Catalysis

Regioselective Copper(I)-Catalyzed Ullmann Amination of Halopyridyl Carboxylates using Sodium Azide: A Route for Aminopyridyl Carboxylates and their Transformation to Pyrido[2,3-d]pyrimidin-4(1H)-ones

Nisha,^{*,[a]} Mr. Chetan Sharma,^[b] Rupesh Kumar,^[b] and Yogesh Kumar^{*,[b, c]}Dedicated to Dr. Gaurav Bhargava on the occasion of his 40th birthday

We report herein an efficient, straightforward and ligand free synthesis of aminopyridyl carboxylates, an important building block used in pharmaceuticals and agrochemicals. The C(sp²)-N bond formation utilize a readily available Cu-catalyst, NaN₃ as the amino source in ethanol, and the corresponding ortho-functionalized aromatic amines were synthesized in good to excellent yields. This ligand free one-pot domino methodology proceeds through Ullmann-type coupling of halopyridyl carboxylates with sodium azide followed by reduction with ethanol. These functionalized aminopyridyl carboxylates provides an easy access to biologically potent pyrido[2,3-d]pyrimidin-4(1H)-one hybrids.

Occurrence of nitrogen-containing heterocyclic compounds in synthetic intermediates, natural products, pharmaceutical and agrochemical agents, and functional materials has provoked synthetic chemists to develop expedient and mild amination reactions.^[1] Over the last decades, transition metal catalysts provides versatile strategies to construct C(sp²)-NH₂ bond and present a great opening to derivatize uncommon chemicals with modest functionality to synthetically novel compounds.^[2–5] In this context, several catalytic methods have been used, particularly the palladium- and copper-catalyzed amination of aryl halides has gained increasing interest.^[6] Since all these methods involve the use of prefunctionalized arene starting materials, recent efforts are focused on the count of new methods by the use of parent arenes as the starting materials. Although the existing methods are quite useful,^[6] however,

developing a direct route to achieve amination of o-functionalized haloheteroarenes with structural diversity from the readily accessible simple substrates would be enthralling while exigent at the same time.

On the other hand, aminopyridyl carboxylates are highly useful and valuable compounds that have numerous applications.^[7] 2-aminonicotinic acid (vitamin B3) and 2-aminonicotinamide moieties appear frequently in medicinal chemistry programs and, are valuable intermediates for the grounding of compounds with prospective as chemotherapeutic agents.^[8–9] In view of the advances made in the formation of CC, CO, CN and C-halogen bonds by modern ortho-CH functionalizations, a similar approach would be interesting also for the regioselective synthesis of aminoheteroarenes.

Based on our previous efforts on developing the synthetic methods for heterocycles,^[10–11] herein we report a novel ligand free one-pot copper-catalyzed direct amination of halopyridyl carboxylates using sodium azide in the presence of ethanol at moderate temperature. This newly exposed reaction is simple, straightforward, utilizing inexpensive copper catalyst and converts the readily available substrates i.e. 2-halonicotinic acid, 2-halonicotinamide into important aminoheteroarenes *via* a ligand free one-pot Ullmann-type coupling with sodium azide followed by reduction. These aminoheteroarenes are novel synthons for the synthesis of highly functionalized pyrido[2,3-d]pyrimidin-4(1H)-ones.

Initially, to find an optimized reaction condition for the synthesis of 2-aminonicotinic acid **2a**, 2-chloronicotinic acid was chosen as the model substrate including the catalysts, bases, and solvents under nitrogen atmosphere as shown in Table 1. We started our experiment with 2-chloronicotinic acid **1a** and NaN₃ (4 mmol) in the presence of CuBr (10 mol %) and

Scheme 1. Copper-Catalyzed Amination of 2-Chloronicotinic acid with NaN₃: Gram Scale Synthesis

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Table 1. Copper-Catalyzed Amination of 2-Chloronicotinic acid with NaN_3 : Optimization of Reaction Conditions.

Entry	Cu metal	Azide	Base	Solvent	Yield (%) ^a
1	CuBr	NaN_3	K_2CO_3	$\text{C}_2\text{H}_5\text{OH}$	60
2	CuBr	TsN_3	K_2CO_3	$\text{C}_2\text{H}_5\text{OH}$	n.d.
3	CuBr	TMSN_3	K_2CO_3	$\text{C}_2\text{H}_5\text{OH}$	n.d.
4	CuCl	NaN_3	K_2CO_3	$\text{C}_2\text{H}_5\text{OH}$	45
5	CuI	NaN_3	K_2CO_3	$\text{C}_2\text{H}_5\text{OH}$	85
6	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$	NaN_3	K_2CO_3	$\text{C}_2\text{H}_5\text{OH}$	70
7	CuCl_2	NaN_3	K_2CO_3	$\text{C}_2\text{H}_5\text{OH}$	65
8	CuBr_2	NaN_3	K_2CO_3	$\text{C}_2\text{H}_5\text{OH}$	n.d.
9	CuI	NaN_3	K_3PO_4	$\text{C}_2\text{H}_5\text{OH}$	75
10	CuI	NaN_3	Cs_2CO_3	$\text{C}_2\text{H}_5\text{OH}$	69
11	CuI	NaN_3	NaOH	$\text{C}_2\text{H}_5\text{OH}$	25
12	CuI	NaN_3	K_2CO_3	CH_3OH	55
13	CuI	NaN_3	K_2CO_3	2-propanol	trace
14	CuI	NaN_3	K_2CO_3	<i>t</i> -butanol	trace
15	CuI	NaN_3	K_2CO_3	DMSO	45
16	-	NaN_3	K_2CO_3	$\text{C}_2\text{H}_5\text{OH}$	n.d.
17	CuI	NaN_3	-	$\text{C}_2\text{H}_5\text{OH}$	n.d.

^aReaction condition: NaN_3 (4 mmol), catalyst (0.1 mmol), base (2 mmol).

K_2CO_3 (2 mmol) as the base in ethanol at 90 °C for 18 h, and only 60% of product was obtained (entry 1, Table 1). Interestingly, reaction of 2-chloronicotinic acid with NaN_3 afforded 2-aminonicotinic acid **2a** rather than 2-azidonicotinic acid. We explored the reactions in presence of different azides such as TsN_3 and TMSN_3 , failed to react and no product was isolated (entries 2 & 3). Next, we screened different copper metals such as CuBr, CuCl, CuI, $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$, CuCl_2 and CuBr_2 , CuI was proven to be most successful leading to **2a** in 85% yield (Entry 5). No target product was isolated in the absence of copper source and NaN_3 (entries 16 & 17). The bases K_3PO_4 , Cs_2CO_3 and NaOH were also investigated, and K_2CO_3 gave the highest yield (compare entries 5, 9–11). Further, we carried out reaction with different solvent systems such as methanol, 2-propanol, *t*-butanol, DMSO and observed ethanol was most suitable solvent for this reaction (entries 5, 13–15). We have also attempted different reaction temperature under the same reaction conditions, but 90 °C was found optimal for smooth amination, as reduced temperature lowers the yield.

Having the optimal reaction conditions in hand, the scope of copper-catalyzed amination for 2-halonicotinic acid and 2-halonicotinamide derivatives was investigated with use of NaN_3 as the amino source under the optimized conditions (Table 2). We performed the amination of ortho-functionalized halonicotinic acids and halonicotinamides with CuI (10 mol %) as the catalyst and K_2CO_3 (2 equiv) as the base at a temperature of 90 °C, the reactions went smoothly to give the desired 2-aminonicotinic acids and 2-aminonicotinamides (**2a** & **2g**) in excellent yields (85% & 75%). Next we evaluated the effect of halo substitution in 2-halonicotinic acids. When we carried out the reaction of halo substituted 2-halonicotinic acids such as 5-

Scheme 2. Treatment of (a) 6-halonicotinic acid and (b) 2-halopyridin-3-amine with NaN_3 under our Standard Conditions.

Scheme 3. Reactions of (a) 6-Azidonicotinic acid and (b) 2-Azidonicotinic Acid under our Standard Conditions.

chloro, 6-chloro, 5-bromo and 6-bromo, all the substituted 2-aminopyridines underwent smooth conversion under the optimized conditions and the required products (**2b-f**) were synthesized to good yields (60–77%). Interestingly, there was no influence of steric hindrance as 2,6-dichloro-4-methylnicotinic acid was underwent coupling and afforded the desired products (**2e**) in good yield (77%). Then the amination of 2-halonicotinamides (**1g-f**) was also investigated. The amination of 2-halonicotinamides was well tolerated under the optimized conditions and furnished the corresponding substituted 2-aminonicotinamides (**2g-f**) in good yields (72–75%). When 2,6-dichloronicotinamide was used as the substrate, the amination selectively occurred at ortho-site C–Cl bond of $-\text{CONH}_2$, which is due to ortho-substituent effect of the amide group.^[12] When 2-bromobenzoic acid was used as the substrate, 80% yield of the target product (**2i**) was obtained under the same condition (entry 11).

Scheme 4. Possible Mechanism of 2-Aminonicotinic Acid.

Table 2. Copper-Catalyzed Synthesis of Ortho-Functionalized Pyridyl Amines.

$\text{R} \begin{array}{c} \text{FG} \\ \text{X} \end{array} + \text{NaN}_3 \xrightarrow[\text{EtOH, 90}^\circ\text{C}]{\text{CuI, K}_2\text{CO}_3} \text{R} \begin{array}{c} \text{FG} \\ \text{NH}_2 \end{array}$ $\text{X} = \text{Br, Cl}$ $\text{FG} = \text{COOH, CONH}_2$				
Entry	Starting	Time (h)	Product	Yield (%) ^a
1		20		85
2		28		65
3		30		60
4		26		75
5		32		77
6		22		75
7		26		70
8		24		65
9		22		75
10		22		72
11		30		80

^aReaction condition: halopyridine (1 mmol), NaN₃ (4 mmol), CuI (0.1 mmol), K₂CO₃ (2 mmol), reaction temperature (90 °C) under nitrogen atmosphere.

To explore the reaction pathway the amination of 2-halonicotinic acid derivatives, the following control experiments were performed using 1a as representative examples under our standard condition as shown in Scheme 1. The ESI-MS analyses of the reaction mixture of 1a and NaN₃ after 3 h revealed the presence of major species 1a, 1aa and 2a (Figure 1). Furthermore, the reaction of 6-halonicotinic acids 3

Figure 1. Major species identified using ESI-MS of reaction mixture of 1a and NaN₃ after 3 h (see Supporting Information).

with NaN₃ did not work due to the absence of an ortho-substituent group (Scheme 2a). Also, 2-halopyridin-3-amines 5 could not react with NaN₃ under the same condition (Scheme 2b).

Scheme 5. Application of the Synthesized Aminopyridyl Carboxylates in Synthesis of Nitrogen-Containing Heterocyclic Compounds.

However, the treatment of 6-azidonicotinic acid (7) provided 6-aminonicotinic acid 8 in moderate yield (52%) (Scheme 3a), and the result showed that aromatic azides could be transformed into the corresponding aromatic amines using our condition. 2-Azidonicotinic acid afforded 2-aminonicotinic acid in 80% yield (Scheme 3b), which indicated an ortho-substituent effect^[13] of the carboxyl group during transformation of azide to amine.

Thus, a possible mechanism was proposed for the formation of 2-aminonicotinic acid as described in Scheme 4 according to the results above. It involves the initial coordination of 2-halonicotinic acid 1 resulted to intermediate I in the presence of CuI and K₂CO₃ and followed by oxidative addition provides intermediate II. The exchange of X with azide leads to intermediate III which further undergone reductive elimination and afforded intermediate IV. The intermediate V was formed by coordination of IV with copper and further with ethanol

provides intermediate **VI**. The intermediate **VI** undergo oxidation-reduction reaction in the presence of base leading to formation of intermediate **VII** with leaving acetaldehyde and N₂ as previously investigated.^[14] Acidification of **VII** affords the 2-aminonicotinic acid **2** with release of copper.^[12]

Further, an attempt has been made to build some nitrogen-containing heterocyclic motifs by using the synthesized ortho-functionalized aminopyridines as the starting material (Scheme 5). Treatment of 2-aminonicotinic acid (**2a**) with acetic anhydride gave compound **10** which was further utilized to afford 2-methyl-3-phenylpyrido[2,3-d]pyrimidin-4(3H)-one **11** by the treatment of aniline in ethanol (Scheme 5).^[15]

Reaction of 2-aminonicotinamide **2g** with benzoyl chloride followed by the treatment with 5% NaOH aqueous solution gave 2-phenylpyrido[2,3-d]pyrimidin-4(3H)-one **13**.^[16] Reaction of 2-amino-6-chloronicotinamide **2h** with benzaldehyde in the presence of TFA furnished the corresponding dihydropyrido[2,3-d]pyrimidin-4(1H)-one **14** in 70% yield (Scheme 5).^[17]

Conclusions

We have developed a simple, unique and direct method for one-pot domino copper-catalyzed amination of halopyridyl carboxylates using sodium azide as the amino source without the aid of toxic oxidants and ligands. This copper-catalyzed strategy based on direct amination affords a complementary way to obtain functionalized aminopyridyl carboxylates i.e. 2-aminonicotinic acids and 2-aminonicotinamides in good yields. The domino methodology proceeds through Ullmann-type coupling of ortho-functionalized halopyridine with sodium azide followed by reduction with ethanol, and ethanol acted as solvent and reductive agent. These aminopyridyl carboxylates serve as novel synthons for the synthesis of highly functionalized pyrido[2,3-d]pyrimidin-4(1H)-ones. The present methodology is an important as it opens a new avenue to the assembly of aminopyridyl carboxylates, and should be helpful for exploring further usages of these unusual compounds.

Supporting Information Summary

The experimental details and characterization of products are provided in the supporting information.

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Conflict of Interest

The authors declare no conflict of interest.

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