SHORT COMMUNICATION

EurJOC European Journal of Organic Chemistry

DOI: 10.1002/ejoc.201500505

Chemoselective Synthesis of 5-Alkylamino-1*H*-pyrazole-4-carbaldehydes by Cesium- and Copper-Mediated Amination

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Keywords: Pyrazoles / Cesium / Copper / Chemoselectivity / Amination reactions

Microwave-assisted synthesis of new 5-alkylamino-pyrazole-4-carbaldehydes was performed efficiently, with yields up to 99 % and short reaction times. Nucleophilic substitution of primary alkylamines with activated 5-chloro-1-(2-pyridyl)-pyrazole-4-carbaldehyde was mediated by the "cesium effect". The amination of deactivated 1-aryl-5-chloropyrazole-4-carbaldehydes was also assisted by the cesium ion and catalyzed by copper(I).

Introduction

Derivatives of 5-aminopyrazole have been found to play an important role as biologically active compounds.[1] As such, they are considered building-blocks of high interest for pharmaceutical agents[2] and agrochemicals.[3] In addition, 5-aminopyrazoles are important intermediates for obtaining useful polyheterocycles.[4] Both 5-aminopyrazoles and 5-aminopyrazole-4-carbaldehydes are key precursors for the synthesis of structures that have found applications as antitumor agents[5] and in the treatment of osteoarthritis.[6] Hence, the development of methods for the synthesis of 5-alkylaminopyrazole-4-carbaldehydes can be seen as an important research goal in organic chemistry. Typically, methods for the synthesis of 5-aminopyrazoles focus on reactions between acrylonitrile derivatives[4c] or, in some cases, β-enaminones[7] with structures containing the hydrazine moiety. In addition, methods for the synthesis of 5-aminopyrazole-4-carbaldehydes are based on reacting 5-chloropyrazole-4-carbaldehydes with secondary amines, aromatic amines, or with the N–H group in heterocyclic compounds.[8] To the best of our knowledge, there is only one report for the reaction of primary alkylamines with 5-chloropyrazole-4-carbaldehydes, with electron-withdrawing groups to favor the reaction.[9]

It has been reported that cesium salts can act as efficient mediators in chemoselective *N*-alkylation of amines. This phenomenon has been named the "cesium effect" due to the fact that cesium ions are "naked" in polar aprotic solvents, thus increasing the nucleophilicity of primary amines.[10] It has also been reported that copper(I) iodide is useful, as it can act as a catalyst in C–N bond formation in pyrazole rings.[11] Accordingly, and continuing with our studies toward the development of synthetic methodologies for the construction of new derivatives of pyrazoles,[4a,4c,12] we now describe an efficient protocol for the chemoselective synthesis of new 5-alkylaminopyrazole-4-carbaldehydes from 5-chloropyrazole-4-carbaldehydes and primary amines mediated by cesium and copper(I) in good to excellent yields. Unexpectedly, under these reaction conditions the corresponding imine formation was not observed.

Results and Discussion

Our initial attempt to synthesize 5-alkylaminopyrazole-4-carbaldehydes began with cyclohexylamine (**2a**), freshly synthesized 5-chloropyrazole-4-carbaldehyde (**1a**) (see Supporting Information), and sodium hydroxide, in dimethylformamide (DMF) and with a microwave reactor at 160 °C for 10 min. Results for this initial test generated the desired product **3a** in a 20% yield (Table 1, entry 1). Increasing the reaction time to 20 min did not increase the yield (Table 1, entry 2). When dimethyl sulfoxide was used as solvent at 160 °C for 10 min, the yield of **3a** decreased instead (Table 1, entry 3). Likewise, the use of conventional heating at 150 °C for 12 h in DMF provided the desired product in a low yield (15%).

The use of potassium hydroxide did not increase the reaction yield (Table 1, entry 5); these latest conditions are similar to those recently reported by Reekie et al.,[8c] this was possibly due to the higher acidity of aniline relative to that of primary alkylamines. The addition of potassium carbonate did not favor the formation of product **3a** (Table 1, entry 6). A significant improvement in the yield of **3a** was observed when 1 equiv. of cesium carbonate was employed with both microwave (98%) and conventional heating (80%) (Table 1, entries 7–9). It is noteworthy to mention that a high reaction yield was observed when

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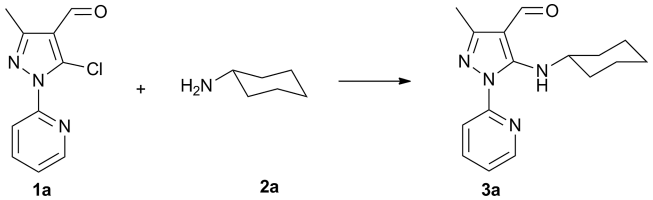
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201500505.

Table 1. Optimization of the reaction conditions for the synthesis of 5-alkylaminopyrazole-4-carbaldehyde **3a**.[a]



1a **2a** **3a**

Entry	Base	Solvent	Temp. [°C]	Time [min]	Yield [%][f]
1	NaOH[b]	DMF	160[d]	10	20
2	NaOH[b]	DMF	160[d]	20	20
3	NaOH[b]	DMSO	160[d]	10	15
4	NaOH[b]	DMF	150[e]	720	15
5	KOH[b]	DMF	160[d]	10	20
6	K_2CO_3[b]	DMF	160[d]	10	0
7	Cs_2CO_3[b]	DMF	160[d]	10	98
8	Cs_2CO_3[b]	DMF	150[e]	720	80
9	Cs_2CO_3[c]	DMF	150[d]	10	98

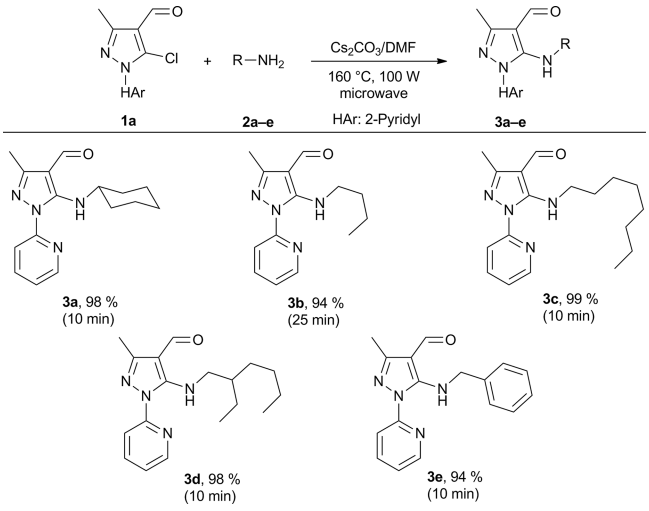
[a] Reaction conditions: **1a** (0.45 mmol), **2a** (0.56 mmol), solvent (2 mL). [b] 1 equiv. of base. [c] 0.2 equiv. of base. [d] Run in a microwave vial (10 mL) sealed and placed in a microwave reactor (100 W). [e] Conventional heating. [f] Isolated yields.

0.2 equiv. of cesium carbonate was used under microwave irradiation (Table 1, entry 9). These preliminary results showed that cesium carbonate and microwave heating play a crucial role for improving the results. Under these reaction conditions, a high selectivity towards the substitution on the aromatic ring instead of imine formation is observed. Surprisingly, the slight excess of amine used in the experimental procedure did not react with the aldehyde. We have hypothesized that these results can be explained by the effect of cesium carbonate in a polar aprotic solvent such as DMF.[9]

As it has been already established, the cesium ion forms complexes with primary amines whose hydrogen atoms are acidic enough to be abstracted by the carbonate ion, leading to the respective cesium amide [**2a**]$^-$ Cs^+.[10] This ionic amide is a good nucleophile for aromatic nucleophilic substitution at the 5-chloropyrazole-4-carbaldehyde (**1a**), which occurs through an addition–elimination sequence (Scheme 1).

Once the optimal conditions for obtaining **3a** were achieved (Table 1, entry 9), the primary amine was varied in order to produce a series of 5-alkylaminopyrazole-4-carbaldehydes; excellent yields starting from **1a** were obtained (Table 2, **3a**–**e**). The success of this reaction can be explained by the electron-withdrawing nature of the 2-pyridyl group in 5-chloropyrazole-4-carbaldehyde (**1a**), which favors the nucleophilic aromatic substitution reaction.

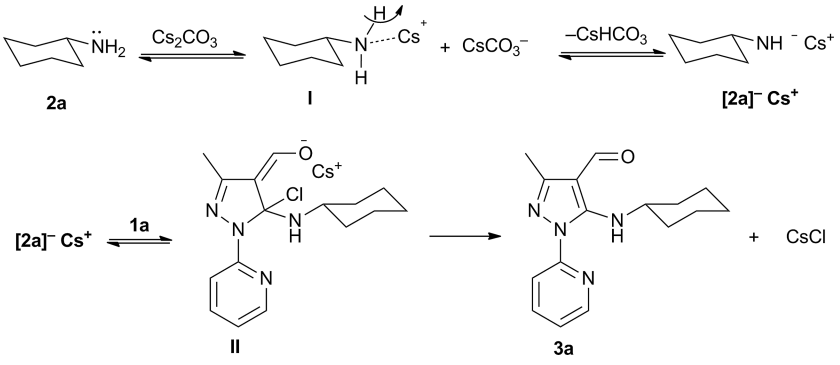
Table 2. Substrate scope of alkylamines for the synthesis of 5-alkylamino-pyrazole-4-carbaldehydes **3a**–**e** under optimized conditions.[a]



1a **2a–e** **3a–e**

[a] Reaction conditions: **1a** (0.45 mmol), **2a**–**e** (0.56 mmol), Cs_2CO_3 (0.09 mmol), DMF (2 mL). Reaction times are shown in parentheses.

Subsequently, we investigated the scope of the method in order to obtain 5-alkylamino-1-arylpyrazole-4-carbaldehydes **3f**–**l** (Table 4) from 1-aryl-5-chloropyrazole-4-carbaldehydes **1b**,**c** containing either a phenyl or 4-chlorophenyl group on the nitrogen N-1. Unfortunately, the desired products **3f**–**l** did not form under these reaction conditions. These aryl groups do not have the electron-withdrawing ability that the 2-pyridyl group does, which explains these results. For this reason, finding optimal conditions for the reaction of pyrazoles **1b**,**c** with primary amines is a remarkable achievement, since they are electron-rich

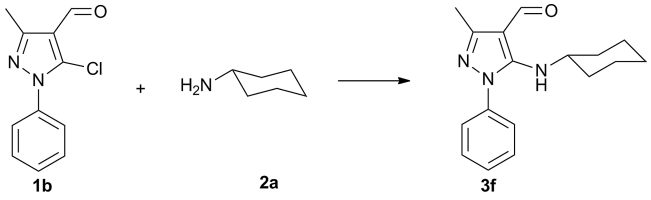


Scheme 1. Possible reaction mechanism for nucleophilic aromatic substitution of 5-chloropyrazole-4-carbaldehyde (**1a**) with cyclohexylamine (**2a**).

heteroaromatic compounds and generally do not react with nucleophiles.

To accomplish our objective, we optimized the reaction conditions by using primary amine **2a** with freshly synthesized 5-chloro-4-formylpyrazole (**1b**) (see Supporting Information). In this latest study, it was found that copper salts favored the amination reaction and the expected product **3f** was obtained (Table 3, entries 1–12). Copper(I) compounds, such as CuI, CuBr, and Cu_2O, were found to be more efficient compared to the copper(II) salt $Cu(OAc)_2$. On the basis of these results, it is possible to say that the catalytic species in this reaction is the copper(I) ion. Moreover, the results showed that the employed base also plays an important role in the reaction. Better yields were obtained when cesium carbonate was used instead of potassium carbonate or sodium carbonate. These results can be explained by the previously mentioned "cesium effect".[9] In addition to the use of copper(I) salts and cesium carbonate, the selection of the solvent and the type of heating are also key to achieving an increase in the reaction yield for **3f**. We found that the use of DMF as solvent and microwave-assisted heating increased the reaction yield (Table 3, entries 4, 8, 12). In general, the best results were obtained when CuI was used as catalyst, cesium carbonate as base, DMF as solvent, and microwave as the heating source (Table 3, entry 4). Once the optimal conditions were established, various primary amines (**2a**–**e**) were studied. The 5-alkylaminopyrazole-4-carbaldehydes were obtained from **1b**,**c** in moderate yields (Table 4, **3f**–**l**).

Table 3. Optimization of the reaction conditions for the synthesis of 5-alkylaminopyrazole-4-carbaldehyde **3f**.[a]

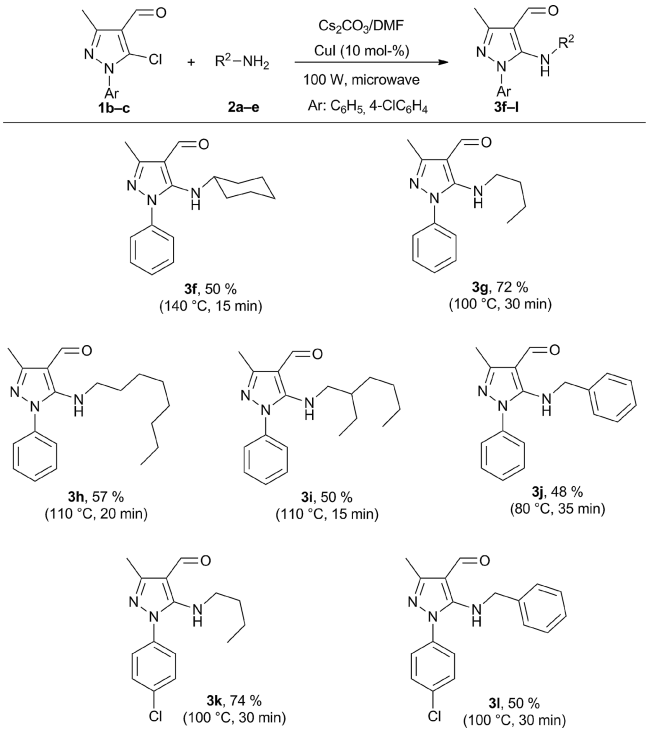


Entry	Catalyst	Base	Solvent	Temp. [°C]	Time [min]	Yield [%][d]
1	CuI	Na_2CO_3	DMF	140[b]	15	0[e]
2	CuI	K_2CO_3	DMF	140[b]	15	13[e]
3	CuI	Cs_2CO_3	DMF	150[c]	720	27[e]
4	CuI	Cs_2CO_3	DMF	140[b]	15	50[e]
5	CuI	Cs_2CO_3	DMSO	140[b]	15	22[e]
6	CuI	Cs_2CO_3	toluene	140[b]	15	15[e]
7	$Cu(OAc)_2$	K_2CO_3	DMF	140[b]	15	0[e]
8	$Cu(OAc)_2$	Cs_2CO_3	DMF	140[b]	15	18[e]
9	CuBr	K_2CO_3	DMF	140[b]	15	30[e]
10	CuBr	Cs_2CO_3	DMF	140[b]	15	38[e]
11	Cu_2O/Cu	K_2CO_3	DMF	140[b]	15	12[f]
12	Cu_2O/Cu	Cs_2CO_3	DMF	140[b]	15	48[f]

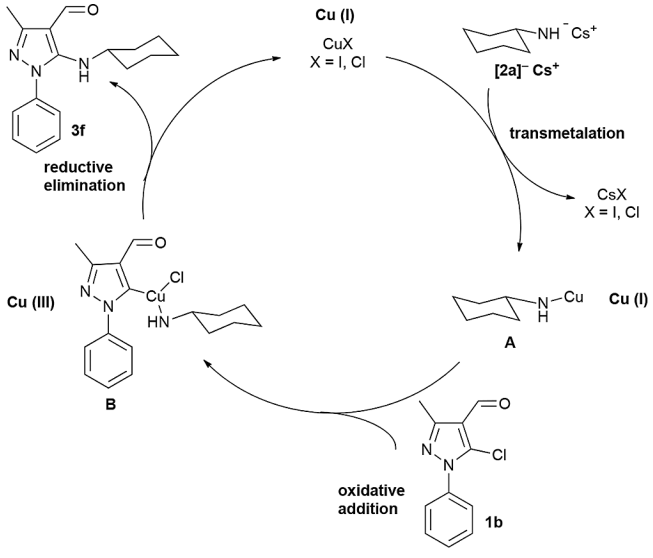
[a] Reaction conditions: **1b** (0.45 mmol), **2a** (0.56 mmol), 1 equiv. of base, solvent (2 mL). [b] Run in a microwave vial (10 mL) sealed and placed in a microwave reactor (100 W). [c] Conventional heating. [d] Isolated yields. [e] 10 mol-% catalyst loading. [f] 10 mol-% Cu_2O and 20 mol-% Cu.

A possible reaction mechanism for the formation of 5-alkylaminopyrazol-4-carbaldehydes **3f**–**l** begins with the coordination of the cesium amide [**2a**]$^-$Cs$^+$ by transmetalation with the catalytically active species of copper(I) (Scheme 2). Once the coordination complex A is formed, oxidative addition occurs to form the intermediate species of Cu^{III} B. Subsequently, the amination product **3f** is obtained by a

Table 4. Substrate scope of alkylamines for the synthesis of 5-alkylamino-pyrazole-4-carbaldehydes **3f**–**l** under optimized conditions.[a]



[a] Reaction conditions: **1b**,**c** (0.45 mmol), **2a**–**e** (0.56 mmol), Cs_2CO_3 (0.45 mmol), DMF (2 mL). Temperature and time of reaction are shown in parentheses.



Scheme 2. Proposed reaction mechanism for catalytic amination of 5-chloropyrazole-4-carbaldehyde (**1b**).

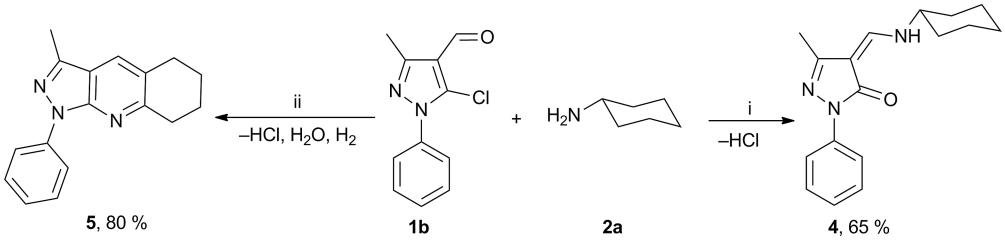
reductive elimination followed by a regeneration of the active Cu^{I} catalyst (Scheme 2).[13] It is possible to hypothesize that copper chloride does not perform well as catalyst due to its higher stability and lower dissociation. It was also noted that increasing the amount of CuI in the reaction mixture did not lead to higher yield for **3f**.

Searching for better reaction conditions for the formation of 5-alkylaminopyrazoles **3f**–**l**, we employed ethanol as the solvent as well as higher temperatures. These latest experiments gave results that support our previous statements on the role of the solvent (Scheme 3). For example, by using 5-chloropyrazole-4-carbaldehyde (**1b**) in the presence of two equivalents of cyclohexylamine **2a**, an equivalent of cesium carbonate, ethanol as solvent, and microwave heating, (*Z*)-4-[(cyclohexylamino)methylene]-1-phenyl-1*H*-pyrazolone (**4**) was isolated in 65% yield. Compound **4** comes from the formation of the imine and subsequent substitution of the chlorine atom with a hydroxyl group from the reaction medium. This result experimentally supports our hypothesis that the solvent plays an important role in the chemoselectivity of the reaction.

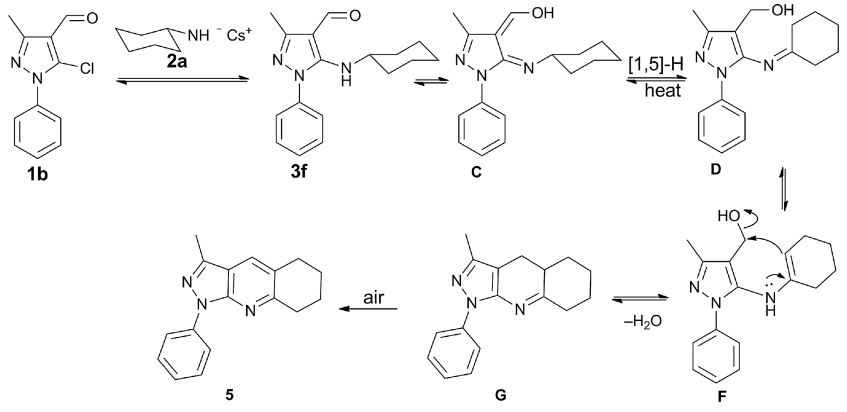
Employing 5-chloropyrazole-4-carbaldehyde (**1b**) in the presence of two equivalents of cyclohexylamine (**2a**), one equivalent of cesium carbonate, DMF as solvent, and microwave heating at 250 °C afforded 3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]quinoline (**5**) in 80% yield (Scheme 3). Although compound **5** has previously been reported in the literature,[14] these new reaction conditions can have a synthetic advantage, since it is possible to obtain tetrahydropyrazolo[3,4-*b*]quinolines and their analogues in one step, which is vastly preferable over other reported multistep methods.[15]

The formation of **5** can be explained by a sequence of tandem reactions that begins with the formation of the substituted product **3f**, which tautomerizes to produce **C**. Subsequently, a 1,5-sigmatropic rearrangement of hydrogen occurs to form alcohol **D**. Intermediate **D** undergoes imine/enamine tautomerization to form tautomer **F**. Then, tautomer **F** forms the dihydropyridine ring **G**, which aromatizes to the pyridine ring (compound **5** in Scheme 4). In this reaction, temperature plays an important role, since under these reaction conditions the sigmatropic rearrangement and tautomerization are favored, which leads to the formation of compound **5**.

The reactions of 5-chloropyrazole-4-carbaldehydes **1a**–**c** with aniline as primary arylamine were examined under the optimized conditions. The results are shown in Table 5. The product of substitution, **6a**, was produced with good yield, confirming the influence of the electron-withdrawing nature of the 2-pyridyl group in the substitution reaction of 5-chloropyrazole-4-carbaldehyde (**1a**). By contrast, the yields were low when 1-aryl-5-chloropyrazole-4-carbaldehydes **1b**,**c** were used. For instance, compounds **6b** and **6c** were formed in 16% and 20% yield, respectively. Furthermore, these reactions occur in competition with the formation of the corresponding imines **7b**,**c**, which were also isolated with low yields. These results can be explained by the low electron-withdrawing ability of the corresponding aryl



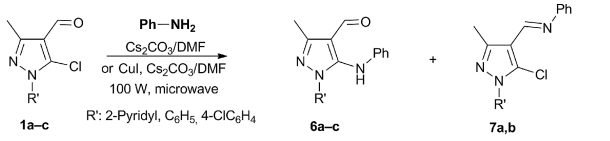
Scheme 3. Synthesis of products **4** and **5**. Reaction conditions: **1b** (0.45 mmol), **2a** (0.90 mmol), Cs_2CO_3 (0.45 mmol). i: Ethanol (2 mL), 160 °C, 150 W, 30 min; ii: DMF (2 mL), 250 °C, 190 W, 30 min.

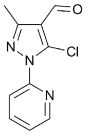
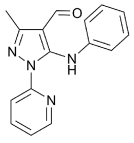
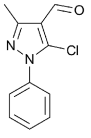
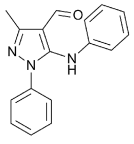
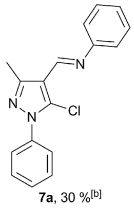
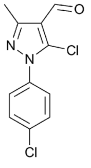
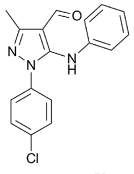
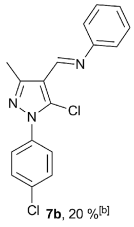


Scheme 4. Proposed mechanism to prepare 3-methyl-1-phenyl-5,6,7,8-tetrahydro-1*H*-pyrazolo[3,4-*b*]quinoline (**5**).

groups on the pyrazole ring. In this case, imine formation was observed probably as a result of the stabilization of the conjugate product.

Table 5. Results obtained for the reaction of 5-chloro-1-arylpyrazole-4-carbaldehydes **1a**–**c** with aniline.



Entry	Substrate	Isolated % yield of **6**	Isolated % yield of **7**
1	 **1a**	 **6a**, 89 %[a]	Not observed
2	 **1b**	 **6b**, 16 %[b]	 **7a**, 30 %[b]
3	 **1c**	 **6c**, 20 %[b]	 **7b**, 20 %[b]

[a] Reaction conditions: **1a** (0.45 mmol), aniline (0.59 mmol), Cs_2CO_3 (0.09 mmol), DMF (2 mL), 160 °C, 20 min. [b] **1b**,**c** (0.45 mmol), aniline (0.59 mmol), CuI (10 mol-%), Cs_2CO_3 (0.45 mmol), DMF (2 mL), 140 °C, 20 min.

The structures of new 5-alkylamino-1*H*-pyrazole-4-carbaldehydes **3a**–**l** and compounds **4**–**7** were appropriately established by the usual spectroscopic methods. Single-crystal X-ray diffraction analysis of compounds **3a** and **4** were used to corroborate the postulated structures.[16]

Conclusions

In conclusion, we have reported a novel and efficient method for the chemoselective synthesis of new 5-alkylaminopyrazole-4-carbaldehydes mediated by cesium and copper(I). Primary alkylamines and 5-chloropyrazole-4-carbaldehydes were used as starting materials in a suitable solvent and at appropriate temperatures. The chemoselective formation of C–N bonds was achieved in one step to give products with good to excellent yields and short reaction times. In addition, two unexpected products (**4** and **5**) were also isolated; the formation of **5** provides a new route for the easy access to new pyrazolo[3,4-*b*]pyridines.

Experimental Section

General Procedure for the Synthesis of 5-Alkylamino-1-(pyridin-2-yl)-1*H*-pyrazole-4-carbaldehydes 3a–e: A mixture of pyrazole **1a** (0.100 g, 0.45 mmol, 1 equiv.), the appropriate amine (0.56 mmol, 1.3 equiv.), cesium carbonate (0.029 g, 20 mol-%, 0.2 equiv.), and DMF (2 mL) was placed in a reaction tube of a CEM Discover™ instrument containing a magnetic stirring bar. The tube was sealed with a plastic microwave septum and was irradiated at 160 °C for 10–25 min at 100 W. The resulting crude product was partitioned between dichloromethane and water. The organic layer was washed with water, then brine, and dried with anhydrous sodium sulfate. Subsequently, the solvent was removed under vacuum, and the residue was purified by silica gel flash chromatography (DCM) to afford compounds **3a**–**e**.

General Procedure for the Synthesis of 5-Alkylamino-1-aryl-1*H*-pyrazole-4-carbaldehydes 3f–l: A mixture of pyrazole **1b**,**c** (0.45 mmol, 1 equiv.), the appropriate amine (0.56 mmol, 1.3 equiv.), cesium carbonate (0.147 g, 0.45 mmol, 1 equiv.), copper(I) iodide (0.0086 g, 10 mol-%, 0.1 equiv.), and DMF (2 mL) was placed in a reaction tube of a CEM Discover™ instrument containing a magnetic stirring bar. The tube was sealed with a plastic microwave septum, and it was then irradiated at 80–140 °C for 15–35 min at 100 W. The resulting crude product was partitioned between dichloromethane and water. The organic layer was washed with water, then brine, and dried with anhydrous sodium sulfate. Subsequently, the solvent was removed under vacuum, and the residue was purified by silica gel column chromatography using DCM/AcOEt (50:1 v/v) as eluent to afford compounds **3f**–**l**.

Synthesis of (*Z*)-4-[(Cyclohexylamino)methylene]-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4):[4] A mixture of pyrazole **1b** (0.0992 g, 0.45 mmol, 1 equiv.), cyclohexylamine **2a** (0.0892 g, 0.90 mmol, 2 equiv.), cesium carbonate (0.147 g, 0.45 mmol, 1 equiv.), and 2 mL of ethanol was placed in a reaction tube of a CEM Discover™ instrument containing a magnetic stirring bar. The tube was sealed with a plastic microwave septum and was irradiated at 160 °C for 30 min at 150 W. The resulting crude product was concentrated in vacuo, and the residue was purified by silica gel column chromatography using DCM/AcOEt (50:1 v/v) as eluent to afford compound **4** as white crystals.

Synthesis of 3-Methyl-1-phenyl-5,6,7,8-tetrahydro-1*H*-pyrazolo[3,4-*b*]quinoline (5): A mixture of pyrazole **1b** (0.0992 g, 0.45 mmol, 1 equiv.), cyclohexylamine **2a** (0.0892 g, 0.90 mmol, 2 equiv.), cesium carbonate (0.147 g, 0.45 mmol, 1 equiv.), and DMF (2 mL) was placed in a reaction tube of a CEM Discover™ instrument containing a magnetic stirring bar. The tube was sealed with a plastic microwave septum and was irradiated at 250 °C for 30 min at 190 W. The resulting crude product was partitioned between dichloromethane and water. The organic layer was washed with water, then brine, and dried with anhydrous sodium sulfate. Subsequently, the solvent was removed under vacuum, and the residue was purified by silica gel column chromatography (DCM) to afford compound **5** as pale-yellow crystals.

Supporting Information (see footnote on the first page of this article): General experimental procedure and spectroscopic data for all products. ^{1}H NMR and ^{13}C NMR spectra and mass spectra (IE) of all compounds; HPLC–HRMS analysis data for compounds **3a**–**l**, **4**, **5**, **6a**–**c**, and **7a**,**b**.

Acknowledgments

The authors are grateful to the Departamento de Química and Facultad de Ciencias of Universidad de los Andes, the University of

Jaén and the Consejería de Economía, Innovación y Ciencia (Junta de Andalucía, Spain) for financial support.

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Received: April 21, 2015
Published Online: July 8, 2015

