramanchi *et al*.[14] Rao and Meshram reported the same reaction using water under microwave irradiation (Scheme 2a).[15] Chatterjee *et al*. described the reaction of 2-methylquinoline and (*E*)-1,4-diphenylbut-2-ene-1,4-dione in the presence of 10 mol % of $InCl_3$ as catalyst in 1,4-dioxane under microwave irradiation (Scheme 2b).[16] Moreover, Jamal *et. al*. described the Michael addition of 2-methylquinolines to chalcones employing $CoCl_2$ as catalyst (Scheme 2c).[17] Besides the use of 2-methylquinolines, Lu and co-workers expanded their methodology to the functionalization of methylpyridines with malononitrile-derived Knoevenagel products, utilizing $Bi(OTf)_3$ as catalyst (Scheme 2d).[18]

Although these works are remarkable, most of them have not been applied to other methylazaarenes. Thus, due to our ongoing interest in quinazoline derivatives, herein we report a facile Cu-catalyzed 1,4-addition of 4-methylquinazolines to β-nitrostyrene followed by dehydration, which showed good functional group tolerance and chemoselectivity.



Scheme 2. Selected reports of 1,4-addition to methylazaarenes.

Results and Discussion

We started our investigation using *trans*-β-nitrostyrene (**1**) and 4-methylquinazoline (**2**) as model substrates. Initially, a wide variety of Lewis acids was screened, using microwave irradiation as shown in Table 1. To our surprise, the Michael adduct was not isolated; instead, only products **3a** and **4** were obtained. The structure of compound **3a** was stablished by X-ray crystallography (Figure 2),[19] confirming the *Z* configuration of the double bond, and it is probably produced by the direct transformation

of the resulting nitroalkane or its salt to the corresponding nitrile, which has been previously reported for different substrates.[20] On the other hand, compound **4** was fully characterized by spectroscopic methods and may be obtained via cyclization of the Michael adduct followed by elimination of HNO_2 in an intramolecular Nef-process.[21]

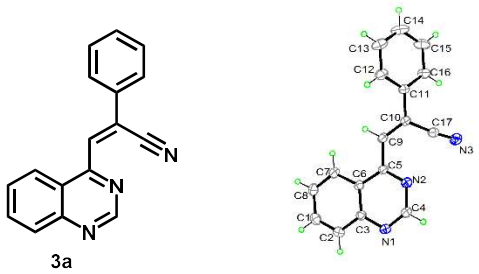
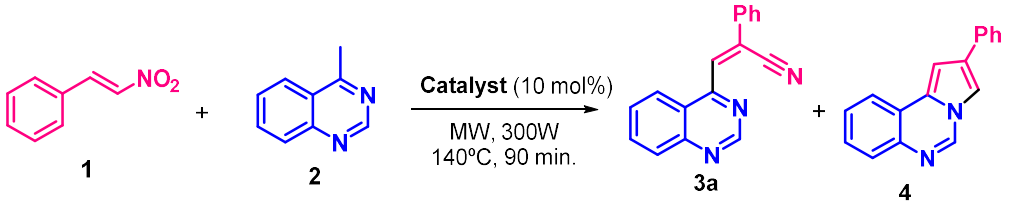


Figure 2. X-ray structure of compound **3a**.

Table 1. Screening of Lewis acids



Entry[a]	Catalyst	Yield of 3a (%)[b]	Yield of 4 (%)[b]
1	$Co(NO_3)_2.6H_2O$	traces	26
2	$CoCl_2.6H_2O$	traces	27
3	$CoCl_2$	16	22
4	$FeCl_3.6H_2O$	-	23
5	$NiBr_2$	-	13
6	$Ni(NO_3)_2$	-	7
7	$AgNO_3$	traces	13
8	$SnCl_2$	-	11
9	$Cu(OAc)_2.2H_2O$	13	32
10	$CuCl_2.2H_2O$	-	20

[a] Reaction conditions: **1** (0.15 mmol), **2** (0.38 mmol, 2.5 eq.), catalyst (0.015 mmol, 10 mol%), ethanol (0.5 mL). [b] Isolated yield.

Continuing the catalyst screening, when $Co(NO_3)_2 \cdot 6H_2O$ or $CoCl_2 \cdot 6H_2O$ were used (Table 1, entries 1-2), compound **4** was isolated in approximately 27% yield and with $CoCl_2$ (Table 1, entry 3) compound **3a** was additionally obtained in 16% yield. With the use of other Lewis acids, it was possible to isolate only product **4**, but still in low yield (Table 1, entries 4-8). When $Cu(OAc)_2 \cdot 2H_2O$ was employed as catalyst, we could isolate

both products (Table 1, entry 9), but when we used $CuCl_2 \cdot 2H_2O$ (Table 1, entry 10), only product **4** was observed.

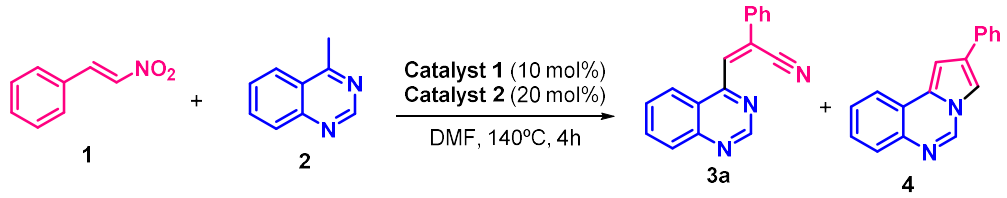
Inspired by a previous report of Fan and coworkers,[22] in which the authors used a combination of a copper salt and a Brønsted acid to perform oxygenation and cyclization reactions, we then tried different combinations of Brønsted acids and copper salts using DMF as the solvent under conventional heating. Initially, the same conditions of Table 1, entry 9, were used in combination with hydrochloric acid and a slight increase in the yield of **3a** was observed, motivating us to continue the optimization with other copper salts. The use of Cu(I) salts significantly increased the yield of **3a**, and the best result was obtained using CuI and HCl as catalysts (Table 2, entry 4). Then, other Brønsted acids were used in combination with CuI (Table 2, entries 5-9), but none of them improved the yield of product **3a**.

Looking for greener conditions,[23] we carried out a large screening of solvents, starting with ethanol (Table 2, entry 1). We then tested dimethyl carbonate (DMC), acetonitrile, ethyl acetate, anisole, toluene, and *N*,*N*′-dimethylpropyleneurea (DMPU) and traces of the desired product were obtained, while DMSO, THF or 1,3-dimethyl-2-imidazolidinone (DMI) furnished low yields (10-26%) and *N*,*N*′-dimethylacetamide (DMAc) gave 52% of compound **3a**. Moreover, other parameters, such as temperature, concentration, catalyst loading, ligands and reaction time were also evaluated without success (see the S.I. for details). Finally, we tried to decrease the amount of HCl solution and, to our delight, the yield of **3a** slightly increased to 71% when we use 10 mol% of HCl (Table 2, entry 10).

With the optimized condition, i.e., a combination of CuI (10 mol%) and HCl (10 mol%) in DMF at 140 ºC for 2 h, we turned our attention to investigate the scope and limitations of this protocol (Scheme 3). Thus, we first evaluated the effect of substituents on the quinazoline in different positions and observed that alkyl (**3b-c**), halogens (**3d-f**) and methoxy (**3g**) groups were well tolerated, affording products with moderated to good yields (47-68%). More importantly, the reaction is regioselective, as shown in **3b** with the methyl group at the 2-position.

Next, different substituents on the *trans*-β-nitrostyrene were evaluated and we were pleased to find that the desired products containing electron-donor substituents such as alkyl (**3h**-**j**), phenyl (**3k**), halogens (**3l**-**n**), methoxy (**3o**-**p**) and a dimethylamino group (**3q**) were obtained in moderate to good isolated yields (40-68%).

Table 2: Catalyst optimization

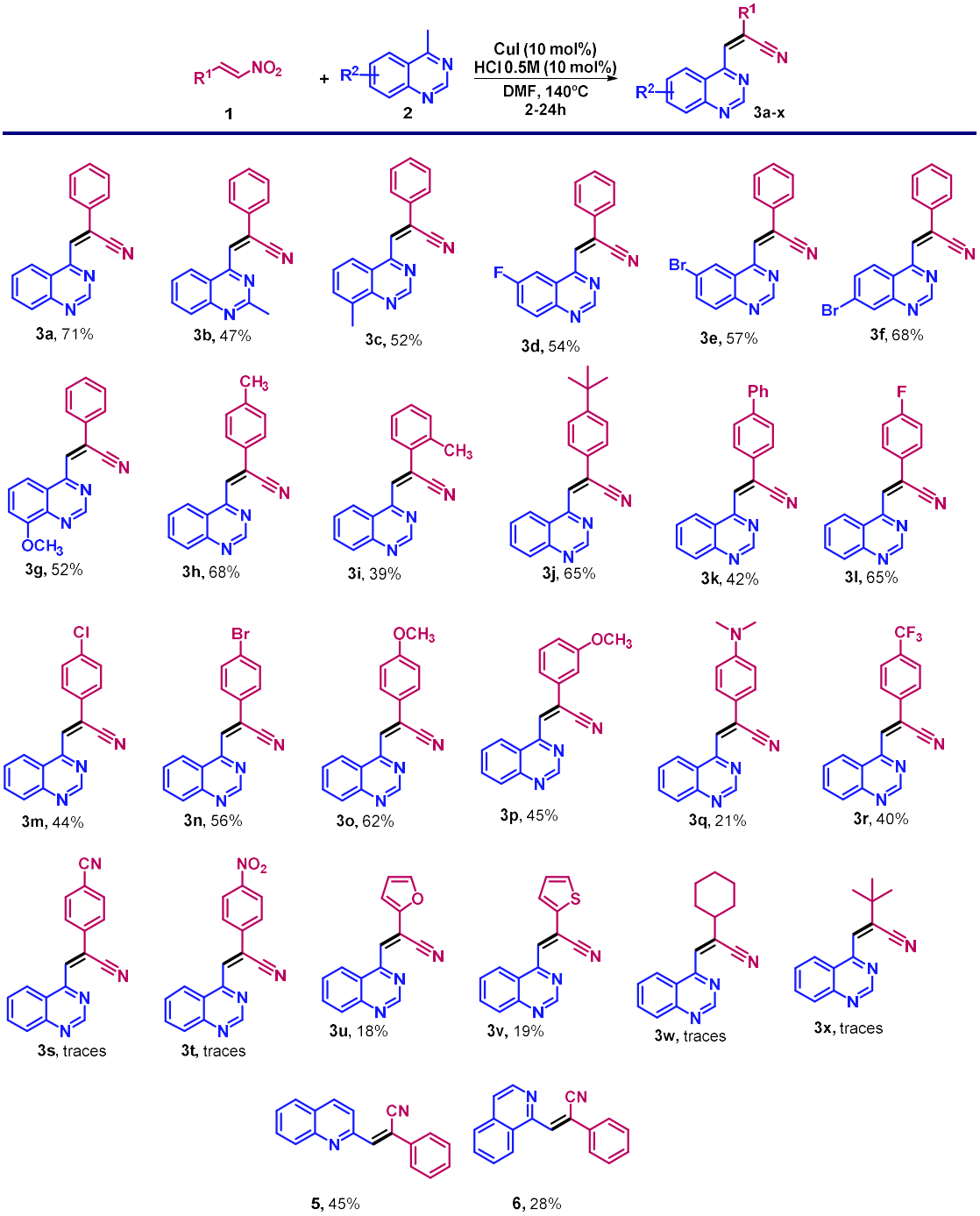


Entry[a]	Cat. 1	Cat. 2[b]	Yield of 3a (%)[c]	Yield of 4 (%)[c]
1[d]	$Cu(OAc)_2$	HCl	26	25
2	CuCl	HCl	53	38
3	CuBr	HCl	56	10
4	CuI	HCl	62	22
5	CuI	H_2SO_4	33	14
6	CuI	AcOH	34	12
7	CuI	*p*-TSA	32	12
8	CuI	TFA	43	13
9	CuI	TfOH	30	13
10[e]	**CuI**	**HCl**	**71**	**traces**
11[f]	-	HCl	44	traces
12[f]	CuI	-	44	25

[a] Reaction conditions: **1** (0.15 mmol), **2** (0.38 mmol, 2.5 eq.), DMF (0.5 mL), sealed tube. [b] substrate concentration = 0.5 mol·L^{-1}. [c] Isolated yield. [d] EtOH instead of DMF. [e] 10 mol% of CuI and 10 mol% of HCl 0.5 M for 2 h. [f] Control experiments using 10 mol% of catalyst for 2 h.

Concerning the *trans*-β-nitrostyrene containing electron-withdrawing groups, product **3r** was obtained in moderate yield (40%) when the reaction was carried out at 120ºC. However, the presence of cyano or nitro groups was not well tolerated and only traces of the corresponding products **3s** and **3t** were observed. The use of heteroaromatic nitroolefins afforded products **3u** and **3v**, albeit in low yields (18 and 19%, respectively). Unfortunately, the methodology was not effective when alkyl nitroolefins such as cyclohexyl and *tert*-butyl were used, for which only traces of the product **3w** and **3x** were observed, respectively.

Furthermore, other *N*-heterocycles such as quinoline (**5**) and isoquinoline (**6**) were well tolerated and when the reactions were carried out at 120 ºC, the products were obtained in moderate yields (45% and 28%, respectively).



Scheme 3. Scope and limitations of the methodology.

In order to have a better understanding of the reaction mechanism, we performed some control experiments. Thus, in the absence of CuI, product **3a** was obtained in lower yield than for the standard conditions (Table 2, entry 11) and without the HCl solution, both products were obtained, albeit in lower yields (Table 2, entry 12). These results indicate that, even though the formation of **3a** is observed without any catalyst, both catalysts play a crucial role to improve the yield of desired product. The use of an inert atmosphere such as nitrogen instead of air did not afford product **3a**, indicating that oxygen is necessary to promote the reaction.

We then performed the reaction in the presence of radical scavengers such as TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) and BHT (3,5-di-*tert*-4-butylhydroxytoluene). In both cases, only traces of product **3a** were observed, which suggested that this transformation involves a free radical mechanism. In order to detect some key intermediates, we analyzed the crude products of these reactions by mass spectrometry (See SI for more details). After 30 minutes reaction time, we were able to detect TEMPO coupled with the Michael adduct (*m/z* = 449) as well as with starting material **2** (*m/z* = 300), as shown in Figure 3. The observation of these intermediates suggests that the conjugated addition might occur in a Giese-type radical pathway.[24]

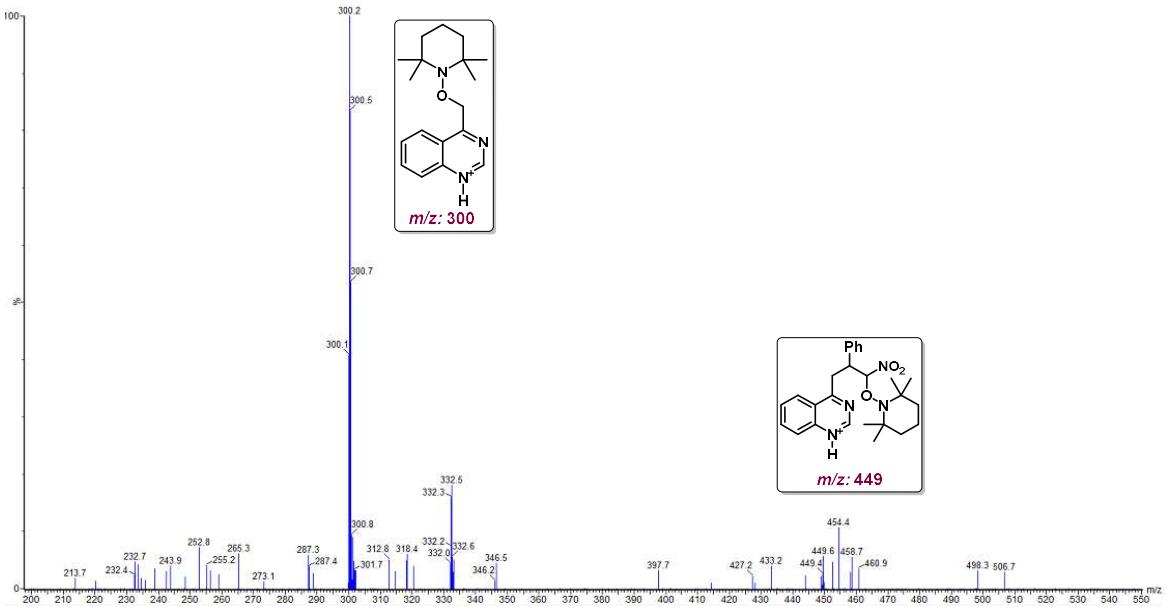
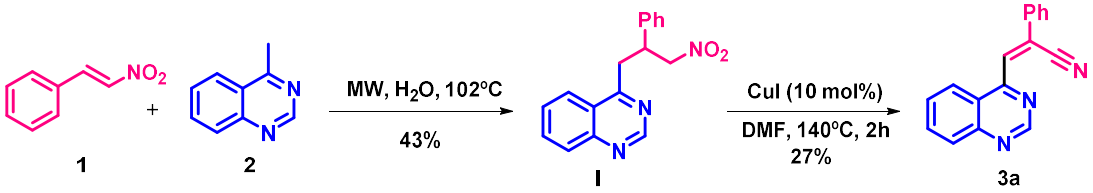


Figure 3. MS analysis of radical scavenger experiment.

With the aim of isolating the Michael adduct formed by nucleophilic attack of quinazoline **2** to β-nitrostyrene **1**, we performed the reaction using conditions described previously by Rao.[17] The reaction was carried out without catalyst in water at 102 ºC under microwave irradiation, and after 35 minutes, the Michael adduct **I** was isolated in 43% yield (Scheme 4). The adduct **I** was then submitted to the reaction for the formation of **3a**, using 10 mol% of CuI, and after 2 hours at 140 ºC, the desired product was obtained in 27% yield. These results are an indicative that the conjugated addition is the first step of this transformation.

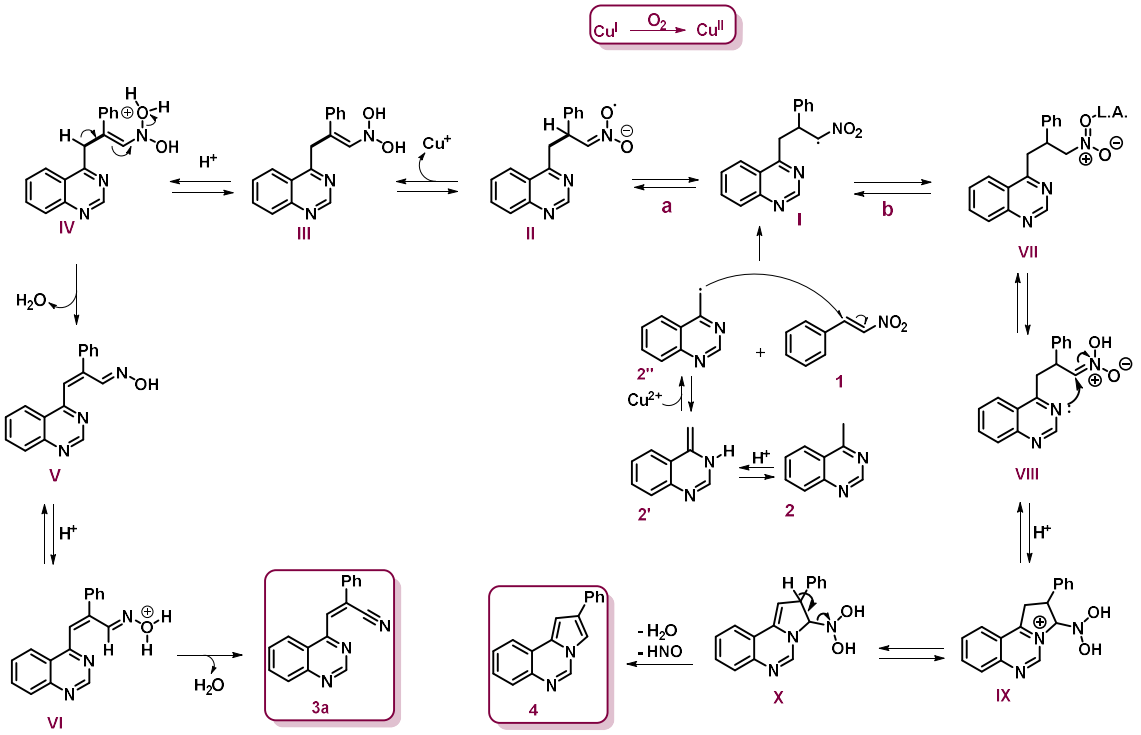


Scheme 4. Formation of **3a** from the isolated Michael adduct **I**.

There are reports where copper salts are used to promote radical reactions, and in some cases, in combination with an oxidizing agent[25] or molecular oxygen from air. Jie *et al.* described a copper-catalyzed dehydrogenation to generate chalcones, which were used in a sequential conjugate addition. The authors proposed that the copper salt reacts with ketone to form a metal-enolate complex, which promotes the formation of a radical intermediate through homolysis of a Cu(II)-enolate.[26] Guo *et al*. described the copper catalyzed synthesis of 3*H*-indol-3-ones through a copper superoxide complex. Recently, Chatterjee and co-workers reported a Cu-catalyzed functionalization of 2-(2-bromophenyl)quinazolin-4(3*H*)-ones in the presence of oxygen atmosphere.[27] The combination of Cu(I) with molecular oxygen is a well-known method to promote the oxidation to Cu(II),[28] with the latter copper species being able to perform oxidative reactions in numerous types of substrates.[29]

Although the full reaction mechanism for the formation of **3a** is still unclear and other pathways cannot be discarded, on the basis of previous reports and in our experimental results, we proposed a plausible mechanism for the formation of **3a** and **4**. Thus, for product **3a** (Scheme 5a), initially the Brønsted acid promotes the formation of quinazoline enolate **2'**. This intermediate is oxidized by Cu(II), produced *in situ*,[30] furnishing benzylic radical **2''**, which undergoes a radical conjugated addition[31] with *trans*-β-nitrostyrene, resulting in the α-nitro radical intermediate **I** that tautomerizes to **II**. This intermediate might be capable of regenerate Cu(I) catalyst. Then, after protonation and a vinylogous elimination of water the double bond is formed (**V**), followed by a second elimination to afford product **3a**.

In the other hand, for the formation of product **4**, after the 1,4-addition, a nucleophilic attack of the nitrogen at 3-position of the quinazoline to the α-position of the nitro group may occur, generating the cyclic intermediate **IX** (Scheme 5b). Then, in order to form a conjugated system, elimination of HNO_2 affords product **4**. This elimination could also be facilitated by the presence of a Brønsted acid, which protonates the oxygen of the nitro group.



Scheme 5. Mechanistic proposal for the synthesis of quinazoline derivatives **3a** and **4**.

Conclusion

In summary, we developed a unprecedent protocol for the one-pot synthesis of new conjugated nitrile compounds, utilizing a combination of Lewis and Brønsted acid catalysts. Based on control experiments, a mechanistic pathway was proposed via a radical conjugated addition of β-nitrostyrenes to methylazaarenes followed by dehydration processes. Using the optimized conditions, 22 derivatives were prepared in 18-71% overall yield. These new compounds can be used in subsequent conjugated additions in order to create more complex molecules, besides the potential biological activity of quinazoline derivatives scaffolds.

Experimental Section

General information

All commercially available reagents were purchased from Sigma-Aldrich. The synthesized products were purified through chromatographic column using silica gel 60, 230–400 mesh. TLC were performed in silica gel 60 F254 supported in aluminum sheets.

^{1}H and ^{13}C NMR spectrum were recorded on a Bruker DRX 400 MHz spectrometer. Chemical shifts (δ) were presented in ppm units and the coupling constants (J) in Hertz (Hz). Signals multiplicity were expressed by the following

abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). The IR spectrum were recorded on a SHIMADZU (IR-Prestige-21).

UltraPerformance Convergence Chromatography™ was carried out using a ACQUITY UPC2 ™ system (Waters Corp., Milford, MA, USA), equipped with achiral stationary phase Viridis HSS C_{18} SB and a mass spectrometer Waters (Xevo TQD Triple Quadrupole Mass Spectrometry). The exact mass measurement was carried out using a micrOTOF Q IITOF Mass Spectrometer (Bruker Daltonics, Billerica, MA, USA) equipped with an ESI ion source (positive ionization mode).

General procedure for the synthesis of 3-(*N*-heteroarenyl)acrylonitriles

A mixture of β-nitrostyrene (0.15 mmol, 1.0 eq), 4-methylquinazoline (0.38 mmol, 2.5 eq), CuI (0.015 mmol, 10 mol%), HCl 0.5 M (0.015 mmol, 10 mol%) and DMF (0.50 mL) were added in a sealed tube equipped with a stir bar. The mixture was stirred for 2-48 hours, at 120ºC or 140ºC. After completion of the reaction, the mixture was extracted with ethyl acetate (3 x 10 mL) and the organic layers were combined and washed with LiCl 5% (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography using a solution of hexane: ethyl acetate 70-30% unless otherwise noted, affording the desired products **3a**-**3v**, **5** and **6**.

(*Z*)-2-phenyl-3-(quinazolin-4-yl)acrylonitrile (3a): The product was isolated in 71% yield (27.5 mg, 0.11 mmol) as a brown solid. M.P.: 151ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.49 (s, 1H), 8.25 (s, 1H), 8.17 (dt, *J*= 8.6, 0.6 Hz, 1H), 8.13 (dt, *J*= 8.6, 0.6 Hz, 1H), 7.97 (ddd, *J*= 8.4, 6.9, 1.3 Hz, 1H), 7.87 – 7.86 (m, 1H), 7.85 – 7.84 (m, 1H), 7.72 (dt, *J*= 8.3, 6.9, 1.3 Hz, 1H), 7.54 – 7.50 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.1, 154.8, 151.3, 134.4, 133.8, 133.4, 131.0, 129.7, 129.5, 128.6, 127.1, 123.5, 123.2, 121.6, 116.7. ^{13}C NMR DEPT 135 (100 MHz, $CDCl_3$) δ 154.7, 134.3, 133.3, 130.9, 129.6, 129.4, 128.5, 127.0, 123.4. IR (KBr, ν_{max}) 3059, 3041, 2200, 1616, 1602, 1564, 1541, 1492, 1450, 1384, 760, 686 cm^{-1}. HRMS (ESI): *m/z* calcd for $C_{17}H_{12}N_3$ $[(M+H)]^+$: 258.1026, found: 258.1028.

(*Z*)-3-(2-methylquinazolin-4-yl)-2-phenylacrylonitrile (3b): The product was isolated in 42% yield (17.0 mg, 0.06 mmol), as a brown solid. M.P.: 123ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14 (s, 1H), 8.05-8.03 (d, *J* = 8.4 Hz, 1H), 7.97-7.95 (d, *J* = 8.4 Hz, 1H), 7.86-7.84 (dd, *J* = 8.3, 7.3 Hz, 1H), 7.79-7.77 (dd, *J* = 6.2, 2.2 Hz, 1H), 7.57-7.54 (dd, *J* = 8.3, 7.3 Hz, 1H), 7.46-7.44 (dd, *J* = 6.2, 2.2 Hz, 1H), 2.92 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.1, 158.9, 151.7, 134.2, 133.8, 133.6, 130.8, 129.3, 128.8, 127.4, 126.9, 123.3, 121.5, 120.9, 116.6, 26.1. HRMS (ESI): *m/z* calcd for $C_{17}H_{12}N_3$ $[(M+H)]^+$: 272.1188, found: 272.1182.

(*Z*)-3-(8-methylquinazolin-4-yl)-2-phenylacrylonitrile (3c): The product was isolated in 52% yield (21.1 mg, 0.08 mmol) as a yellow solid. M.P.: 154ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.53 (s, 1H), 8.26 (s, 1H), 8.01 (d, *J* = 8.5 Hz, 1H), 7.87-7.85 (m, 2H), 7.81-7.79 (m, 1H), 7.62-7.58 (t, *J* = 7.8 Hz, 1H), 7.55 – 7.49 (m, 3H), 2.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.1, 153.7, 150.4, 137.9, 134.1, 133.9, 130.8, 129.3, 128.7, 128.0, 126.9, 123.1, 122.4, 121.1, 116.7, 17.6. HRMS (ESI): *m/z* calcd for $C_{18}H_{14}N_3$ $[(M+H)]^+$: 272.1188, found: 272.1180.

(*Z*)-3-(6-fluoroquinazolin-4-yl)-2-phenylacrylonitrile (3d): The product was isolated in 54% yield (22.3 mg, 0.08 mmol), as a yellow solid. M.P.: 136ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.50 (s, 1H), 8.18 (dd, *J* = 8.9, 5.1 Hz, 1H), 8.12 (s, 1H), 7.91 – 7.84 (m, 2H), 7.84 – 7.72 (m, 2H), 7.59 – 7.51 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.9 (d, $J_{C\text{-}F}$= 253.4 Hz), 158.6 (d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$ = 6.1 Hz), 154.1, 148.5, 133.5, 132.6, 132.5 (d, *J* c-c-c-F= 9.3 Hz), 131.1, 129.4, 127.0, 124.8 (d, $J_{C\text{-}C\text{-}F}$ = 25.8 Hz), 123.8 (d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 9.1 Hz), 121.8, 116.5, 107.1 (d, $J_{C\text{-}C\text{-}F}$= 22.8 Hz). HRMS (ESI): *m/z* calcd for $C_{17}H_{12}FN_3$ $[(M+H)]^+$: 276.0937, found: 276.0930.

(*Z*)-3-(6-bromoquinazolin-4-yl)-2-phenylacrylonitrile (3e): The product was isolated in 57% yield (28.4 mg, 0.08 mmol) as a yellow solid. M.P.: 165.9 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.49 (s, 1H), 8.30 (s, 1H), 8.14 (s, 1H), 7.87 (dd, *J* = 6.3, 2.7 Hz, 2H), 7.54 (dd, *J* = 6.3, 2.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.1, 154.9, 149.9, 137.8, 133.5, 132.3, 131.3, 131.1, 129.4, 127.1, 125.8, 124.1, 122.5, 122.2, 116.5. HRMS (ESI): *m/z* calcd for $C_{17}H_{12}N_3$ $[(M+H)]^+$: 336.0136, found: 336.0131.

(*Z*)-3-(7-bromoquinazolin-4-yl)-2-phenylacrylonitrile (3f): The product was isolated in 68% yield (34.1 mg, 0.10 mmol) as a green solid. M.P.: 184ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.48 (s, 1H), 8.30 (sl, 1H), 8.13 (s, 1H), 8.00 (s, 2H), 7.86 (dd, *J* = 6.4, 2.8 Hz, 2H), 7.55 – 7.50 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.1, 154.8, 149.9, 137.8, 133.5, 132.3, 131.3, 131.1, 129.4, 127.1, 125.8, 124.0, 122.5, 122.1, 116.5. HRMS (ESI): *m/z* calcd for $C_{17}H_{10}N_3$ $[(M+H)]^+$: 336.0136, found: 336.0131.

(*Z*)-3-(8-methoxyquinazolin-4-yl)-2-phenylacrylonitrile (3g): The product was isolated in 54% yield (23.3 mg, 0.08 mmol) as a yellow solid. M.P.: 143.1ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.53 (s, 1H), 8.22 (s, 1H), 7.86 (dd, *J* = 8.9, 4.0 Hz, 2H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.64 (t, *J* = 8.1 Hz, 1H), 7.56 – 7.48 (m, 3H), 7.28 (d, *J* = 7.7 Hz, 1H), 4.13 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.7, 155.5, 153.8, 143.6, 133.8, 133.6, 130.9, 129.3, 128.7, 127.0, 124.1, 121.4, 116.6, 114.6, 111.7, 56.3. HRMS (ESI): *m/z* calcd for $C_{17}H_{14}N_3O[(M+H)]^+$: 288.1137, found: 288.1135.

(*Z*)-3-(quinazolin-4-yl)-2-(p-tolyl)acrylonitrile (3h): The product was isolated in 68% yield (27.7 mg, 0.10 mmol) as a yellow solid. M.P.: 183ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.50 (s, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.97 (dd, *J* = 8.1, 7.2 Hz,

1H), 7.77 (d, *J* = 7.9 Hz, 2H), 7.72 (dd, *J* = 8.1, 7.2 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 2H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.2, 154.7, 151.2, 141.5, 134.2, 132.1, 130.9, 130.1, 129.6, 128.4, 126.9, 123.4, 123.2, 116.7, 21.4. HRMS (ESI): *m/z* calcd for $C_{18}H_{14}N_3$ $[(M+H)]^+$: 272.1188, found: 272.1182.

(*Z*)-3-(quinazolin-4-yl)-2-(o-tolyl)acrylonitrile (3i): The product was isolated in 39% yield (15.7 mg, 0.06 mmol) as a yellow solid. M.P.: 145.5ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.52 (s, 1H), 8.14 (d, *J* = 8.5 Hz, 1H), 8.11 (d, *J* = 8.5 Hz, 1H), 7.97 (dd, *J* = 8.2, 7.2 Hz, 1H), 7.71 (dd, *J* = 8.2, 7.2 Hz, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.35 – 7.28 (m, 2H), 2.58 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.8, 154.7, 151.3, 138.4, 136.5, 134.8, 134.3, 131.3, 130.1, 129.6, 129.5, 128.5, 126.7, 123.3, 123.0, 121.7, 116.6, 20.33. HRMS (ESI): *m/z* calcd for $C_{18}H_{14}N_3$ $[(M+H)]^+$: 272.1182, found: 272.1183.

(*Z*)-2-(4-(*tert*-butyl)phenyl)-3-(quinazolin-4-yl)acrylonitrile (3j): The product was isolated in 66% yield (30.9 mg, 0.10 mmol) as a brown solid. M.P.: 257 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.50 (s, 1H), 8.23 (s, 1H), 8.17 (d, *J* = 8.5 Hz, 1H), 8.14 (d, *J* = 8.5 Hz, 1H), 7.97 (dd, *J* = 8.5, 7.31 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.72 (dd, *J* = 8.5, 7.3 Hz, 1H), 7.55 (d, *J* = 8.3 Hz, 2H), 1.38 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.2, 154.7, 151.2, 134.2, 132.24, 130.9, 129.6, 128.4, 126.8, 126.3, 123.4, 123.2, 121.4, 121.3, 116.7, 34.9, 31.2. HRMS (ESI): *m/z* calcd for $C_{20}H_{20}N_3$ $[(M+H)]^+$: 314.1657, found: 314.1653.

(*Z*)-2-([1,1'-biphenyl]-4-yl)-3-(quinazolin-4-yl)acrylonitrile (3k): The product was isolated in 42% yield (21.1 mg) as a brown solid. M.P.: 210.7ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.51 (s, 1H), 8.30 (s, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 8.15 (d, *J* = 8.5 Hz, 1H), 7.99 (d, *J* = 7.4 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 2H), 7.76-7.73 (m, 3H), 7.67-7.65 (m, 2H), 7.50 (t, *J* = 7.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.0, 154.7, 151.3, 143.8, 139.6, 134.3, 132.7, 132.5, 129.6, 129.1, 128.5, 128.3, 127.9, 127.5, 127.2, 123.4, 123.2, 121.1, 116.6. HRMS (ESI): *m/z* calcd for $C_{20}H_{20}N_3$ $[(M+H)]^+$: 334.1339 found: 334.1339.

(*Z*)-2-(4-fluorophenyl)-3-(quinazolin-4-yl)acrylonitrile (3l): The product was isolated in 65% yield (26.6 mg, 0.01 mmol) as a yellow solid. M.P.: 128ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H), 8.23 (s, 1H), 8.19 (t, *J* = 7.9 Hz, 2H), 8.02 (t, *J* = 7.7 Hz, 1H), 7.90 (dd, *J* = 8.5, 5.3 Hz, 2H), 7.77 (t, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 6.5 Hz, 1H), 7.24 – 7.22 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.24 (d, $J_{C\text{-}F}$= 253.0 Hz), 158.8, 154.6, 151.2, 134.3, 133.1, 129.9 (d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$= 2.9 Hz), 129.6, 129.1 (d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 8.7 Hz), 129.0, 128.5, 123.3, 123.1, 120.4, 116.6 (d, *J* = 22.2 Hz).HRMS (ESI): *m/z* calcd for $C_{17}H_{10}FN_3$ $[(M+H)]^+$: 276.0937, found: 276.0933.

(*Z*)-2-(4-chlorophenyl)-3-(quinazolin-4-yl)acrylonitrile (3m): The product was isolated in 44% yield (19.1 mg, 0.07 mmol) as a yellow solid, M.P.: 198 ºC. ^{1}H NMR (400

MHz, $CDCl_3$) δ: 9.49 (s, 1H), 8.23 (s, 1H), 8.18 – 8.12 (m, 2H), 8.00 – 7.95 (ddd, *J* = 8.3, 6.9, 1.1 Hz, 1H), 7.82 – 7.78 (dt, *J* = 9,3, 2,5 Hz, 2H), 7.73 (ddd, *J* = 8.3, 6.9, 1.1 Hz, 1H), 7.52 – 7.48 (dt, *J* = 9.3, 2.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.7, 154.6, 151.3, 137.2, 134.4, 133.5, 132.1, 129.7, 129.6, 128.6, 128.3, 123.3, 123.1, 120.3, 116.3. HRMS (ESI): *m/z* calcd for $C_{17}H_{12}ClN_3$ $[(M+H)]^+$: 292.0642, found: 292.0636.

(*Z*)-2-(4-bromophenyl)-3-(quinazolin-4-yl)acrylonitrile (3n): The product was isolated in 56% yield (28.1 mg, 0.08 mmol) as a green solid. M.P.: 176ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.44 (s, 1H), 8.18 (s, 1H), 8.11-8.09 (dd, *J* = 4.1, 0.6 Hz, 1H), 8.09 – 8.07 (dd, *J* = 3.8, 1.3 Hz, 1H), 7.92 (ddd, *J* = 8.5, 6.9, 1.3 Hz, 1H), 7.69 – 7.67 (m, 1H), 7.67 – 7.64 (m, 2H), 7.62 – 7.57 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.7, 154.7, 151.3, 134.4, 133.6, 132.6, 129.7, 128.6, 128.4, 125.5, 123.2, 123.1, 120.4, 116.3. HRMS (ESI): *m/z* calcd for $C_{17}H_{10}BrN_3$ $[(M+H)]^+$: 336.0136, found: 336.0132.

(*Z*)-2-(4-methoxyphenyl)-3-(quinazolin-4-yl)acrylonitrile (3o): The product was isolated in 62% yield (26.9 mg, 0.09 mmol) as a yellow solid. M.P.: 184 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.38 (s, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 8.05 (s, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.87 (dd, *J* = 8.1, 7.3 Hz, 1H), 7.73 (d, *J* = 8.7 Hz, 2H), 7.62 (dd, *J* = 8.0, 7.3 Hz, 1H), 6.93 (d, *J* = 8.7 Hz, 2H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.0, 159.4, 154.8, 151.3, 134.3, 130.6, 129.7, 128.7, 128.4, 126.3, 123.5, 123.3, 121.1, 116.9, 114.9, 55.7. HRMS (ESI): *m/z* calcd for $C_{18}H_{14}N_3O$ $[(M+H)]^+$: 288.1137, found: 288.1133.

(*Z*)-2-(3-methoxyphenyl)-3-(quinazolin-4-yl)acrylonitrile (3p): The product was isolated in 64% yield (27.7 mg, 0.096 mmol) as a yellow solid. M.P.: 157.3ºC. ^{1}H NMR (400 MHz, $CDCl_3$) 9.51 (s, 1H), 8.25 (s, 1H), 8.16 (t, *J* = 8.7 Hz, 1H), 7.98 (t, *J* = 7.7 Hz, 1H), 7.73 (t, *J* = 7.7 Hz, 1H), 7.47 – 7.42 (m, 1H), 7.39 – 7.35 (m, 1H), 7.08 – 7.04 (m, 1H), 3.91 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.2, 159.0, 154.7, 151.2, 135.1, 134.3, 133.6, 130.4, 129.6, 128.5, 123.4, 123.2, 121.4, 119.3, 116.6, 116.4, 112.7, 55.6. HRMS (ESI): *m/z* calcd for $C_{18}H_{14}N_3O$ $[(M+H)]^+$:288.1137 found: 288.1135.

(*Z*)-2-(4-(dimethylamino)phenyl)-3-(quinazolin-4-yl)acrylonitrile (3q): The product was isolated in 21% yield (9.5 mg, 0.03 mmol) as a brown solid. M.P.: 195.9 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.43 (s, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 8.10 (d, *J* = 8.5 Hz, 1H), 8.03 (s, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.68 (t, *J* = 7.6 Hz, 1H), 6.75 (d, *J* = 8.5 Hz, 2H), 3.08 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.8, 154.6, 152.0, 150.9, 133.9, 129.3, 128.5, 128.0, 126.2, 123.5, 123.2, 121.3, 121.2, 117.1, 111.9, 40.2. HRMS (ESI): *m/z* calcd for $C_{19}H_{16}N_4$ $[(M+H)]^+$: 301.1448, found: 301.1447.

(*Z*)-3-(quinazolin-4-yl)-2-(4-(trifluoromethyl)phenyl)acrylonitrile (3q): The product was isolated in 40% yield (19.3 mg, 0.06 mmol) as a yellow solid. M.P.: 215 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.53 (s, 1H), 8.33 (s, 1H), 8.17 (d, *J* = 8.4 Hz, 2H), 7.99 (d, *J* = 7.9

Hz, 3H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.75 (t, *J* = 7.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.4, 154.7, 151.4, 137.0, 135.5, 134.5, 129.8, 128.7, 127.4, 126.39, 126.36, 123.2, 123.1, 120.1, 116.1. HRMS (ESI): *m/z* calcd for $C_{18}H_{11}N_3F_3$ $[(M+H)]^+$: 326.0905, found: 326.0896.

(*E*)-2-(furan-2-yl)-3-(quinazolin-4-yl)acrylonitrile (3u): The product was isolated in 19% yield (7.2 mg, 0.03 mmol) as a brown solid. M.P.: 211.3 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.53 (s, 1H), 8.14 (d, *J* = 4.8 Hz, 1H), 8.09 (d, *J* = 7.9 Hz, 1H), 7.88 (d, *J* = 7.9 Hz, 1H), 7.62 (d, *J* = 7.5 Hz, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.24 – 7.21 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.6, 141.9, 140.2, 136.7, 133.5, 130.8, 130.7, 129.0, 128.8, 127.7, 126.9, 125.3, 123.5, 119.9, 100.1. HRMS (ESI): *m/z* calcd for $C_{15}H_9N_3O[(M+H)]^+$: 248.0819, found: 248.0816.

(*E*)-3-(quinazolin-4-yl)-2-(thiophen-2-yl)acrylonitrile (3v): The product was isolated in 20% yield (7.9 mg, 0.30 mmol) as a brown solid. M.P.: 117.3ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.48 (s, 1H), 8.17 (d, *J* = 8.5 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 8.09 (s, 1H), 8.00 - 7.97 (m, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 3.8 Hz, 1H), 7.49 (d, *J* = 5.1 Hz, 1H), 7.18 (dd, *J* = 3.8, 5.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.6, 138.8, 138.3, 134.2, 133.7, 130.9, 129.6, 129.4, 128.9, 128.8, 128.4, 123.2, 123.0, 115.7, 115.2. HRMS (ESI): *m/z* calcd for $C_{15}H_9N_3S[(M+H)]^+$: 264.0590, found: 264.0589.

2-phenylpyrrolo[1,2-c]quinazoline (4): The product was isolated in 34% yield (12.44 mg, 0.051 mmol) as a brown solid. ^{1}H NMR: (400 MHz, $CDCl_3$) δ: 8.67 (d, *J*= 0.30 Hz, 1H), 8.02-7.97 (m, 1H), 7.82-7.78 (m, 1H), 7.70 (m, 1H), 7.68 (m, 1H), 7.62 (d, *J*= 1.38 Hz, 1H), 7.50-7.49 (ddd, *J*= 1.81, 5.17, 7.62, 2H), 7.47-7.40 (ddd, *J*= 1.81, 5.17, 7.62, 2H), 7.34-7.29 (m, 1H), 7.21-7.19 (dd, *J*= 0.30,1.38 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.08, 137.17, 130.53, 129.87, 128.95, 128.28, 127.91, 127.50, 127.57, 126.27, 121.79, 121.42, 109.67, 98.91. ^{13}C DEPT 135 (100 MHz, $CDCl_3$) δ 138.08, 128.95, 127.91, 127.27, 126.27, 121.79, 109.67. HRMS (ESI): *m/z* calcd for $C_{17}H_{12}N_2$ $[(M+H)]^+$: 245.1079, found: 257.1072.

(Z)-2-fenil-3-(quinolin-2-il)acrilonitrila (5): The product was isolated in 45% yield (17.4 mg, 0.07 mmol) as a yellow solid. M.P.: 94.8 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.28 (d, *J* = 8.6 Hz, 1H), 8.16 (dd, *J* = 15.5, 8.6 Hz, 2H), 7.53 – 7.44 (m, 2H), 7.83 – 7.74 (m, 3H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.45 – 7.37 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.2, 148.1, 143.9, 141.4, 136.9, 135.9, 134.0, 129.2, 129.0, 127.8, 127.6, 126.5, 121.7, 120.8, 117.4, 116.1. HRMS (ESI): *m/z* calcd for $C_{18}H_{12}N_2$ $[(M+H)]^+$: 257.1073, found: 257.1073.

(*Z*)-3-(isoquinolin-1-yl)-2-phenylacrylonitrile (6): The product was isolated in 20% yield (7.6 mg, 0.03 mmol) as a brown solid. M.P.: 144.2ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.73 (d, *J* = 5.7 Hz, 1H), 8.32 (s, 1H), 8.19 (d, *J* = 8.3 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H),

7.85 (d, *J* = 7.7 Hz, 2H), 7.77 – 7.71 (m, 2H), 7.70 – 7.62 (m, 1H), 7.54 – 7.45 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.5, 140.4, 136.5, 136.5, 134.4, 130.4, 130.0, 129.2, 128.7, 128.1, 127.7, 126.7, 126.6, 125.2, 123.9, 122.3, 117.5. HRMS (ESI): *m/z* calcd for $C_{18}H_{12}N_2$ $[(M+H)]^+$: 257.1073, found: 257.1070.

4-(3-nitro-2-phenylpropyl)quinazoline (I): The product was isolated in 43% yield (38 mg, 0.13 mmol) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 7.95 (t, *J* = 8.3 Hz, 2H), 7.81 (t, *J* = 7.7 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.25 – 7.20 (m, 3H), 7.18 – 7.12 (m, 2H), 4.87 (dd, *J* = 12.8, 6.3 Hz, 1H), 4.71 (dd, *J* = 12.7, 8.6 Hz, 1H), 4.39 – 4.26 (m, 1H), 3.61 (qd, *J* = 15.4, 7.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 154.3, 149.9, 139.0, 133.9, 129.3, 129.1, 128.0, 127.9, 127.4, 124.01 (overlapping signal), 123.98, 79.5, 42.2, 37.3.

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