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Microwave assisted solvent free amination of halo-(pyridine or pyrimidine) without transition metal catalyst

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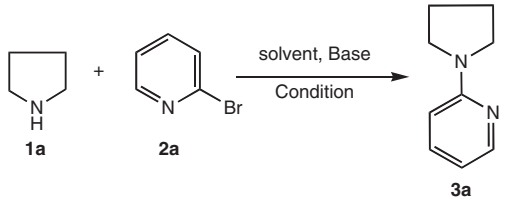
Abstract—A solvent free direct amination of halo-(pyridine or pyrimidine) has been developed in good to high yields under computer-controlled microwave irradiation without transition metal catalyst. This reaction is a solvent and metal free, useful method for coupling of halo-(pyridine or pyrimidine) with pyrrolidine and piperidine derivatives by nucleophilic aromatic substitution (S_NAr).

In the past few years, the utilization of microwave irradiation in chemical transformations has attracted considerable interest and is of significant importance in the search for green synthesis and sustainable chemistry. Microwave-mediated protocols have been widely applied for the formation of carbon–hetero atom and carbon–carbon bonds (aromatic substitution, cycloaddition, cyclization, and catalysis).[1] Many of these reactions have been demonstrated to result in higher yield and selectivity under microwave irradiation compared to conventional methods.[2]

Aminopyridines are commonly used as ligands (inorganic and organometallic chemistry),[3] fluorescent dyes[4] and the aminopyridine moiety is present in pharmaceuticals.[5] Aminolysis of halo-pyridines usually requires somewhat rigorous reaction conditions, for example, temperatures higher than 150 °C, pressure 6–8 kbar[6] and often the presence of catalysts (such as acids, Zn, Cu, Pd, or Ni complexes).[7] Highly negative activation volumes are reported for S_NAr reactions with secondary amines ($\sim -70\ cm^3/mol$) in certain cases.[8] In general the use of transition metal catalysts leads to generation of waste (hazards associated with metals) and solvent disposal. To the best of our knowledge, metal and solvent free amination of halo-(pyridine or pyrimidine) using microwave techniques has not been described.

Herein we report the results of a preliminary investigation into computer-controlled microwave[9] assisted amination of halo-(pyridine or pyrimidine) with piperidine and pyrrolidine derivatives. In contrast to most other C–N bond forming protocols the valuable features of our reported reaction includes (i) a shorter reaction time and high yields; (ii) the elimination of a transition-metal catalyst; and (iii) solvent free reaction approach to green chemistry.

As a starting point, we studied the microwave assisted coupling of 2-bromopyridine (**2a**) with pyrrolidine (**1a**) (Scheme 1). Table 1 shows the results of this optimization studies, which were conducted using a computer-controlled microwave equipped with an internal temperature/pressure monitoring probe. Initially, we tried K_2CO_3 (in water), or triethylamine (in toluene), but in both cases TLC analysis indicated the presence of unreacted 2-bromopyridine. Solvent free conditions



Scheme 1. Optimization studies.

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Table 1. Optimization studies[9]

Entry	**1a** (equiv)	**2a** (equiv)	Base	Solvent	Condition (temperature/time)	**3a** (Yield, %)
1	1	1	K_2CO_3	Water	120 °C/20 min	40
2	1	1	Et_3N	Toluene	120 °C/20 min	40
3	2.25	1	None	None	120 °C/20 min	92

using 2.15 equiv of pyrrolidine gave a better yield; additionally, this reaction was found to be insensitive to air or moisture, so one can use water as a co-solvent.

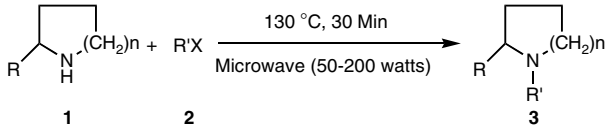
We further investigated the coupling reaction of different halo-(pyridines or pyrimidines) with several pyrrolidines and piperidines. From the results shown in Table 2,[10] it can be seen that the yields for the piperidine are less than the corresponding pyrrolidine. The reactions of 2- and 4-halopyridines give very good yield but as expected, 3-halopyridine is less reactive. The microwave assisted reaction of 3-bromopyridine with pyrrolidine in the presence of NaO-*t*-Bu afforded a mixture of 3- and 4-substituted products indicating that the reaction proceeds via benzyne like intermediates under these conditions.[2b,11]

In the case of entry 12, we used water as solvent because of the low solubility of 4-chloropyridinehydrochloride (**2e·HCl**) salt in piperidine. Best yields were obtained by heating at 130 °C for 30 min in most of the cases (Scheme 2). In the case of entries 16 and 17, we used NaOH as a base in water to give desired product. In the case of entry 16 we used the temperature 120 °C because

Table 2. Direct amination of halo-pyridine or -pyrimidine with amines[9,10]

Entry	Amine	Halo-pyridine or -pyrimidine	Product (%)[a]
1	Pyrrolidine (**1a**)	2-Bromopyridine (**2a**)	**3a** (92)
2	**1a**	2-Chloropyridine (**2b**)	**3a** (90)
3	**1a**	3-Bromopyridine (**2c**)	**3b** (<5)
4	**1a**	3-Chloropyridine (**2d**)	**3b** (<2)
5	**1a**	4-Chloropyridine·HCl (**2e·HCl**)	**3c** (85)
6	**1a**	**2e** (Free base)	**3c** (85)
7	**1a**	2-Chloropyrimidine (**2f**)	**3d** (83)
8	Piperidine (**1b**)	**2a**	**3e** (88)
9	**1b**	**2b**	**3e** (40)
10	**1b**	**2c**	**3f** (<1)
11	**1b**	**2d**	**3f** (<1)
12	**1b**	**2e·HCl**	**3g** (25), (85)[b]
13	**1b**	**2e** (free base)	**3g** (75)
14	**1b**	**2f**	**3h** (83)
15	**1c**[c]	**2a**	**3i** (65)
16	**1d·HI**[d]	**2a**	**3j** (60)
17	**1e·HI**[e]	**2a**	**3k** (55)

[a] Isolated yield.
[b] Water as a co-solvent.
[c] 2 equiv NaH in DMF.
[d] 2 equiv NaOH in water, 120 °C.
[e] 2 equiv NaOH in water, 150 °C.



1 **2** **3**

1a: R=H, H; n = 1
1b: R=H, H; n = 2
1c: R==O; n = 1
1d: R=H; $SnBu_3$, n = 1
1e: R=H; $SnBu_3$, n = 2

2a: 2-bromopyridine
2b: 2-chloropyridine
2c: 3-bromopyridine
2d: 3-chloropyridine
2e: 4-chloropyridine
2f: 2-chloropyrimidine

3a: R=H, H; n =1; R' = 2-pyridyl
3b: R=H, H; n =1; R' = 3-pyridyl
3c: R=H, H; n =1; R' = 4-pyridyl
3d: R=H, H; n =1; R' = 2-pyrimidyl
3e: R=H, H; n =2; R' = 2-pyridyl
3f: R=H, H; n =2; R' = 3-pyridyl
3g: R=H, H; n =2; R' = 4-pyridyl
3h: R=H, H; n =2; R' = 2-pyrimidyl
3i: R==O; n =1; R' = 2-pyridyl
3j: R=H, $SnBu_3$; n=1; R' = 2-pyridyl
3k: R=H, $SnBu_3$; n=2; R' = 2-pyridyl

Scheme 2.

the product decomposed at 130 °C when heated for 20 min. But in the case of entry 17 the reaction was very slow, so 150 °C for 30 min was required. We have found that this method is effective for making chiralstannyl compound in moderate yield.

The microwave assisted solvent free amination of the halo-(pyridine or pyrimidine) C–N bond can be achieved by this method without solvent and metal catalyst. This method has also shown potential in the synthesis of enantioenriched *N*-(2-pyridyl)-2-tributylstannyl-pyrrolidine (**3j**) or -piperidine (**3k**), which are the object of ongoing research.[12]

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9. In this work, we used a CEM Discover microwave apparatus, which is equipped with internal probe that monitors reaction temperature and pressure, and maintains the desired temperature by computer control. Even with water as a co-solvent the pressure did not exceed 50–60 psi at 130 °C.
10. Typical experimental procedure: *N*-(2-pyrimidine)pyrrolidine (**3h**). The pyrrolidine (2.0 mL, 1.72 g, 24.2 mmol), was added slowly in a 10 mL microwave vial containing 2-chloropyrimidine (0.50 g, 4.37 mmol). The vial was sealed by a crimped cap and was placed in a CEM Discover microwave apparatus. The initial power supplied was 150 W; once the temperature reached 130 °C, the instrument adjusted the power to maintain constant temperature. The total heating time of the reaction was 30 min. After completion of the reaction, the reaction mixture was cooled, diluted with dichloromethane (25 mL), washed with Na_2CO_3 solution, water, and finally with brine. The organic layer was dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude product was purified by column chromatography (EE/hexane, 20:80) to give 0.540 g (83%). ^{1}H NMR (270 MHz, $CDCl_3$):[7a] 8.26 (m, 2H), 6.40 (m, 1H), 3.52 (m, 4H), 1.94 (m, 4H). ^{13}C NMR (67 MHz, $CDCl_3$): δ 160.3, 157.7, 108.9, 46.6, 25.6.
11. During this experiment we found that by applying high power (250 W), the pressure rose out of instrument control, causing the crimped seal to fail. Therefore, we used 50 W for NaO^{t}Bu containing experiments.
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