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Cu-Catalyzed Pyridine Synthesis via Oxidative Annulation of Cyclic Ketones with Propargylamine

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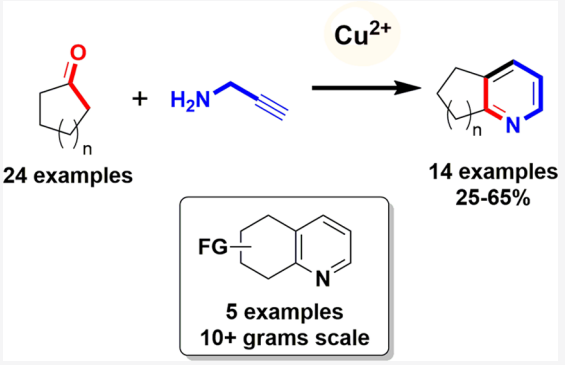
ABSTRACT: A Cu-catalyzed, easily scalable one-pot synthesis of fused pyridines by the reaction of cyclic ketones with propargylamine is described. The protocol was optimized based on the results of more than 30 experiments. The highest product yields were achieved in *i*-PrOH as a solvent in the presence of 5.0 mol % $CuCl_2$ in air. In contrast to the well-known Au-catalyzed protocol, our procedure is "laboratory friendly", cost-effective, and suitable for preparing dozens of grams of fused pyridine-based building blocks and does not require a high-pressure autoclave technique. Decreasing the catalyst amount in the reaction to 1.25 mol % $CuCl_2$ provided a yield comparable to that achieved with 5 mol % catalyst, though a longer reaction time was required. A plausible reaction mechanism was proposed. The scope and limitation of the reaction were studied using 24 different cyclic ketones as starting materials. The fused pyridine yield decreased among cyclic ketones in the following order: six-membered ≫ eight-membered > five-membered ∼ seven-membered. The elaborated reaction conditions demonstrated tolerance to a number of protective functional groups in ketone such as ester, *tert*-butoxycarbonyl (Boc)-protected amine, and acetal moieties.



INTRODUCTION

Modern drug design requires screening compounds (SCs) based on sophisticated structural motifs,[1] in particular, aromatic heterocycles fused with saturated cyclic hydrocarbons or non-aromatic heterocycles,[2] possessing desired physicochemical properties.[3,4] Nowadays, the development of organic synthesis is significantly determined by drug discovery,[4] but often the preparation stage remains a rate-limiting factor for projects in medicinal chemistry.[5] Therefore, studies of new catalytic reactions for simple, cost-effective, and easily scalable preparation of drug candidates, as well as corresponding building blocks (BBs), are strongly required. Continuing our ongoing monitoring of the commercially available space of SCs and BBs, as well as to identify existing "white spots" in "chemical space",[6,7] we turned our attention to the development of methods for large-scale synthesis of pyridines annulated to (functionalized) saturated cycles (PASCs) because many representative examples of this group of structures are currently proceeding as active compounds in different phases of clinical trials (Figure 1).[8−14]

Most of the existing methods proposed for the synthesis of pyridine derivatives and suitable for preparing PASCs are retrosynthetically based on the cyclization of cycloalkanones **16** or their derivatives (parent pyridines **9** fused with cyclopentane, cyclohexane, and cycloheptane are provided in Figure 2 as representative examples). In particular, the application of the intermolecular inverse electron demand Diels−Alder (IEDDA) reaction of 1,2,3-triazine **14** with the corresponding enamines **13** (method A)[15] is one of the most promising synthetic approaches at present. Unfortunately, the poor availability of heterocycles **14** prevents multigram syntheses. Thermal oxygen-induced cyclization of oxime *O*-allyl ethers **15** (method B)[16] requires harsh reaction conditions (sealed glass tube, heating at 190 °C). Besides, yields of the target compounds using such a method are usually low. That is why a scale-up possibility has not been investigated for the reaction. Application of [4 + 2]-cyclocondensation of the corresponding cyclic ketones with (*Z*)-3-aminoacrolein (**17**) (method C)[17] is restricted by the limited availability of **17** and again troublesome scale-up of the process.

Several transition metal-mediated catalytic procedures have been elaborated for preparing PASCs from the corresponding ketones or alcohols as starting materials. Propargylamine **18** (method D),[18] 1,3-diaminopropane **19** (method E),[19] and 3-aminopropan-1-ol **21** (method F)[20−22] have been used as

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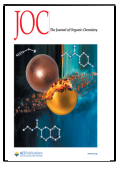

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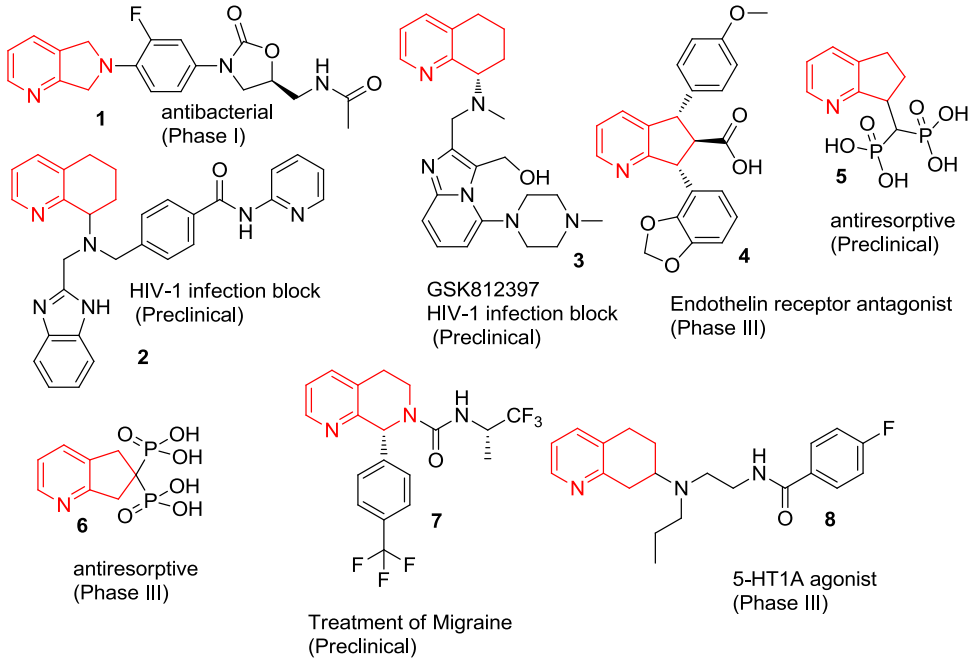

Figure 1. Representative examples of biologically active PASCs.

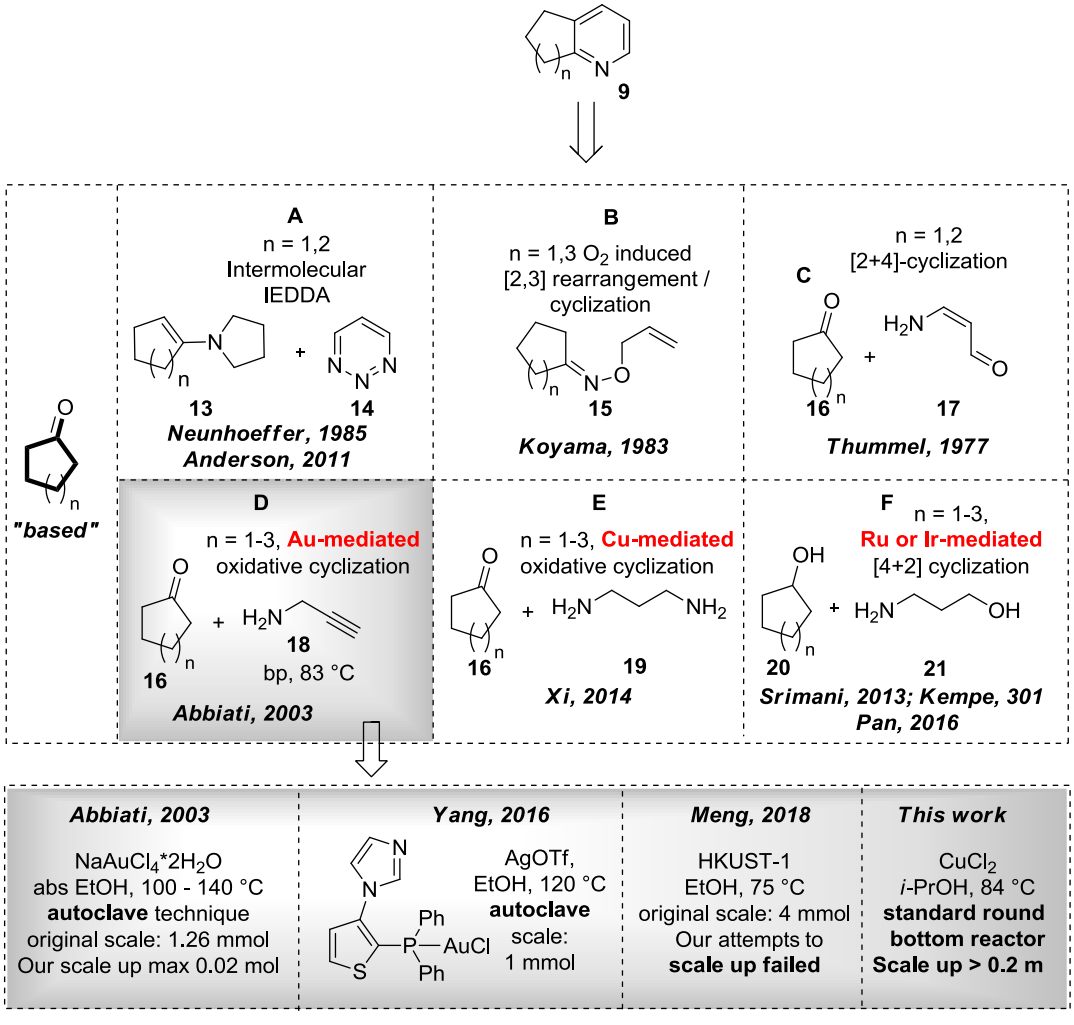

Figure 2. Known approaches (A–F) for the synthesis of pyridines fused with saturated cyclic fragments.

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cyclization partners (Figure 2). However, in most cases, these methods were not suitable for the cost-effective multigram synthesis of annulated pyridines. The high cost of gold catalysts, the necessity to perform the reaction in an autoclave (method D)[18] or using commercially unavailable and expensive Ru and Ir catalysts (methods E and F),[20−22] along with undetermined tolerance to commonly used protected functional groups, and, finally, the poor or unknown applicability to scaling-up are the reasons for continuing efforts in looking for more efficient reaction procedures.[23] Herein, we turned our attention to the Au-catalyzed method F. In our hands, this method could be reproduced on a 10 g scale of starting ketones with moderate preparative yields of PASCs. However, such a procedure lacked wide implementation. Despite our significant experience with the autoclave technique,[24] even in the presence of hazardous gases[25] (the autoclave was filled with oxygen for the pyridine synthesis by method D), the method could not be easily scaled up for preparing multigram quantities of the target compounds. The availability and cost efficiency of Au catalysts also left much to be desired. Thus, this study aimed to develop a method for multigram (20+ g) synthesis of PASCs from propargylamine and cyclic ketones based on noble metal-free catalysts, as well as to reveal the influence of various factors on the reaction course.

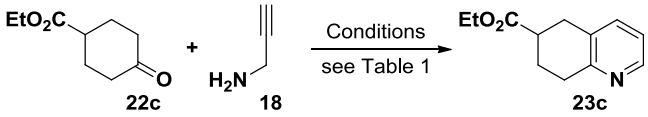
As a result, the mild "laboratory friendly" conditions for the multigram synthesis of PASCs were found. The method has prospects for further semi-industrial applications.

RESULTS AND DISCUSSION

First, we tried to avoid using the expensive $NaAuCl_4$ salt as the catalyst. In a seminal Abbiati paper,[18] Cu salts have been tested compared to the Au-based catalysts, but the former catalysts have demonstrated significantly lower efficiency. Also, during our project, Meng and co-workers published a report, where copper(II) 1,3,5-benzenetricarboxylate (HKUST-1) is used as the reaction catalyst but with the low scaling of the reaction (only up to ca. 500 mg of a ketone).[26] This report is consistent with our preliminary results on the catalytic synthesis of pyridines starting from propargylamine in the presence of HKUST-1.[27] Therefore, the study was focused on using copper(II) salts as catalysts for the synthesis of PASCs. As a model reaction, the synthesis of ethyl 5,6,7,8-tetrahydroquinoline-6-carboxylate was chosen. This compound contained the quite sensitive ester group (potentially able to react with amines or to undergo hydrolysis), and ester tolerance to the reagents was shown. This process is quite typical in the series, and the product is a valuable building block for MedChem.[28] In the first step, the reaction was tested on a 1.5 g scale of the starting ketone with different Cu(II) salts using the autoclave technique similar to the method reported in the Abbiati paper.[18] The yields in these experiments were lower than those obtained in our experiments using $NaAuCl_4·2H_2O$ as the catalyst (Table 1, entries 1−7). The reaction time (8 h) was chosen based on unification reasons. In model experiments, the product yield did not change after 2 h of heating at 5% Cu(II) loading or after 4 h of heating at 1.25% Cu(II) loading, as was shown in separate experiments.

In the second step, we carried out the same reaction of ketone **22c** with propargylamine **18** in the presence of Cu(II) catalysts in a round-bottom flask in air at atmospheric pressure using an efficient condenser to prevent volatilization of **18** (bp = 83 °C). To our delight, this approach gave more promising results. In the presence of 2.5 mol % $CuCl_2$ (Table 1, entry 12), the yield of the product was comparable to those obtained in the synthesis using

Table 1. Optimization of the Synthesis of Ethyl 5,6,7,8-Tetrahydroquinoline-6-carboxylate 23c[a,b]



entry	catalyst	solvent	T (°C)	yield[c] (%)
1[d]	2.5 mol % $NaAuCl_4·2H_2O$	EtOH	100	48
2[d]	7.3 mol % HKUST-1	EtOH	100	44
3[d]	8.7 mol % $CuCl_2·2H_2O$	EtOH	100	42
4[d]	8.7 mol % $CuCl_2$	EtOH	100	36
5[d]	3.7 mol % $Cu(Piv)_2$	EtOH	100	31
6[d]	8.7 mol % $Cu(NO_3)_2·6H_2O$	EtOH	100	39
7[d,e]	8.7 mol % $CuCl_2$	EtOH	100	38
8	1.3 mol % $CuCl_2·2H_2O$	EtOH	79	48
9	2.5 mol % $CuCl_2·2H_2O$	EtOH	79	45
10	5.0 mol % $CuCl_2·2H_2O$	EtOH	79	50
11	1.3 mol % $CuCl_2$	EtOH	79	48
12	2.5 mol % $CuCl_2$	EtOH	79	41
13	5.0 mol % $CuCl_2$	EtOH	79	49
14	5.0 mol % $CuCl_2$, 5.0 mol% $K_3[Fe(CN)_6]$	EtOH	79	43
15[f]	5.0 mol % $CuCl_2$	EtOH	79	66
16	5.0 mol % $Cu(OAc)_2$	EtOH	79	59
17	5.0 mol % $Cu(NO_3)_2·6H_2O$	EtOH	79	46
18	5.0 mol % $Cu(OTf)_2$	EtOH	79	60
19	5.0 mol % HKUST-1	EtOH	79	50
20	5.0 mol % $FeCl_3$	EtOH	79	41
21	2.5 mol % $CuCl_2$	*i*-PrOH	83	65
22	5.0 mol % $CuCl_2$	***i*-PrOH**[g]	**83**	**75**
23	10.0 mol % $CuCl_2$	*i*-PrOH	83	60
24[h]	5.0 mol % $CuCl_2$	*i*-PrOH	83	59
25	5.0 mol % $CuCl_2$, 5.0 mol % $K_3[Fe(CN)_6]$	*i*-PrOH	83	62
26	5.0 mol % $CuCl_2$, 10 mol % quinhydrone	*i*-PrOH	83	57
27	5.0 mol % $CuCl_2$, 10 mol % ascorbic acid	*i*-PrOH	83	67
28	5.0 mol % $Cu(NO_3)_2·6H_2O$	*i*-PrOH	83	58
29	5.0 mol % CuCl	*i*-PrOH	83	61
30	5.0 mol % CuI	*i*-PrOH	83	63
31	5.0 mol % $CuCl_2$	$(CF_3)_2CHOH$	58	42
32	5.0 mol % $CuCl_2$	*t*-BuOH	82	57
33	5.0 mol % $CuCl_2$	*i*-AmOH	131	62
34	5.0 mol % $CuCl_2$	dioxane	101	61

[a]The experiments for a 1.5 g scale of ketone **22c**. [b]The reaction time was 8 h. [c]The yield was determined according to the NMR spectra of pretreated aliquots using 1,3,5-trimethoxybenzene as a standard. [d]In autoclave under an O_2 atmosphere. [e]KNO_3 was added as a co-oxidant. [f]Propargylamine was added in three portions with 2 h intervals. [g]The best reaction conditions, which were chosen for subsequent research, are highlighted in bold. [h]With barbotage of air through the reaction mixture.

autoclave techniques. As the next step of screening the reaction conditions, the Cu(II) source was optimized. In particular, it included variations of the catalyst type ($CuCl_2·2H_2O$, $CuCl_2$, $Cu(OAc)_2$, $Cu(OTf)_2$, $Cu(NO_3)_2·6H_2O$, HKUST-1, CuCl, CuI), catalyst loading, and solvent (EtOH, *i*-PrOH, $(CF_3)_2CHOH$, *t*-BuOH, $(CH_3)_2CHCH_2CH_2OH$, dioxane). Since the reaction scheme involved oxidation at a certain step (the plausible mechanism is presented below), the agents potentially facilitating electron transfer in a $Cu^{I/II}$ redox couple

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were also added ($K_3[Fe(CN)_6]$, quinhydrone, ascorbic acid) and respective modifications of the procedure (e.g., air barbotage, slower reagent addition, etc.) were tested. To determine the role of oxygen in the catalytic process, air bubbling through the reaction mixture was carried out. Air barbotage led to a slight decrease of product yield because it could cause the blowing off of propargylamine from the reaction vessel by air flow. More intense oxidative dimerization of propargylamine could also contribute to lower yield in this case. The main results of the optimization are summarized in Table 1. Among Cu sources, anhydrous $CuCl_2$ turned out to be the best choice. The optimal value of Cu(II) loading depended on the solvent in different ways (ca. 2.5 mol % in EtOH and ca. 5.0 mol % in *i*-PrOH; see Table 1, entries 11−13 and 21−23, respectively). The increase of the catalyst loading led to lower yields. This observation can be referred to as a significant contribution of side reactions in the presence of high Cu(II) salt concentration. Such side reactions can include oxidative coupling of propargylamine in the presence of $CuCl_2$,[29] as well as self-condensation of ketones.[30,31]

Isopropanol was found to be the optimal solvent for the reaction (Table 1, entries 12, 22, 29−32). Adding $K_3[Fe(CN)_6]$, quinhydrone, or ascorbic acid did not lead to rising yields. Moreover, $K_3[Fe(CN)_6]$ or ascorbic acid slightly decreased the yields, and an even more significant decrease of the yield was observed in the presence of quinhydrone (Table 1, entries 25−27). Replacement of $CuCl_2$ by CuCl or CuI led to similar product yields. This observation is consistent with the proposed plausible reaction mechanism, where both Cu(II) and Cu(I) played their roles in the catalytic cycle. Notably, both CuCl, in which Cu(I) can be easily oxidized by oxygen to Cu(II), and CuI, where Cu(I) is stable in air, are effective. Other deviations from the initially chosen conditions also did not make a positive effect on the reaction outcome (Table 1, entries 12, 15). Therefore, stirring of the reaction mixture under reflux in *i*-PrOH in the presence of 5.0 mol % $CuCl_2$ as a catalyst with air oxygen access proved to be the optimal protocol. Under these conditions, the model reaction of ethyl cyclohexa-4-one-1-carboxylate with propargylamine yielded 75% of the desired ethyl 5,6,7,8-tetrahydroquinoline-6-carboxylate **23c** (Table 1, entry 22).

To reveal the rate of product accumulation in the reaction mixture and to get insight into the reaction mechanism (for example, the formation of any intermediate, which slowly transforms into the target compound), we studied the dependence of the product yield on the reaction time in two systems: *i*-PrOH−1.25 mol % $CuCl_2$ and *i*-PrOH−5.0 mol % $CuCl_2$. In both cases, the reaction proceeded relatively fast and only compound **23c** was detected by gas chromatography−mass spectrometry (GCMS) (this analysis does not exclude the possible formation of some minor impurities, for example, condensation products). Several conclusions can be made from the analysis of the curves. All reactions leading to **23c** demonstrated comparable rates. The yield of **23c** did not decrease after its formation, proving its stability. Thus, the lower yield upon addition of 10 mol % $CuCl_2$ (entry 23) can be explained by quick competitive reactions rather than degradation of the product **23c**. There was no oxygen deficit under the reaction conditions, as the yield of **23c** quickly reached the highest value in the case of 5 mol % $CuCl_2$. Finally, in conditions of 2-fold propargylamine excess, its loss due to volatilization did not make a significant influence on the product yield, because the yield of **23c** in the experiment with 1.25 mol % $CuCl_2$ was comparable to that in the reaction with 5 mol % catalyst, though a longer reaction time was necessary (Figure 3).

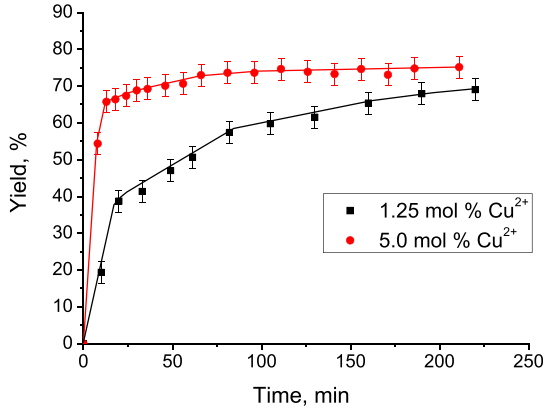

Figure 3. Dependence of the yield of **23c** on time for different loadings of $CuCl_2$. Solid lines are to guide the eye.

The product concentration vs time dependencies for **23c** formation could not be fitted by the first- or the second-order kinetic equations. The values of turnover frequency (average TOF, the ratio of the quantity of **23c** formed to $CuCl_2$ content) calculated for the initial parts of the yield vs time curves (0−25 min range) were equal to 0.38 min^{-1} for 1.25 mol % $CuCl_2$ loading and 1.0 min^{-1} for 5 mol % $CuCl_2$ loading. Taking into account failure to fit the kinetic curve by simple equations along with the fact that TOF was not proportional to the catalyst loading (4 times increase of the catalyst loading resulted in 2.6 times increase of the TOF value), we conclude that the reaction mechanism is complex and there is no single rate-limiting stage.

To evaluate the scope and limitations of the developed protocol, a set of ketones were tested in the reaction under the above-mentioned optimized conditions (Scheme 1). Among 24 substrates, the desired products were not detected in the reaction mixture only for 7 ketones: ethyl 2-oxocyclohexanecarboxylate **22f**,[32] dihydrothiophen-3(2*H*)-one **22j**, 2-fluorocyclohexanone **22t**, monoprotected 1,3-cyclohexanedione **22s**, furan-2,4(3*H*,5*H*)-dione **22u**, and *α*,*β*-unsaturated cyclic ketones **22v** and **22w**.[33,34] In other cases, the desired fused pyridines formed in 5−65% yields (see Table 2). Interestingly, among all ketones, the best results were obtained for the six-membered species: the yields were ca. 60% except for sulfur-containing ketones **22n** and **22o**. Generally, the yields as a function of the ketone ring size decreased in the following order: six-membered (**22a**) ≫ eight-membered (**22e**) > five-membered (**22b**) ∼ seven-membered ketones (**22d**). This order is in agreement with the yields of enamines reported for the reaction of the corresponding ketones with dialkylamines.[35,36] In the case of possible formation of regioisomers, the reaction proceeded at the more CH-acidic center (products **23k**, **23p**, and **23u**). The CH-acidity dominated over steric hindrance from two possible reactive centers in ketone **22p**, defining the annulation regioselectivity. In the case of ketone **22g**, the steric hindrance became more important and the product of annulation at the less sterically hindered center was isolated as the major one. Also, the reaction conditions appeared to be tolerant to acid-sensitive protecting groups, such as a *tert*-butoxycarbonyl (Boc) substituent at nitrogen (ketones **22m**, **22q**, and **22p**) or acetal protection of the second keto-function (ketone **22r**).

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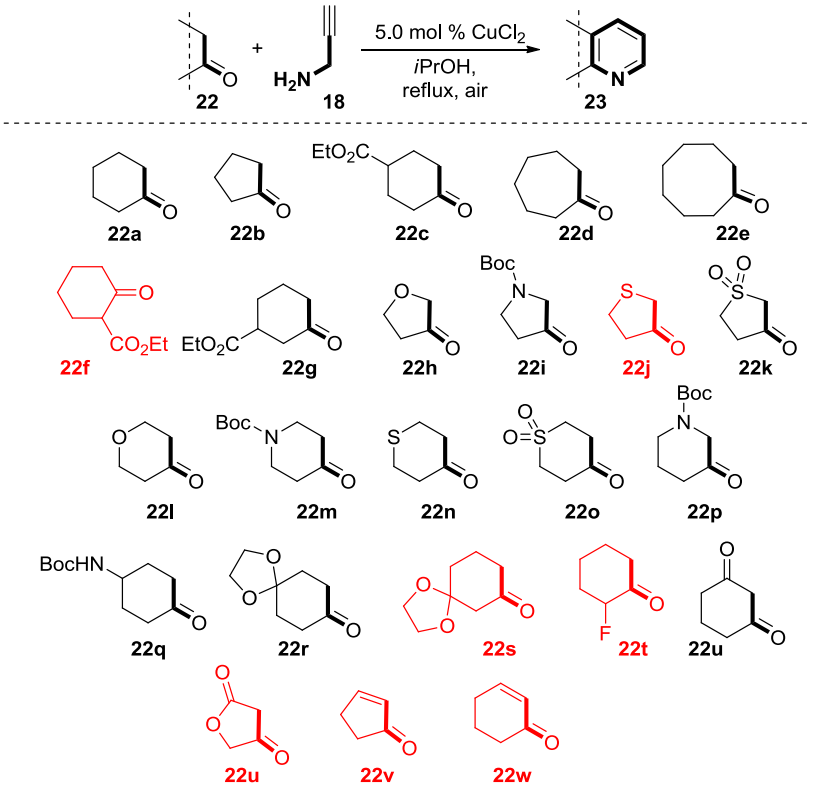
Scheme 1. Set of Substrates for Cu-Catalyzed Pyridine Annulation Used in This Study



The most important achievement of this study is the possibility of easy scale-up for the $CuCl_2$-catalyzed reaction to ca. 0.15−0.4 mol of the starting ketones (Table 2, entries 1, 11, 15, and 16; see the Experimental Section). This feature was also illustrated by the multigram synthesis of a few building blocks formed by deprotection of compounds **23** (Scheme 2). It makes the reaction very promising for the design and synthesis of MedChem-relevant BBs.

Based on our observations and the current state of the art evaluated by analyzing the literature data, we can propose an alternative mechanism of the reaction, which differs from that originally proposed by Abbiati and other authors.[18,40] As suggested in the seminal Abbiati paper, the formation of the pyridine ring proceeded through the sequential amination of the carbonyl compounds, followed by regioselective 6-endo-dig cyclization of the *N*-propargylenamine intermediate with further aromatization. Both steps, amination and 6-endo-dig cyclization, were catalyzed by Au(III) salts, but a more detailed description of the catalyst role was not proposed. In the recent paper of Yamauchi[39] dealing with transition metal (TM)-free thermal reactions in nitrobenzene at 190 °C, it has been postulated that after the enamine formation the reaction proceeds by a more complicated mechanism. It includes an aza-Claisen rearrangement, followed by tautomerization of *N*-propargylenamine providing the allenic enamine. After the 1,5-sigmatropic hydrogen shift, 6π-electron cyclization to the dihydropyridine takes place, followed by oxidation of the latter to the corresponding pyridine. The propargyl aza-Claisen rearrangement is a logical step of the proposed mechanism. The thermal propargyl Claisen rearrangements need harsh conditions due to the disfavored geometry of the starting molecule bearing an alkyne fragment. The best catalysts for such types of rearrangements are Au(I) compounds,[41,42] but Cu(I) derivatives also possess catalytic activity in this process.[43,44] This fact can explain the advantages of Au(I)-based catalysts in some cases (Table 2, entries 2, 5). To the best of our knowledge, the formation of π-type complexes for Cu(II) species with alkynes required for the catalytic activity in the propargyl Claisen rearrangement is still unknown.[45,46] However, the generation of Cu(I) compounds from Cu(II) ones has been well documented for the copper(II) acetate-accelerated azide−alkyne cycloaddition. It proceeds via Cu(II) reduction and oxidation of alcohols, used as solvents, or as a result of a Glaser reaction of terminal alkynes employed as substrates.[47] Therefore, it would be logical to propose that Cu(II) compounds play an important role in the catalytic cycle, as they are known catalysts for imine formation,[48] as well as for dihydropyridine oxidative aromatization.[49,50] The modified plausible mechanism proposed by us is represented in Scheme 3. In the first step, imine **29** is formed from the corresponding ketone **22** and propargylamine **18**. This reaction is obviously catalyzed by Cu(II). Imine **29** exists in equilibrium with the corresponding enamine **30**. The next step of transformation is the Cu(I)-catalyzed propargyl aza-Claisen rearrangement, leading to allene **33**. The following steps are similar to the TM-free reaction and include tautomerization, 1,5-sigmatropic hydrogen shift, and 6π-electron cyclization to dihydropyridine. The latter is oxidized to a pyridine derivative directly by O_2 or through a Cu(II)-catalyzed process. Such a sequence of steps explains the advantage of Au-based catalysts over other ones because in this case the transformations of **30** into **33** are very efficient. In addition, the imine−enamine tautomerism can determine the regioselectivity of the reactions with the substituents stabilizing the corresponding enamine form (see ketones **22k**, **22p**, and **22u**). In the reaction course, Cu(I) could be oxidized to Cu(II) by air, but this step was not critical. The proposed mechanism implies that the reaction requires some

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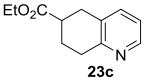
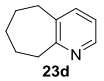
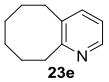
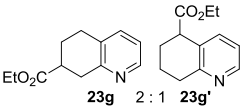
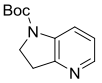
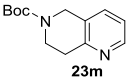
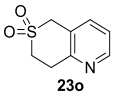
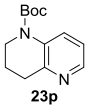
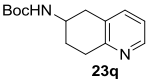
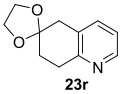
Table 2. Cu-Catalyzed Pyridine Annulation to Cyclic Ketones

Entry	Substrate	Product	Scale, mol[a]	Yield, %[b]	Previously reported results
1	**22a**	 **23a**	0.031	65	-
2	**22b**	 **23b**	0.036	22	77%, $NaAuCl_4 \cdot 2H_2O$ [18]; 89%, $HetPh_2PAuCl$ [c 37]
3	**22c**	 **23c**	0.15	63	Yield n.d., $NaAuCl_4 \cdot 2H_2O$ [28]
4	**22d**	 **23d**	0.027	20	-
5	**22e**	 **23e**	0.024	29	67%, $NaAuCl_4 \cdot 2H_2O$ [18]; 78%, $HetPh_2PAuCl$ [c 34]
6	**22g**	 **23g** 2 : 1 **23g'**	0.017	58[d]	-
7	**22h**	 **23h**	0.006	5[e]	-
8	**22i**	 **23i**	0.006	6[e]	-
9	**22k**	 **23k**	0.022	44	-
10	**22l**	 **23l**	0.030	34	-
11	**22m**	 **23m**	0.38	64	74%, $NaAuCl_4 \cdot 2H_2O$ [38]
12	**22n**	 **23n**	0.006	25[e]	-
13	**22o**	 **23o**	0.006	5[e]	-
14	**22p**	 **23p**	0.015	48	-
15	**22q**	 **23q**	0.23	61	-
16	**22r**	 **23r**	0.30	59	-
17	**22u**	 **23u**	0.028	52	32%, TM free, 190 °C, nitrobenzene, air [39]

[a]Amount of the starting ketone **22**. [b]Isolated yields. [c]$HetPh_2P$ = 1-(2-(diphenylphosphino)thiophen-3-yl)-1*H*-imidazole; EtOH, 120 °C. [d]Preparative yield for the mixture of regioisomers; separation failed. [e]Yield according to GCMS of the reaction mixture; isolation failed.

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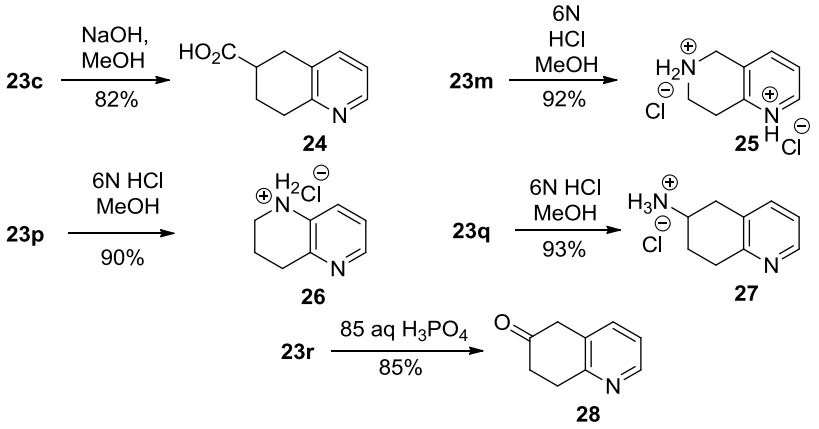
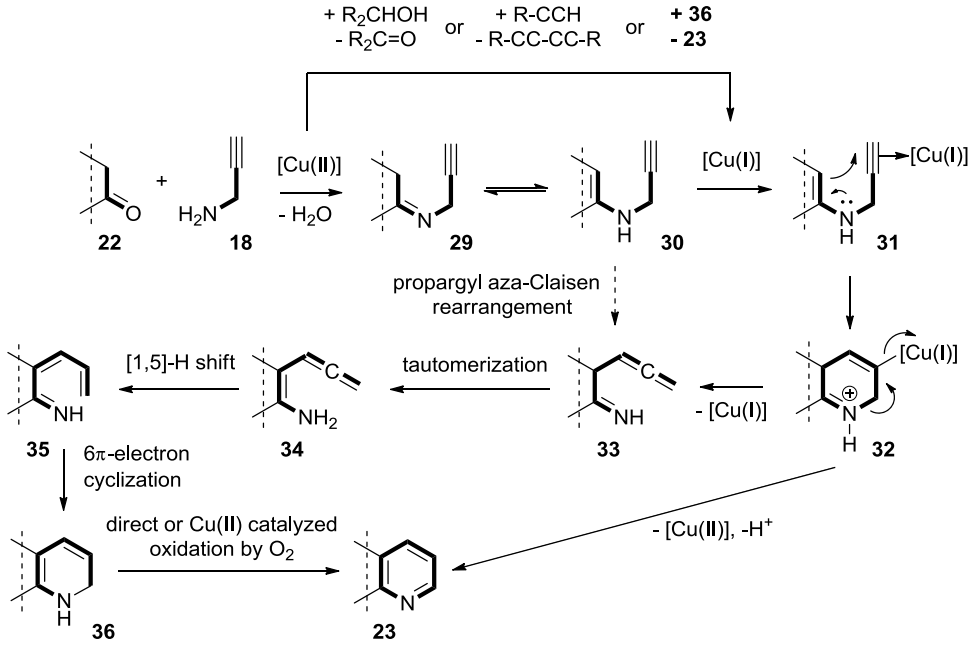
J. Org. Chem. 2021, 86, 7315−7325

Scheme 2. Synthesis of MedChem-Relevant Building Blocks as a Follow-Up of Cu-Catalyzed Formation of Pyridines



Scheme 3. Plausible Mechanism of Cu-Catalyzed Pyridine Annulation



quantity of Cu(II) and Cu(I) to be simultaneously present in the reaction mixture. However, the proposed above-mentioned sequence of steps is still declarative, and more thorough mechanistic studies are needed, which are beyond the scope of the current paper.

CONCLUSIONS

As a result of this study, we demonstrated that the reaction of cyclic ketones with propargylamine catalyzed by $CuCl_2$ in air led to the formation of fused pyridines with high yields. The approach was efficiently used for the synthesis of fused cycloalkenopyridines on a multigram scale. The optimal conditions for pyridine annulation included refluxing the starting materials in *i*-PrOH in the presence of 5.0 mol % $CuCl_2$ with free access to air oxygen. For the tested ketones, the elaborated reaction conditions were suitable for preparing a wide range of fused pyridines but did not lead to the formation of pyridines starting from 2-oxocycloalkane carboxylates, dihydrothiophen-3(2*H*)-one, 2-fluorocyclohexanone, monoprotected 1,3-cyclohexandione, furan-2,4(3*H*,5*H*)-dione, and α,β-unsaturated cyclic ketones. The product yields in the case of the cycloalkanones with ring size from 5 to 8, as well as their oxa-, aza-, and thia-analogues, were significantly different. The best results were found in the case of six-membered ketones, which afforded the desired fused pyridines in ca. 60% yield with an exception of thiopyranone and its oxidized derivative. The dependence of product yields on ketone ring size is in the following order: six-membered ≫ eight-membered > five-membered ∼ seven-membered. In the case of unsymmetrical ketones, two factors can control regiochemistry: "push−pull" stabilization of the intermediate enamine and steric hindrance, with the major role of the former. The reaction conditions were tolerant to several protecting functional groups in ketones, such as ester, Boc-protected amine, and acetal. These groups were not affected under the used reaction conditions, but afterward, the products could be easily deprotected producing functionalized fused cycloalkyl pyridines.

The elaborated catalytic procedure avoids harsh conditions, problems with availability of starting materials, using autoclave techniques, and expensive catalysts based on noble metals. In addition, the method includes only two operationally simple steps and relies on readily available and nontoxic starting

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J. Org. Chem. 2021, 86, 7315−7325

materials. It provides 40−60% overall yields of the target products, has been efficiently used on an up to several dozen gram scale, and, based on our experience, has the potential for further scale-up. This makes functionalized fused cycloalkyl pyridines readily available to the chemical community, most importantly for their use as building blocks in medicinal chemistry programs.

EXPERIMENTAL SECTION

General Information. The solvents were purified according to the standard procedures. Absolute ethanol and isopropanol were used. All starting materials were obtained from Enamine Ltd. Melting points were measured on an automated melting point system. ^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance 500 spectrometer (at 500 MHz for ^{1}H and 126 MHz for ^{13}C nuclei) and a Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H and 101 MHz for ^{13}C nuclei). Tetramethylsilane (^{1}H, ^{13}C) was used as an internal standard. Elemental analyses were performed at the Laboratory of Organic Analysis, Institute of Organic Chemistry, National Academy of Sciences of Ukraine. Their results were found to be in good agreement (±0.4%) with the calculated values. Preparative high-performance liquid chromatography (HPLC) analyses were done on an Agilent 1200. Mass spectra were measured on an Agilent 1100 LCMSD SL instrument (atmospheric pressure chemical ionization (APCI)) and an Agilent 5890 series II 5972 GCMS instrument (electron impact ionization (EI)). Kinetic experiments were carried out using reaction mixtures containing 1 M **22c** and 2 M propargylamine and 1.25 or 5 mol % $CuCl_2$ in isopropanol. The total volume of the reaction mixtures at the beginning of the experiment was 10 mL. Aliquots (0.2 mL) were taken after certain time periods, and these aliquots were quickly cooled to room temperature, purified from $CuCl_2$ using flash chromatography on silica gel (the column was washed out with 10 mL of chloroform, followed by 25 mL of chloroform and then 25 mL of ethyl acetate, to elute the organic compounds). The liquids were concentrated under reduced pressure and analyzed by GCMS. The GC signal intensities were calibrated using solutions with known concentrations of **22c** and **23c**. *n*-Dodecane was added as a standard to five aliquots. However, it was found that the **22c**/**23c** ratio was sufficiently accurate in determining the product yield. This procedure does not ensure the preservation of all propargylamine in the aliquot. Error bars were evaluated by analysis of 10 specially prepared model solutions with specified quantities of **22c**, **23c**, and $CuCl_2$ (5 mol %), which were treated as described above for the aliquots; the error bar equals the highest deviations of **23c** concentration from the specified values, observed in these experiments. The same error bars were used for all measurements.

General Procedure for the Synthesis of Pyridines 23. $CuCl_2 \cdot 2H_2O$ (0.262 g, 1.52 mmol) was placed in a 25 mL beaker on a preheated 150 °C plate and heated for 2−4 min to brown color. Propargylamine (3.36 g, 61.0 mmol, 3.90 mL) and isopropanol (30 mL) were placed in a 100 mL round-bottom flask. The flask was placed in an oil bath heated to 60 °C, and anhydrous $CuCl_2$ and a solution of ketone **22** (30.6 mmol) in isopropanol (5.0 mL) were added under vigorous stirring. A water-cooled condenser was installed. The mixture was boiled under vigorous stirring overnight (12 h) at 84 °C. The reaction mixture was evaporated under reduced pressure, and the residue was dissolved in $CHCl_3$ (100 mL). The crude product was prepurified by flash chromatography (eluent $CHCl_3$, then EtOAc). The resulting solution was evaporated, and the crude product was purified by column chromatography (eluent hexane/EtOAc (0−50% EtOAc)) to obtain desired product **23**.

*5,6,7,8-Tetrahydroquinoline (**23a**).* The compound was obtained starting from cyclohexanone (3.0 g, 30.6 mmol), prop-2-yn-1-amine (3.36 g, 61.0 mmol), and $CuCl_2 \cdot 2H_2O$ (0.262 g, 1.52 mmol) in 35 mL of *i*-PrOH. Yield = 2.63 g (65%). Purified by column chromatography (hexane/EtOAc 9:1). Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 4.7 Hz, 1H), 7.30 (d, J = 7.7 Hz, 1H), 6.97 (dd, J = 7.7, 4.6 Hz, 1H), 2.88 (t, J = 6.4 Hz, 2H), 2.72 (t, J = 6.2 Hz, 2H), 1.86 (p, J = 6.3 Hz, 2H), 1.77 (p, J = 6.1 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.3, 146.7, 136.7, 132.2, 120.8, 32.5, 28.7, 23.0, 22.7. Liquid chromatography−mass spectrometry (LCMS), positive mode, m/z: 134 $[M + H]^+$. Anal. calcd for $C_9H_{11}N$: C, 81.16; H, 8.32; N, 10.52. Found: C, 81.22; H, 8.48; N, 10.20.

*6,7-Dihydro-5H-cyclopenta[b]pyridine (**23b**).* The compound was obtained starting from cyclopentanone (3.0 g, 35.7 mmol), propargylamine (3.98 g, 71.3 mmol), and $CuCl_2 \cdot 2H_2O$ (0.304 g, 1.78 mmol) in 35 mL of *i*-PrOH. Purified by column chromatography (hexane/EtOAc 9:1). Yield = 0.92 g (22%). Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 5.1 Hz, 1H), 7.45 (d, J = 7.0 Hz, 1H), 6.97 (dd, J = 7.5, 5.1 Hz, 1H), 2.98 (t, J = 7.6 Hz, 2H), 2.90 (t, J = 7.4 Hz, 2H), 2.09 (p, J = 7.6, 7.2 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.5, 147.3, 136.9, 132.0, 120.9, 34.2, 30.7, 23.0. LCMS, positive mode, m/z: 120 $[M + H]^+$. Anal. calcd for C_8H_9N: C, 80.63; H, 7.61; N, 11.75. Found: C, 80.70; H, 7.71; N, 11.59.

*Ethyl 5,6,7,8-Tetrahydroquinoline-6-carboxylate (**23c**).* The compound was obtained starting from ethyl 4-oxocyclohexane-1-carboxylate (25.0 g, 0.147 mol), propargylamine (16.2 g, 0.294 mol), and $CuCl_2 \cdot 2H_2O$ (1.25 g, 7.35 mmol) in 150 mL of *i*-PrOH. Yield = 19.1 g (63%). Purified by column chromatography (hexane/EtOAc 7:3). Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, J = 4.7 Hz, 1H), 7.36 (d, J = 7.7 Hz, 1H), 7.01 (dd, J = 7.7, 4.8 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.07−2.85 (m, 4H), 2.79−2.66 (m, 1H), 2.33−2.20 (m, 1H), 2.02−1.87 (m, 1H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 174.8, 156.0, 147.2, 136.8, 130.2, 121.2, 60.7, 39.4, 31.4, 30.9, 25.8, 14.2. LCMS, positive mode, m/z: 206 $[M + H]^+$. Anal. calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.19; H, 7.24; N, 6.67.

*6,7,8,9-Tetrahydro-5H-cyclohepta[b]pyridine (**23d**).* The compound was obtained starting from cycloheptanone (3.0 g, 26.8 mmol), propargylamine (2.98 g, 63.5 mmol), and $CuCl_2 \cdot 2H_2O$ (0.220 g, 1.30 mmol) in 25 mL of *i*-PrOH. Yield = 0.78 g (20%). Purified by column chromatography (hexane/EtOAc 19:1). Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 5.0 Hz, 1H), 7.32 (d, J = 7.5 Hz, 1H), 6.96 (dd, J = 7.5, 4.9 Hz, 1H), 3.12−2.86 (m, 2H), 2.82−2.64 (m, 2H), 1.83 (p, J = 5.8 Hz, 2H), 1.73−1.56 (m, 4H). ^{13}C{H} NMR (101 MHz, $CDCl_3$) δ 163.2, 146.1, 138.1, 136.4, 121.1, 39.4, 35.3, 32.5, 27.9, 26.4. LCMS, positive mode, m/z: 148 $[M + H]^+$. Anal. calcd for $C_{10}H_{13}N$: C, 81.58; H, 8.90; N, 9.51. Found: C, 81.41; H, 8.76; N, 9.31.

*5,6,7,8,9,10-Hexahydrocycloocta[b]pyridine (**23e**).* The compound was obtained starting from cyclooctanone (3.0 g, 23.7 mmol), propargylamine (2.65 g, 48.1 mmol), and $CuCl_2 \cdot 2H_2O$ (0.202 g, 1.18 mmol) in 22 mL of *i*-PrOH. Yield = 1.12 g (29%). Purified by column chromatography (hexane). Light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, J = 4.7 Hz, 1H), 7.36 (d, J = 7.5 Hz, 1H), 7.04 (dd, J = 7.6, 4.8 Hz, 1H), 2.96 (t, J = 6.2 Hz, 2H), 2.75 (t, J = 6.2 Hz, 2H), 1.85−1.73 (m, 2H), 1.73−1.60 (m, 2H), 1.42−1.30 (m, 4H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 161.0, 147.0, 136.5, 136.2, 121.4, 34.6, 32.1, 31.9, 30.6, 25.9, 25.9. LCMS, positive mode, m/z: 162 $[M + H]^+$. Anal. calcd for $C_{11}H_{15}N$: C, 81.94; H, 9.38; N, 8.69. Found: C, 81.77; H, 9.24; N, 8.86.

*Ethyl 5,6,7,8-Tetrahydroquinoline-7-carboxylate (**23g**).* The compound was obtained starting from ethyl 3-oxocyclohexane-1-carboxylate (5.0 g, 0.029 mol), propargylamine (3.2 g, 0.059 mol), and $CuCl_2 \cdot 2H_2O$ (0.25 g, 1.47 mmol) in 50 mL of *i*-PrOH as a gray oil and mixture of two regioisomers in 2:1 ratio. Total yield of the mixture = 3.5 g (58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (dd, J = 4.7, 1.9 Hz, 1H), 8.34* (d, J = 4.8 Hz, 1H), 7.47* (d, J = 7.8 Hz, 1H), 7.34 (d, J = 7.7 Hz, 1H), 7.07−7.03 (m, 1H), 7.05−6.97* (m, 1H), 4.21−4.09* (m, 4H), 3.76* (t, J = 5.8 Hz, 1H), 3.25−3.02 (m, 2H), 3.03−2.83 (m, 2H), 2.87−2.75 (m,3H), 2.25−2.08 (m, 2H), 2.08−1.93 (m, 2H), 1.93−1.77 (m, 2H), 1.29−1.21 (m, 3H), 1.23−1.20* (m, 3H) (*—another isomer ethyl 5,6,7,8-tetrahydroquinoline-5-carboxylate). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 174.8, 173.9*, 157.2*, 155.3, 147.9, 147.2*, 137.3*, 136.5, 131.0, 129.1*, 121.2*, 121.0, 61.0*, 60.6, 44.4*, 39.9, 34.5, 32.2*, 27.5*, 26.1, 25.3, 20.5*, 14.2 (*—another isomer ethyl 5,6,7,8-tetrahydroquinoline-5-carboxylate). LCMS, positive mode, m/z: 206 $[M + H]^+$.

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J. Org. Chem. 2021, 86, 7315−7325

*2,3-Dihydrothieno[3,2-b]pyridine 1,1-Dioxide (**23k**).* The compound was obtained from dihydrothiophen-3(2*H*)-one 1,1-dioxide (3.0 g, 22.4 mmol), propargylamine (2.46 g, 44.8 mmol), and $CuCl_2 \cdot 2H_2O$ (0.191 g, 1.12 mmol) in 20 mL of *i*-PrOH. Purified by column chromatography (hexane/EtOAc 4:1). Yield = 1.66 g (44%). Light yellow solid; m.p. = 120−121 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (dd, J = 4.9, 1.7 Hz, 1H), 8.02 (dd, J = 7.9, 1.6 Hz, 1H), 7.38 (dd, J = 7.9, 4.8 Hz, 1H), 3.61−3.55 (m, 2H), 3.55−3.48 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.0, 154.9, 133.5, 130.2, 123.1, 50.7, 28.7. LCMS, positive mode, m/z: 170 $[M + H]^+$. Anal. calcd for $C_7H_7NO_2S$: C, 49.69; H, 4.17; N, 8.28; S, 18.95. Found: C, 49.98; H, 4.24; N, 8.02; S, 19.10.

*7,8-Dihydro-5H-pyrano[4,3-b]pyridine (**23l**).* The compound was obtained starting from tetrahydro-4*H*-pyran-4-one (3.0 g, 29.9 mmol), propargylamine (3.30 g, 60.0 mmol), and $CuCl_2 \cdot 2H_2O$ (0.255 g, 1.50 mmol) in 30 mL of *i*-PrOH. Yield = 1.38 g (34%). Purified by column chromatography (hexane/EtOAc 3:2). Light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, J = 5.0 Hz, 1H), 7.28 (d, J = 7.9 Hz, 1H), 7.09 (dd, J = 7.7, 4.8 Hz, 1H), 4.75 (s, 2H), 4.06 (t, J = 5.8 Hz, 2H), 3.01 (t, J = 5.9 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 153.5, 147.8, 132.3, 130.3, 121.3, 67.1, 65.7, 31.7. LCMS, positive mode, m/z: 136 $[M + H]^+$. Anal. calcd for C_8H_9NO: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.39; H, 6.82; N, 10.18.

*tert-Butyl 7,8-Dihydro-1,6-naphthyridine-6(5H)-carboxylate (**23m**).* The compound was obtained starting from *tert*-butyl 4-oxopiperidine-1-carboxylate (75.0 g, 0.376 mol), propargylamine (41.4 g, 0.752 mol), and $CuCl_2 \cdot 2H_2O$ (3.20 g, 18.8 mmol) in 350 mL of *i*-PrOH. Purified by column chromatography (hexane/EtOAc 7:3). Yield = 56.2 g (64%). Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 4.8 Hz, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.12 (dd, J = 7.8, 4.8 Hz, 1H), 4.58 (s, 2H), 3.75 (t, J = 6.0 Hz, 2H), 3.00 (t, J = 6.1 Hz, 2H), 1.49 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 154.7, 147.6, 147.6, 134.1, 129.1, 121.4, 80.2, 32.1, 31.7, 28.4, 28.3. LCMS, positive mode, m/z: 235 $[M + H]^+$. Anal. calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.63; H, 7.88; N, 11.73.

*tert-Butyl 3,4-Dihydro-1,5-naphthyridine-1(2H)-carboxylate (**23p**).* The compound was obtained from *tert*-butyl 3-oxopiperidine-1-carboxylate (3.0 g, 15.0 mmol), propargylamine (1.65 g, 30.0 mmol), and $CuCl_2 \cdot 2H_2O$ (0.255 g, 1.50 mmol) in 20 mL of *i*-PrOH. Purified by column chromatography (hexane/EtOAc 4:1). Yield = 1.68 g (48%). Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (dd, J = 4.7, 1.5 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.04 (dd, J = 8.4, 4.7 Hz, 1H), 3.70 (t, J = 5.8 Hz 2H), 2.93 (t, J = 6.7 Hz, 2H), 1.97 (p, J = 6.5 Hz, 2H), 1.49 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.6, 149.3, 143.7, 135.2, 130.8, 120.9, 81.4, 44.5, 30.8, 28.3, 22.7. LCMS, positive mode, m/z: 235 $[M + H]^+$. Anal. calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.92; H, 8.13; N, 11.84.

*tert-Butyl (5,6,7,8-Tetrahydroquinolin-6-yl)carbamate (**23q**).* The compound was obtained from *tert*-butyl (4-oxocyclohexyl)carbamate (50.0 g, 0.234 mol), propargylamine (25.8 g, 0.468 mol), and $CuCl_2 \cdot 2H_2O$ (1.99 g, 11.7 mmol) in 240 mL of *i*-PrOH. Purified by column chromatography (hexane/EtOAc 7:3). Yield = 35.3 g (61%). Colorless solid; m.p. = 101−102 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 4.8 Hz, 1H), 7.32 (d, J = 7.7 Hz, 1H), 7.02 (dd, J = 7.7, 4.8 Hz, 1H), 4.60 (br s, 1H), 3.97 (br s, 1H), 3.10 (dd, J = 16.3, 4.9 Hz, 1H), 3.01 (t, J = 6.8 Hz, 2H), 2.63 (dd, J = 16.3, 8.3 Hz, 1H), 2.18−2.07 (m, 1H), 1.91−1.76 (m, 1H), 1.43 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 155.8, 155.3, 147.5, 137.2, 129.5, 121.2, 79.5, 45.7, 35.4, 30.3, 28.9, 28.4. LCMS, positive mode, m/z: 249 $[M + H]^+$. Anal. calcd for $C_{14}H_{20}N_2O_2$: C, 67.72; H, 8.12; N, 11.28. Found: C, 67.36; H, 7.86; N, 11.00.

*7′,8′-Dihydro-5′H-spiro[[1,3]dioxolane-2,6′-quinoline] (**23r**).* The compound was obtained from 1,4-dioxaspiro[4.5]decan-8-one (50.0 g, 0.30 mol), propargylamine (33.0 g, 0.60 mol), and $CuCl_2 \cdot 2H_2O$ (2.56 g, 15.0 mmol) in 280 mL of *i*-PrOH. Purified by column chromatography (hexane/EtOAc 4:1). Yield = 33.8 g (59%). Light yellow oil. ^{1}H NMR (500 MHz, CDCl3) δ 8.38 (d, J = 4.6 Hz, 1H), 7.34 (d, J = 7.5 Hz, 1H), 7.05 (dd, J = 7.7, 4.8 Hz, 1H), 4.04 (s, 4H), 3.14 (t, J = 6.8 Hz, 2H), 3.00 (s, 2H), 2.06 (t, J = 6.6 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 155.8, 147.3, 137.0, 129.4, 121.0, 107.5, 64.6, 38.5, 31.5, 30.9. LCMS, positive mode, m/z: 192 $[M + H]^+$. Anal. calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.48; H, 7.16; N, 7.34.

*7,8-Dihydroquinolin-5(6H)-one (**23u**).* The compound was obtained from cyclohexane-1,3-dione (3.0 g, 26.8 mmol), propargylamine (2.95 g, 53.5 mmol), and $CuCl_2 \cdot 2H_2O$ (0.228 g, 1.34 mmol) in 23 mL of *i*-PrOH. Yield = 2.05 g (52%). Purified by column chromatography (hexane/EtOAc 4:1). Light yellow oil. ^{1}H NMR (500 MHz, dimethyl sulfoxide (DMSO)-d_6) δ 8.64 (dd, J = 4.8, 2.0 Hz, 1H), 8.23 (dd, J = 7.9, 1.9 Hz, 1H), 7.25 (dd, J = 8.0, 4.9 Hz, 1H), 3.13 (t, J = 6.3 Hz, 2H), 2.66 (t, J = 6.5 Hz, 2H), 2.17 (p, J = 6.5 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 197.9, 163.6, 153.4, 135.0, 128.1, 122.2, 38.5, 32.5, 21.8. LCMS, positive mode, m/z: 148 $[M + H]^+$. Anal. calcd for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.46; H, 6.23; N, 9.70.

*5,6,7,8-Tetrahydroquinoline-6-carboxylic Acid (**24**).* A solution of NaOH (8.80 g, 0.22 mol) in H_2O (200 mL) was added to a stirred solution of ethyl 5,6,7,8-tetrahydroquinoline-6-carboxylate (30.0 g, 0.146 mol) in MeOH (300 mL). The reaction mixture was refluxed for 4 h in an oil bath and cooled, and then a solution of $NaHSO_4$ (26.4 g, 0.220 mol) in H_2O (150 mL) was added. The mixture was stirred for 30 min and evaporated. The residue was treated with boiling dry EtOH (2 × 500 mL), inorganic salts were filtered, and the organic solution was evaporated. The crude product was treated with dry EtOH (50 mL) and filtered. The product was washed with CH_3CN (2 × 30 mL) to give the desired product as a white powder. Yield = 21.2 g (82%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.38 (brs, 1H), 8.29 (d, J = 4.6 Hz, 1H), 7.49 (d, J = 7.7 Hz, 1H), 7.12 (dd, J = 7.7, 4.7 Hz, 1H), 3.00−2.80 (m, 4H), 2.77−2.64 (m, 1H), 2.24−2.04 (m,1H), 1.93−1.76 (m, 1H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 176.3, 156.2, 147.1, 137.1, 130.7, 121.6, 38.8, 31.3, 30.7, 25.7. LCMS, positive mode, m/z: 178 $[M + H]^+$. Anal. calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.44; H, 6.29; N, 8.29.

*5,6,7,8-Tetrahydro-1,6-naphthyridine-1,6-diium Chloride (**25**).* HCl (6 N, 50 mL) was added to a stirred solution of *tert*-butyl 7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate (25.0 g, 0.107 mol) in MeOH (200 mL). The reaction mixture was refluxed for 2 h in an oil bath and evaporated. The solid residue was treated with hot dry MeOH (100 mL), cooled, filtered, washed with MeOH (2 × 20 mL), and dried to give the desired product as a white powder. Yield = 20.4 g (92%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.33 (brs, 2H), 8.75 (d, J = 5.5 Hz, 1H), 8.33 (d, J = 8.0 Hz, 1H), 7.84 (dd, J = 8.0, 5.5 Hz, 1H), 4.43 (s, 2H), 3.49 (brs, 2H), 3.40 (t, J = 6.2 Hz, 2H) (Py-H$^+$ was not observed due to its strong broadening at 7.0−12.0). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 148.8, 142.8, 142.4, 129.7, 124.8, 42.6, 40.9, 25.0. LCMS, positive mode, m/z: 135 $[M - 2HCl + H]^+$. Anal. calcd for $C_8H_{12}Cl_2N_2$: C, 46.40; H, 5.84; N, 13.53; Cl, 34.23. Found: C, 46.59; H, 5.63; N, 13.32; Cl, 33.95.

*1,2,3,4-Tetrahydro-1,5-naphthyridine Chloride (**26**).* HCl (6 N, 50 mL) was added to a stirred solution of *tert*-butyl 5,6,7,8-tetrahydro-1,6-naphthyridine-6-carboxylate (25.1 g, 0.107 mol) in MeOH (200 mL). The reaction mixture was refluxed for 2 h in an oil bath and evaporated. The solid residue was treated with hot dry MeOH (100 mL), cooled, filtered, washed with MeOH (2 × 20 mL), and dried to give the desired product as a white powder. Yield = 16.4 g (90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.84 (d, J = 4.6, 1H), 6.87 (dd, J = 8.0, 4.7, 1H), 6.70 (dd, J = 8.2, 1.6, 1H), 3.91 (s, 1H), 3.31−3.24 (m, 2H), 2.92 (t, J = 6.5, 2H), 2.01 (p, J = 6.4, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ = 142.7, 140.9, 137.8, 121.9, 120.1, 77.3, 77.1, 76.9, 41.4, 30.3, 21.7. LCMS, positive mode, m/z: 135 [M + H]. Anal. calcd for $C_8H_{10}N_2$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.80; H, 7.44; N, 20.83.

*5,6,7,8-Tetrahydroquinolin-6-aminium Chloride (**27**).* HCl (6 N, 50 mL) was added to a stirred solution of *tert*-butyl *N*-(5,6,7,8-tetrahydroquinolin-6-yl)carbamate (26.6 g, 0.107 mol) in MeOH (200 mL). The reaction mixture was refluxed for 2 h in an oil bath and evaporated. The solid residue was treated with hot dry MeOH (100 mL), cooled, filtered, washed with MeOH (2 × 20 mL), and dried to give the desired product as a white powder. Yield = 18.4 g (93%). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.66 (d, J = 5.8, 4H), 8.36 (d, J = 7.9, 1H), 7.80 (dd, J = 7.9, 5.7, 1H), 3.37−3.24 (m, 2H), 3.28−3.12 (m, 1H), 3.06 (dd, J = 17.1, 9.1, 1H), 2.54 (s, 0H), 2.25 (s, 1H), 2.10−1.95

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J. Org. Chem. 2021, 86, 7315−7325

(m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ = 151.5, 146.0, 140.2, 133.9, 124.53, 44.9, 31.4, 25.6, 24.9. LCMS, positive mode, m/z: 149 [M + H]. Anal. calcd for $C_9H_{13}ClN_2$: C, 58.54; H, 7.10; N, 15.17; Cl, 19.20. Found: C, 58.90; H, 6.96; N, 15.02; Cl, 19.07.

*7,8-Dihydroquinolin-6(5H)-one (**28**).* Water (400 mL), 85% phosphoric acid (200.0 g), and 7′,8′-dihydro-5′*H*-spiro[1,3]-dioxolane-2,6′-quinoline (35.0 g, 0.183 mol) were added to a 1 L flask. The reaction mixture was stirred and heated to 80 °C for 8 h in an oil bath. The reaction solution was adjusted to pH = 6 with sodium carbonate solution and then extracted with EtOAc (3 × 200 mL). The extract was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The crude product was purified by gravity column chromatography (hexane/EtOAc 7:3) to give the desired product as a white powder. Yield = 22.95 g (85%). Yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 5.0, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.12 (dd, J = 7.7, 4.9 Hz, 1H), 3.56 (s, 2H), 3.23 (t, J = 6.9 Hz, 2H), 2.62 (t, J = 6.9 Hz, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 208.6, 156.7, 147.7, 136.0, 128.3, 122.1, 43.7, 37.7, 31.1. LCMS, positive mode, m/z: 148 $[M + H]^+$. Anal. calcd for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.44; H, 6.28; N, 9.35.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c03038.

Copies of ^1H and ^{13}C NMR spectra of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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