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Synthesis of 4-tosyl quinazoline derivatives with the assistance of ultrasound irradiation as a guide to the reaction pathway

Manijeh Nematpour

In this study, we tried to show the role of ultrasonic waves in the reaction pathway of quinazolines with an amide functional group. At first, 4-tosyl quinazolines were prepared using a simple, rapid, and one-pot reaction of Cu-catalyzed cross-coupling reactions of 2-iodoaniline and tosyl methyl isocyanide (TosMIC) in THF solvent under ultrasonic conditions in 30 min with good efficiency. The role of ultrasound in this reaction is to reduce the time and increase the efficiency of product preparation. Then, considering the potential of some synthesized derivatives to carry out the cross-coupling reaction with the help of isocyanides, copper iodide catalyst, and cesium carbonate as a base in THF solvent was investigated. Spectroscopic evidence ^{1}H-NMR, ^{13}C-NMR, IR, and Mass) shows interesting results that the reaction proceeds under ultrasonic conditions towards C–H activation and without the use of ultrasonic towards cross-coupling reaction. Finally, 22 new heterocyclic compounds from the 4-tosylquinazoline family have been synthesized under ultrasonic conditions in this project with a simple, rapid, and efficient method.

Keywords Ultrasound-assisted, Cross-coupling, C–H activation, 4-tosyl quinazoline, Copper-catalyzed, Tosyl methyl isocyanide

Nitrogen-containing heterocycles, which have two fused six-membered rings, benzene, and pyrimidine, are called quinazolines[1]. Heterocyclic compounds containing the quinazoline structure exhibit a wide range of biological activities, such as antioxidant,[2] analgesic,[3] anti-inflammatory,[4] antiviral,[5] anti-bacterial,[6] anti-diabetic,[7] anti-hypertensive,[8] anti-malarial,[9] and anti-cancer activities[10–12]. The discovery of quinazoline and its derivatives revealed their great potential as promising kinase inhibitors, which are among the most well-known targets in anticancer drug discovery and were found in approved drugs targeting the kinases EGFR, HER-2, VEGFR-2, and PI3K[13–16]. In Fig. 1, some quinazoline derivatives with diverse biological activities are shown[17,18].

Due to the wide range of biological activities investigated, quinazoline derivatives have received much attention in medicinal chemistry research and organic compound synthesis[19]. The structural versatility and pharmacological diversity of quinazoline derivatives make them valuable tools in drug discovery and highlight the importance of further research and development in this area. Therefore, it is highly desirable to develop efficient and simple protocols for the synthesis of various quinazoline derivatives with diverse functional groups[20,21]. However, most of the reported methods have limitations such as toxic reagents, inconvenient multi-step reactions, harsh conditions, high temperatures, expensive catalysts, long reaction times, and undesirable side products[22–26]. Given the extensive and interesting chemistry of quinazoline and the diverse applications of these compounds in the pharmaceutical industry, efforts to achieve optimal and suitable methods in the synthesis of these compounds are important and efficient[27–30].

In recent research, various heterocyclic compounds have been synthesized using the cross-coupling reaction method. Many of these compounds have been used in the synthesis of special pharmaceutical compounds and a variety of chemical reactions. By applying the Ullmann coupling method to the synthesis of novel heterocyclic compounds with biological properties, the efficiency and versatility of the synthesis can be increased[31–34]. Based on the results of our previous work on cross-coupling reactions with the help of copper iodide catalyst[35–40] and performing new reactions under ultrasonic conditions,[41–45] in this work, we have studied the synthesis of new 4-tosyl quinazoline derivatives. The one-pot, Cu-catalyzed cross-coupling reactions of 2-iodoaniline and tosyl methyl isocyanide (TosMIC) for synthesizing quinazoline as shown in (Fig. 2). The advantages of this method include easy method, availability and cheapness of required materials and catalyst, the achievement

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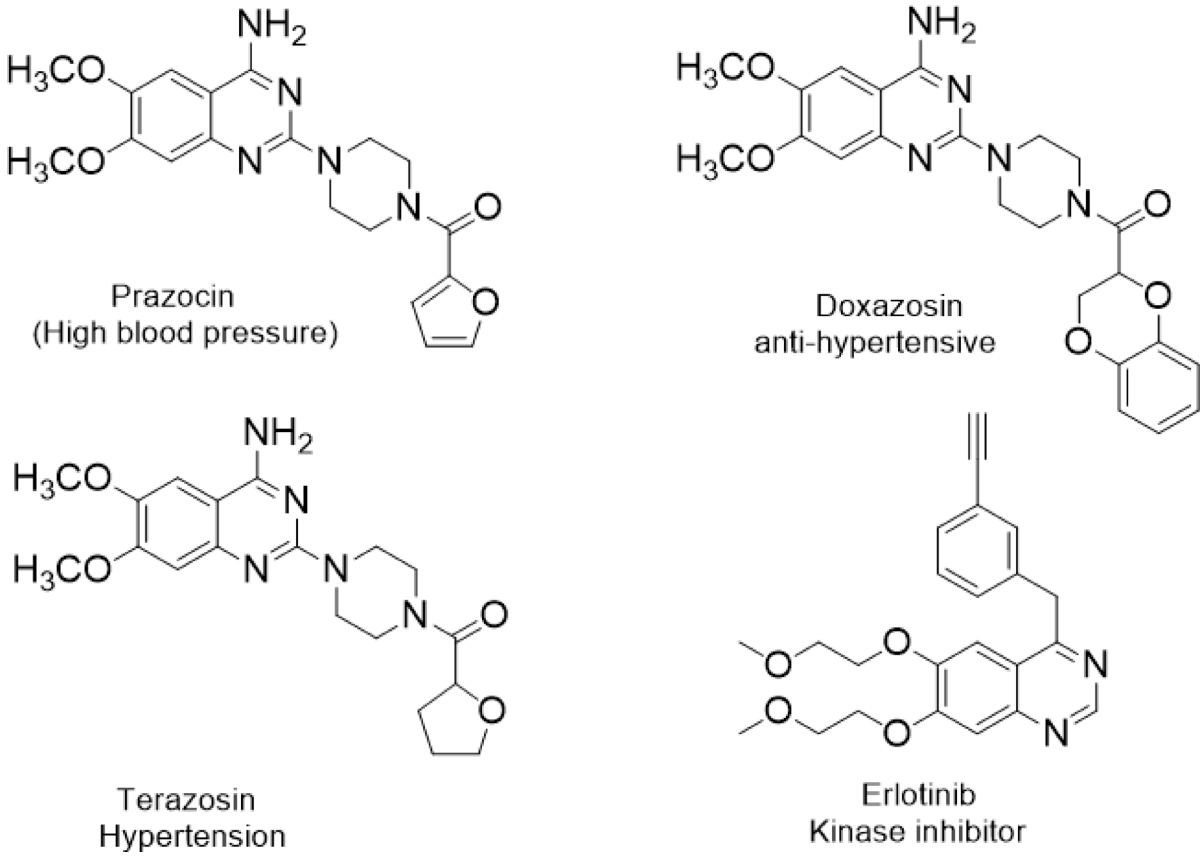


Fig. 1. Examples of some popular drugs containing the quinazoline nucleus.

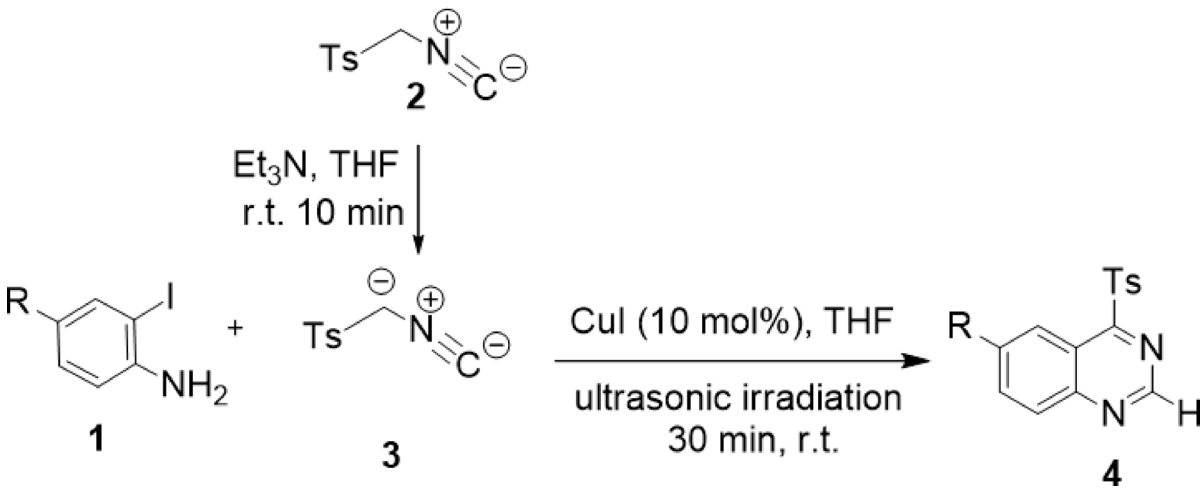


Fig. 2. Synthesis of various 4-tosyl quinazolines by Cu-catalyzed cross-coupling reactions at room temperature under ultrasonic irradiation for 30 min.

of appropriate efficiency (82–92%), without the help of ligands, and the use of ultrasonic technique to increase the efficiency and speed of the reaction making this approach attractive and outstanding for the synthesis of products.

Experimental section

General remarks

The chemicals used in the study were obtained commercially from Merck or Aldrich Company without further purification. Uncorrected melting points (M.p) were measured using an Electrothermal 9100 apparatus.

Ultrasonic generation was performed in an ultrasonic bath SONICA-2200 EP at a frequency of 40 kHz. Infrared spectra were recorded on a Shimadzu-IR-460 spectrometer, with bond positions reported in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra were obtained using a Bruker DRX-500 Avance instrument, with TMS serving as the internal standard and $CDCl_3$ as the solvent at frequencies of 500.1 and 125.7 MHz. Mass spectrometry data was acquired using a Finnigan-MAT-8430EI-MS instrument at 70 eV, with mass-to-charge ratios (m/z) reported in relative percentages.

General procedure for preparation of compounds 4a

The 1.5 mmol of tosyl methyl isocyanide **2** and 1.0 mmol of Et_3N were stirred in THF solvent (2 mL) for 10 min. Then, we slowly add the prepared solution from the previous step to the mixture containing 1.0 mmol of 2-iodoaniline **1a**, 10 mol% of CuI catalyst in THF solvent (2 mL) at ambient temperature. The mixture was sonicated in an ultrasonic apparatus with 60 watts of power for 30 min. After the reaction was complete, the mixture was diluted with CH_2Cl_2 (4 mL) and aqueous NH_4Cl (5 mL). Then the aqueous layer is extracted with CH_2Cl_2 to separate the product into the organic phase. The organic phase is dried with the help of sodium sulfate to remove water. The solvent is then removed under reduced pressure to form a solid product. To purify the final product, we used diethyl ether solvent to remove the remaining impurity of the reaction product.

Results and discussion

The optimization process for the synthesis of 4-tosyl quinazolines through the Cu-catalyzed cross-coupling reaction is a crucial step in developing an efficient and reliable protocol. By systematically varying the reaction conditions, such as catalyst and solvent, we were able to identify the optimal parameters for achieving high yields in a 30-minute reaction time. The reaction with different catalysts of copper salt including CuCl, Cu_2O, CuBr, and CuI has been investigated. It has also been tested using different solvents such as MeCN, DMF, CH_2Cl_2, EtOH, and THF. The results show the selection of THF as the best solvent and CuI as the most optimal catalyst. Also, to further investigate the catalytic role of copper salts, we have performed the reaction in the vicinity of copper metal and without adding a catalyst under the same conditions. The evidence shows that the intended product is not formed (see Table 1, Entry 14–16). Also, by reducing the amount of optimal catalyst (5 mol% of CuI), the reaction time (80 min) has increased. By using these optimized conditions in combination, we were able to further accelerate the reaction and improve the overall yield of the desired product. Therefore, the reaction is tested in THF by 10 mol% of CuI as the catalyst, 1.0 mmol of Et_3N as the base, 1.0 mmol of 2-iodoaniline, and 1.5 mmol of tosyl methyl isocyanide (see Table 1).

Considering the previous results of our work using ultrasound technique and the role of ultrasonic radiation and the effect of different radiation powers in improving the speed and efficiency of reactions, in this study we have used ultrasound technique to achieve the optimal conditions of efficiency and reaction time. The evidence in Table 2 confirms that ultrasound plays an important role in the efficiency and speed of the reaction. The comparison between the reaction under reflux conditions and ultrasonic radiation shows the superiority of the ultrasonic method. Achieving appropriate efficiency in shorter reaction times under ultrasonic radiation emphasizes the efficiency and effectiveness of this technique in promoting the optimization of conditions.

The successful synthesis of various 4-tosyl quinazolines using the optimized conditions, involving CuI catalyst, Et_3N as the base, tosyl methyl isocyanide **2**, and 2-iodoaniline **1** with different electron-withdrawing or electron-donating substituents on the aromatic rings, highlights the versatility and applicability of the developed method.

Entry	Catalyst	Solvent	Yields 4a (%)[a]
1[b]	**CuI**	**THF**	**87**
2	CuI	DMF	67
3	CuI	MeCN	56
4	CuI	CH_2Cl_2	33
5	CuI	EtOH	31
6	CuBr	THF	71
7	CuBr	MeCN	52
8	CuBr	EtOH	29
9	Cu_2O	THF	64
10	Cu_2O	CH_2Cl_2	26
11	CuCl	MeCN	45
12	CuCl	DMF	60
13	CuCl	CH_2Cl_2	21
14	Cu	DMF	–
15	Cu	THF	–
16	–	THF	–

Table 1. Optimization of reaction conditions for the formation of product 4a from 1.0 mmol of 2-iodoaniline, 1.5 mmol of Tosyl Methyl isocyanide, 10 mol% of copper salt as the catalyst, and 1.0 mmol of Et_3N as the base, at room temperature under ultrasonic irradiation for 30 min. [a]Reaction time of 30 min. [b]5 mol% catalyst, reaction time was 80 min.

Entry	Power (W)	Time	Yield (%)
1	30	90 min	52
2	40	70 min	64
3	50	50 min	74
4	**60**	**30 min**	**87**
5	70	30 min	87
6[b]	–	4 h	70

Table 2. Study of the effect of ultrasonic irradiation on the formation of various 4-tosyl quinazolines. [a]Isolated yields. [b]The reaction was carried out under reflux conditions, the reaction time was 4 h.

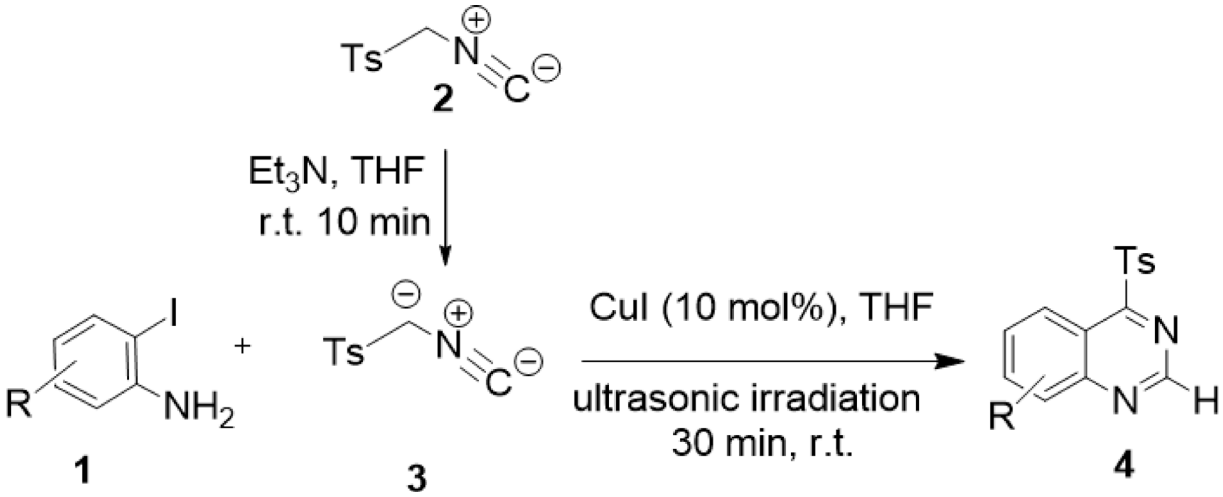


Fig. 3. Synthesis of various 4-tosyl quinazolines by Cu-catalyzed under ultrasonic irradiation.

In this reaction, the addition of triethylamine as a base to tosyl methyl isocyanide produces the 1,3-dipolar intermediate **3**[46] This active intermediate quickly reacts with 2-iodoaniline. To expand the derivatization, we have used 4-iodopyrimidin-5-amine and 3-iodopyridin-2-amine instead of 2-iodoaniline. The reaction under the same conditions has included the synthesis of interesting heterocycle compounds of 4-tosyl pyrimido (or pyrido) [5,4-*d*] pyrimidine with good efficiency (see Table 2, Entry 7, 8). Applying these optimized conditions to a range of substrates with varied substituents on the aromatic rings demonstrated the broad scope and flexibility of the Cu-catalyzed cross-coupling reaction for synthesizing various 4-tosyl quinazolines (see Fig. 3; Table 3).

The detailed characterization of compounds **4a-h** using IR,^{1}H-NMR,^{13}C-NMR, and mass spectral data provides crucial information about their structures and confirms the successful synthesis of various 4-tosyl quinazolines. The presence of characteristic signals in the^{1}H-NMR spectra, such as singlets for Me and C-H groups in compound **4a**, along with signals for phenyl protons, supports the proposed structures for the synthesized compounds. The agreement between the experimental data and the proposed structures, as well as the observation of characteristic signals for substituents in the^{13}C-NMR spectra of the other compounds, further validates the synthesis and characterization process. The mass spectrum of compound **4a** showing the molecular ion peak at m/z = 384 indicates the molecular weight of compound **4a**.

A proposed reaction mechanism is shown in (Fig. 4). It seems that the oxidative addition of 2-iodoaniline **1** and CuI leads to intermediate **5**[47,48] Also, from the reaction of tosyl methyl isocyanide **2** and triethylamine base, 1,3-dipolar intermediates of **3** are formed. Treatment of **3** with intermediate **5** provides intermediate **6** *via* cycloaddition reaction. Intermediate **6** undergoes reductive elimination and removal of copper iodide to form the *C*-arylation compound **7**, which is ultimately formed by aromatization of the ring by air oxidation of the final product.

To extend the work for the synthesis of new quinazoline derivatives with an amide functional group using the Ullmann coupling reaction, we have used compounds **4b** and **4c** as starting materials to continue the work. These compounds are susceptible to cross-coupling reactions with the help of copper catalysts due to the presence of chlorine and bromine halogens on the quinazoline ring. Isocyanides are also among the materials that form amide functional groups in coupling reactions[49] The reaction of compounds **4b** and **4c** with isocyanides **8**, 10 mol% of copper iodide as the catalyst and 2.0 mmol of cesium carbonate as the base in THF as solvent has been investigated under ultrasonic conditions for 50 min. Interestingly, spectroscopic evidence confirms that the reaction under ultrasonic conditions went towards C–H activation. Contrary to our expectations, no cross-coupling products were observed under these conditions. To optimize the work, we have carried out the reaction under the same conditions (starting materials, catalyst, solvent, and base) without ultrasonic conditions, at

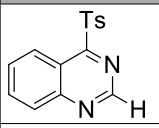
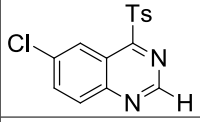
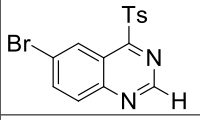
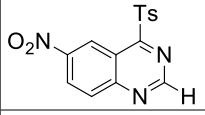
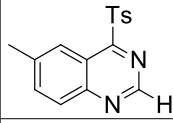
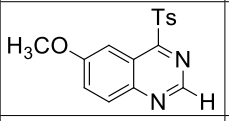
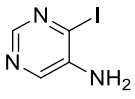
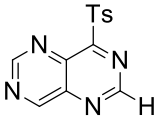
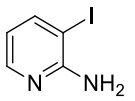
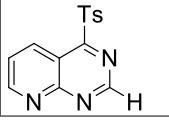
Entry	4a-h	*R*	Product	Yield%
1	4a	H		87
2	4b	4-Cl		90
3	4c	4-Br		89
4	4d	4-NO_2		92
5	4e	4-CH_3		86
6	4f	4-OCH_3		82
7	4 g			90
8	4 h			88

Table 3. Synthesis of various 4-tosyl Quinazolines at room temperature under ultrasonic irradiation.

room temperature for 4 h. Spectroscopic studies confirm the reaction pathway towards cross-coupling. Thus, the reaction pathway under ultrasonic conditions proceeded towards C–H activation, and without ultrasonic conditions at room temperature towards cross-coupling. To investigate the role of ultrasonic waves in determining the mechanism, we repeated the reaction without adding copper iodide catalyst under ultrasonic conditions and room temperature (Entry 1). Thin-layer chromatography studies have shown that no product was formed within a certain time. Also, for further investigation, we performed the reaction without cesium carbonate base under the same conditions using a ten-mole percent copper iodide catalyst and tetrahydrofuran solvent in both ultrasonic conditions and room temperature (Entry 1). Evidence confirms that under ultrasonic conditions the reaction proceeded towards C–H activation with an efficiency of 28% and under room temperature conditions the reaction proceeded towards cross-coupling with an efficiency of 31%. Therefore, adding cesium carbonate as a base in both routes is necessary to increase the optimal efficiency and reaction rate, but it does not determine the reaction route. According to the studies conducted on the role of ultrasound in chemical reactions, it is believed that the reaction chemistry changes due to the formation of free radicals[50,51] Ultrasound waves cause the breaking of some chemical bonds in compounds. However, part of these changes can be due to mechanical factors such as increasing the contact surface between the reacting components and accelerating dissolution and distribution. It is likely that under ultrasonic conditions, the C–H bond is broken faster than the C–X bond due to the formation of a more stable radical. Therefore, it seems that ultrasound helps to replace copper between the carbon-hydrogen bond and C–H activation occurs faster than cross-coupling. These two conditions led to the formation of a wide range of diverse amide-functionalized quinazolines with good yields, cheap and readily available starting materials and catalysts, and simple purification without the aid of column chromatography. Characterization of compounds **9** and **10** using IR,^{1}H-NMR,^{13}C-NMR, and mass spectral data provides a comprehensive understanding of their structure and properties (see Fig. 5).

The results in Table 4; Fig. 6 show that the reaction under both conditions was carried out with suitable efficiency with different isocyanides having electron-donating and electron-withdrawing groups. Also, the bromine halogen, due to its better-leaving group than the chlorine halogen, carried out the cross-coupling reaction with higher efficiency. The successful synthesis of compounds **9a-g** and **10a-g** and their identification

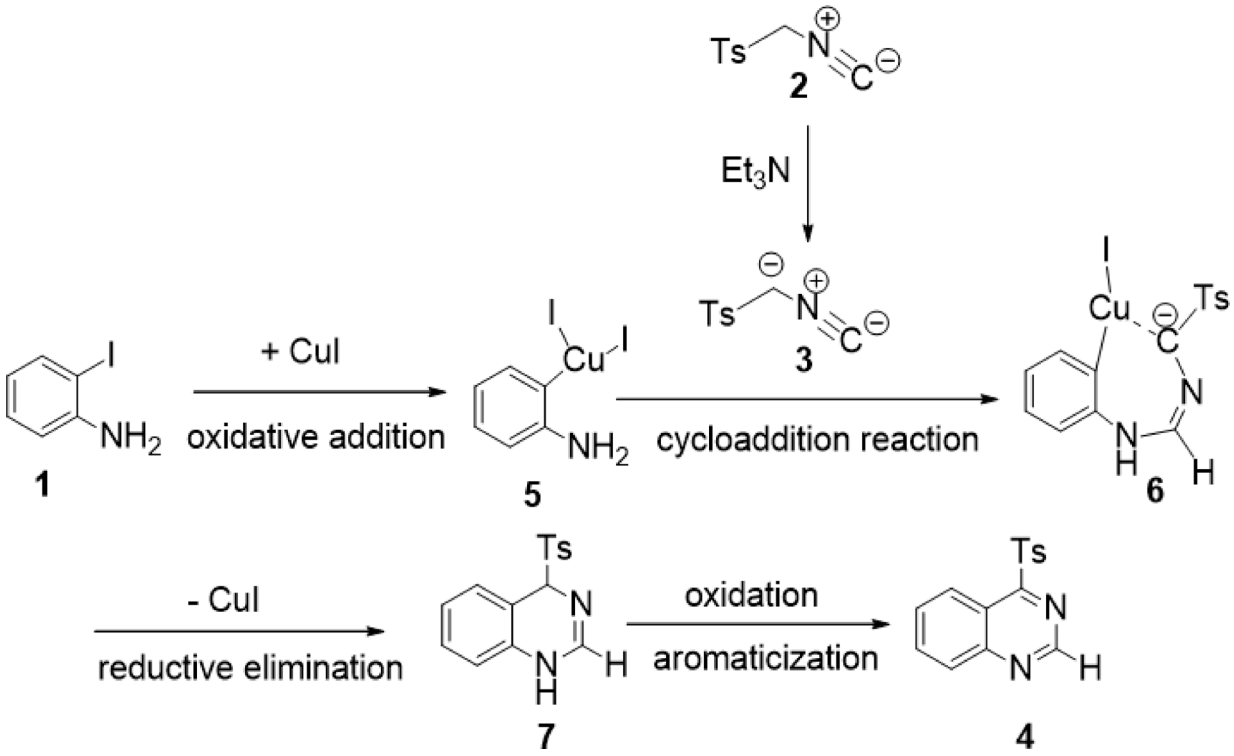


Fig. 4. A suggested mechanism for the formation of compounds **4**.

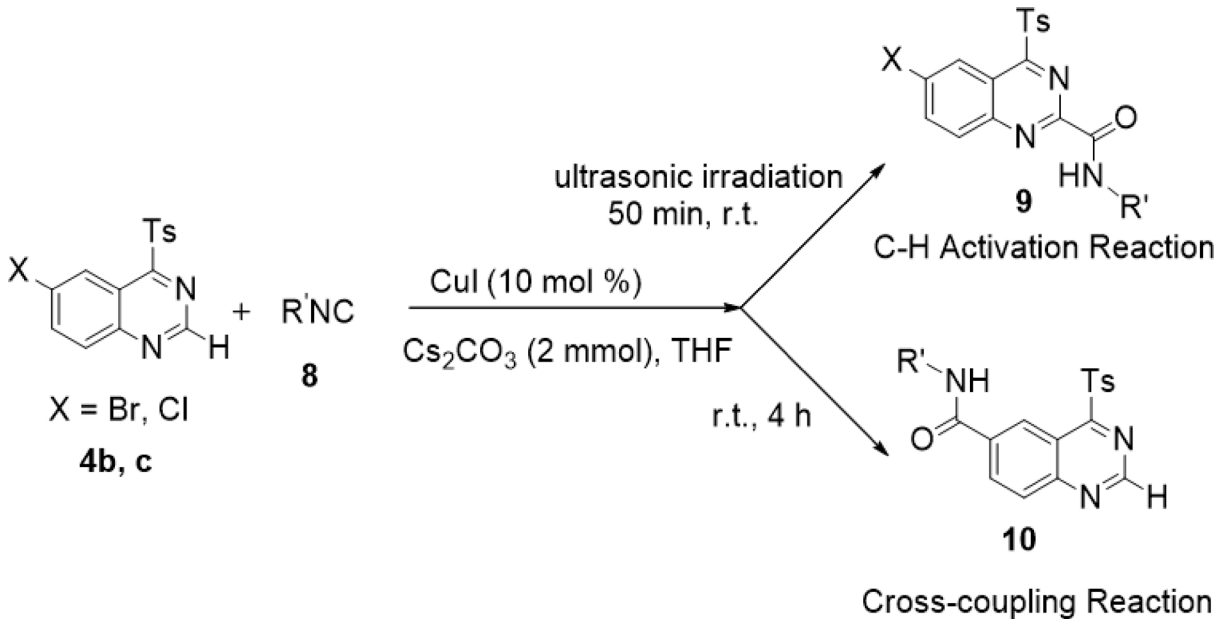


Fig. 5. Synthesis of various quinazoline by Cu-catalyzed cross-coupling without ultrasonic conditions or C–H activation reactions with ultrasonic irradiation.

through spectral analysis confirms the effectiveness of the optimized conditions in facilitating the desired transformations.

The detailed characterization of compounds **9a**-**g** and **10a**-**g** using IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectral data provides crucial information about their structures and confirms the successful synthesis of various quinazoline. In the ^{1}H-NMR spectrum of compound **9a**, two single-branched signals corresponding to the methyl group at 2.21 ppm and the NH group at 9.00 ppm are seen. In the ^{13}C–NMR, 18 distinct peaks appear. The Mass spectrum shows a molecular mass of 482. The evidence confirms that the C–H of the quinazoline ring

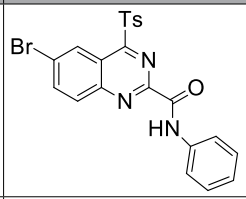
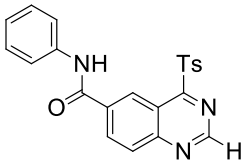
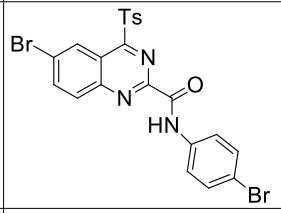
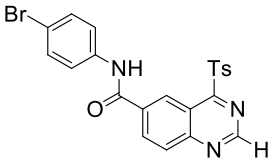
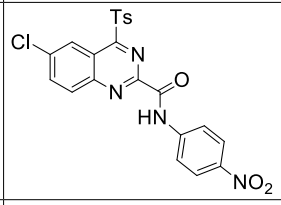
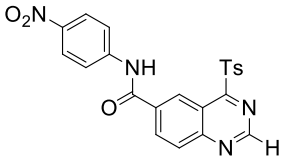
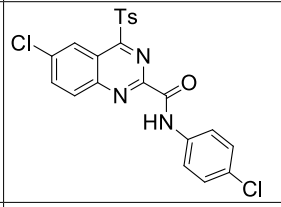
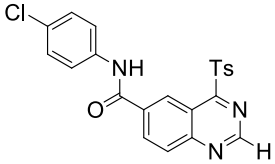
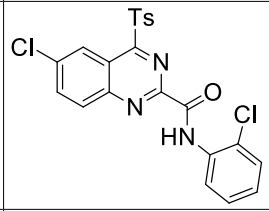
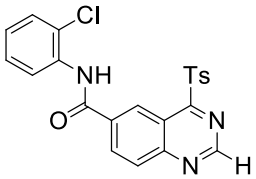
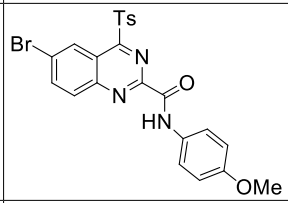
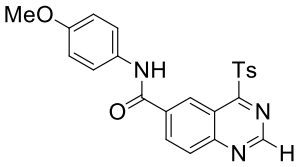
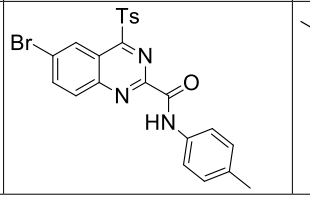
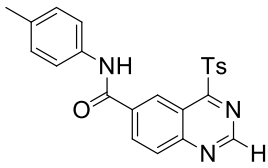
Entry	9(a-g)	10(a-g)	X	*R'*	%Yield 9: 10
1			Br	Ph	85: 87
2			Br	4-Br-C_6H_4	83: 85
3			Cl	4-NO_2-C_6H_4	80: 78
4			Cl	4-Cl-C_6H_4	81: 79
5			Cl	2-Cl-C_6H_4	79: 77
6			Br	4-OMe-C_6H_4	90: 92
7			Br	4-Me-C_6H_4	89: 91

Table 4. Synthesis of various Quinazoline by Cu-catalyzed cross-coupling or C–H activation reactions.

in the ^{1}H-NMR spectrum, which appears in the region of approximately 8.00 ppm, is not seen in the spectrum. This observation indicates that the reaction proceeds towards the C–H activation. In the ^{1}H-NMR spectrum of compound **10a**, four singlet peaks related to the methyl group at 2.29ppm, C-H of the benzene ring at 7.61 ppm, C-H of the quinazoline ring at 8.06 ppm and NH group at 9.02 ppm were observed. In the ^{13}C-NMR of this compound, 18 distinct peaks appeared. The Mass spectrum shows a molecular mass at 403. The appearance of the C-H peak of the quinazoline ring in the ^{1}H-NMR spectrum at 8.06 ppm and the decrease in the molecular mass of the compound (removal of bromine from the system) confirm the reaction path towards cross-coupling.

A proposed reaction mechanism is shown in (Fig. 7). It seems that the oxidative addition of the Cu (I) with compound **4c** in the presence of the base Cs_2CO_3 led to intermediate **11** under ultrasound irradiation conditions and intermediate **12** without ultrasound irradiation conditions that both intermediates stabilized

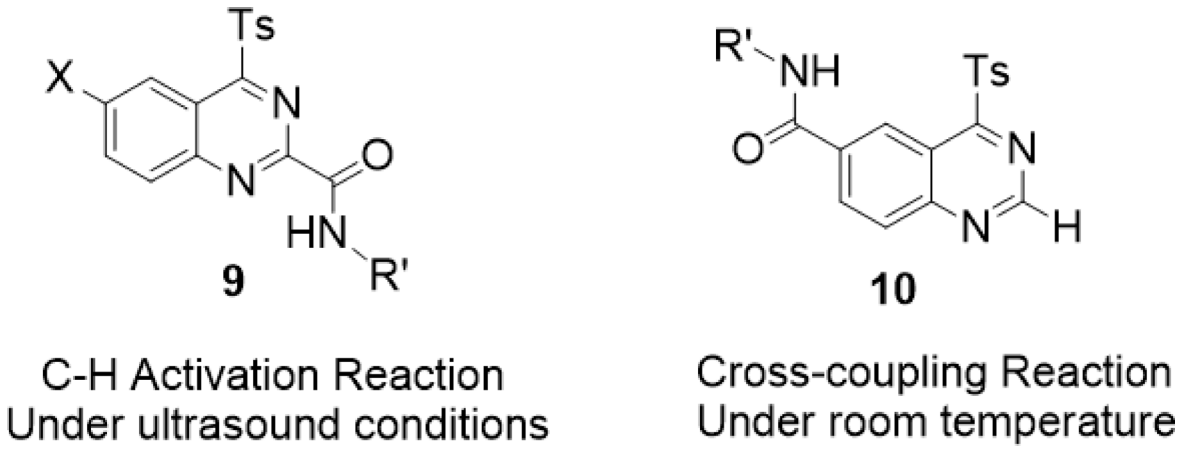


Fig. 6. Synthesis of various quinazoline by cross-coupling and C-H activation reactions.

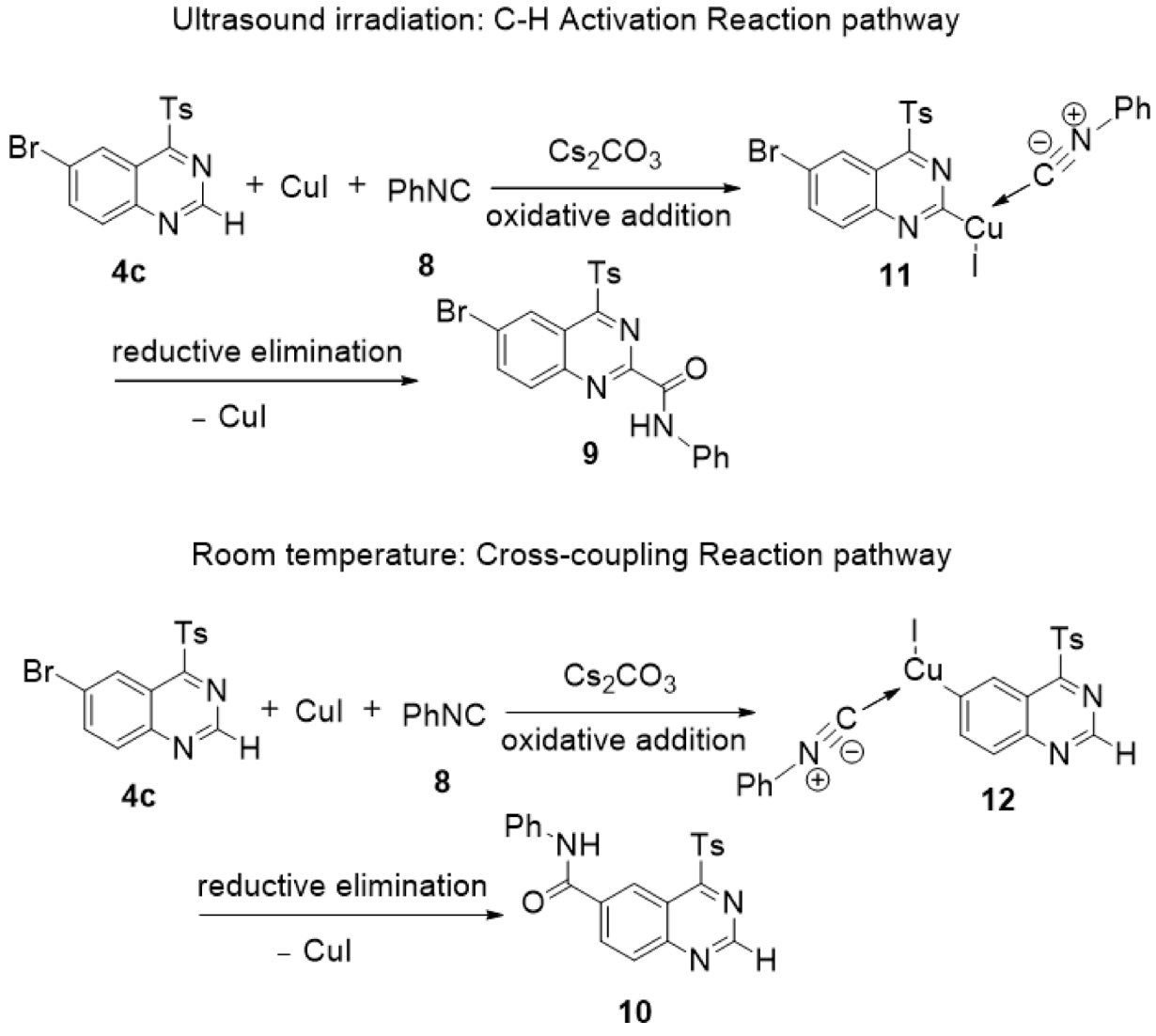


Fig. 7. A logical mechanism for the formation of compounds **9** and **10**.

by the isocyanide carbon atom may coordinate to Cu. The reductive elimination of intermediates **11** and **12** afforded the products **9** and **10** leaving the catalyst.

Conclusion

Initially, a novel, simple, one-pot method for the synthesis of diverse 4-tosyl quinazolines via a catalyst-assisted cyclization reaction with successful efficiency is reported. The reaction involves the cyclization of 2-iodoaniline and tosyl methyl isocyanide for 30 min in THF under ultrasound irradiation conditions, resulting in the formation of the desired products with good yields. To expand the work and synthesize new compounds from the quinazolines family with an amide functional group and considering the potential of products **4b** and **4c**, we have used isocyanides as starting materials to form amide functional group under both ultrasonic and non-ultrasonic conditions. Spectroscopic studies report interesting results. Ultrasound in this reaction determines the reaction path toward C–H activation, while under normal conditions (without ultrasonic) the reaction proceeds toward cross-coupling. As a result, we have been able to synthesize and identify a series of different quinazolines with amide functional groups using copper iodide catalyst, cesium carbonate as the base, and available starting materials under simple purification conditions.

Data availability

All data generated or analyzed during this study are included in this published article [and its Supplementary Information file].

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Author contributions

All work on the article (design, methodology, writing, editing, and proofreading) was done by Manijeh Nematpour.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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