Pergamon

Tetrahedron Letters 42 (2001) 3251–3254

TETRAHEDRON LETTERS

Amination of aryl halides using copper catalysis

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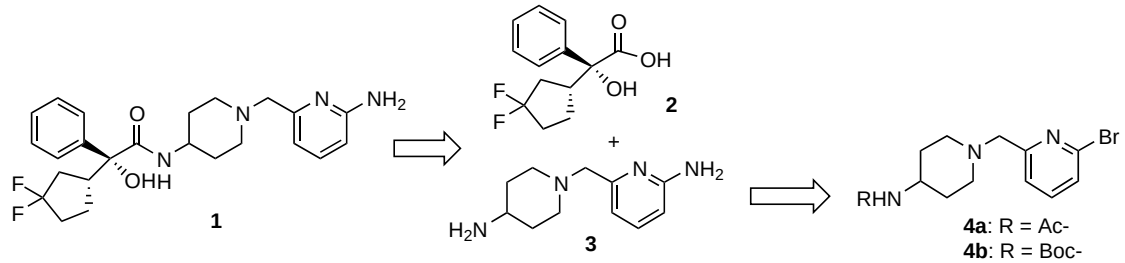
Received 16 February 2001; revised 12 March 2001; accepted 13 March 2001

Abstract—Bromopyridine **4** was converted into aminopyridine **5** under Cu_2O catalysis with an ethylene glycol solution of ammonia in excellent yield (90%). The amination reaction features low (0.5 mol%) catalyst loading, mild reaction temperature (80°C) and low reaction pressure (50 psi). This protocol is further studied in the amination of a variety of aryl halides. © 2001 Elsevier Science Ltd. All rights reserved.

Aryl amines in general, and aminopyridines in particular, are useful pharmacophores or intermediates[1] in several classes of drug candidates. Traditionally, the most common way to access these compounds is by amination of the corresponding aryl halides using ammonia or ammonium hydroxide as the nucleophile under high temperature and pressure. More recently, significant progress in palladium-catalyzed amination reactions has been achieved by Buchwald[2] and Hartwig[3], demonstrating mild conditions and tolerance for a wide range of functional groups. Subsequently, this methodology has seen useful applications[4] in the preparation of pharmaceuticals and other interesting compounds. However, the lone shortcoming of this palladium-catalyzed amination technology is that it does not provide direct entry to primary aryl amines, and additional step(s) are necessary to unmask latent or protected primary amine surrogates. Hence, a direct amination of aryl halides under mild conditions will complement the existing palladium-catalyzed aminations technology.

In our recent efforts toward the synthesis of muscarinic (M3) antagonist **1**,[5] the amine portion **3** could indeed be prepared by amination of the bromopyridine **4** using benzophenone imine as a primary amine surrogate following the Buchwald/Hartwig protocol. However, a more direct amination strategy was desirable.[5] Herein we report a direct, practical, and efficient conversion of **4** to the desired aminopyridine **3** using copper(I) oxide (Cu_2O) catalysis (Scheme 1).

Copper salts have been reported to catalyze the amination of halopyridines[6] and earlier examples have shown that the amination generally initiates at temperatures between 150°–250°C with either aqueous ammonium hydroxide or anhydrous ammonia.[7,8] More recently[9], the amination of an aryl bromide was reported using liquid ammonia as solvent and Cu/CuCl couple to induce the transformation. Although a mild temperature (70°C) was used and a good yield was achieved in the reaction, high pressure and a long reaction time were associated with this process and 75 mol% Cu loading was required. In our studies, we were constrained by safety concerns and scale-up issues and thus required considerably milder reaction conditions.



Scheme 1. Synthesis of M3-antagonist **1**.

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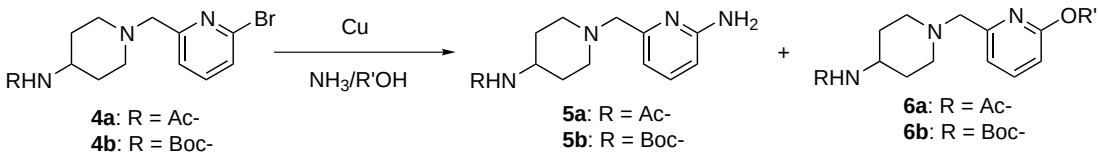
PII: S0040-4039(01)00458-0

Table 1. Amination of bromopyridine **4a** in different solvents[a]

Entry	Cu	Solvents	Conversion (%)	**5a**:**6a**	Assayed yield (%)
1	$CuCl_2$	H_2O	100	78:22	65
2	$CuCl_2$	MeOH	<10	83:17	–
3	Cu/CuCl	MeOH	100	83:17	70
4	Cu/CuCl	EtOH	<10	–	–
5	$CuCl_2$	*i*PrOH	<5	–	–
6	$CuCl_2$	ACN	0	–	–
7	$CuCl_2$	NMP	50	100:0	–
8	$CuCl_2$	DMF	<2	–	–
9	$CuCl_2$	THF	<2	–	–
10[b]	Cu/CuCl	Ethylene glycol	100	94:6	91
11[b]	Cu_2O	Ethylene glycol	100	94:6	91

[a] General procedure for the amination reactions: In a 25 mL stainless steel vessel were mixed 1.0 g bromopyridine **5a**, 10 mL solvent, 2 mL liquid ammonia and 5.0 mg Cu catalyst. The vessel was sealed and heated to 100°C overnight. Reaction products were analyzed by HPLC.
[b] In the absence of the copper catalysts, under otherwise identical conditions, no conversion to the product was observed.



4a: R = Ac-
4b: R = Boc-

5a: R = Ac-
5b: R = Boc-

6a: R = Ac-
6b: R = Boc-

(1)

Initially, we were pleased to find that the amination of **4a** (Eq. (1)) proceeded smoothly in aqueous ammonium hydroxide under $CuCl_2$ catalysis to afford **5a** in 65% yield. The major by-product was pyridone **6a** from competing hydroxide attack on the aryl halide. To optimize the amination reaction, a variety of solvent systems as well as several forms of copper catalyst were investigated (at 100°C in a closed vessel) and the results are summarized in Table 1.

The experimental data shows that the amination reaction worked best in aqueous or alcoholic solvents within a reaction temperature range of 70–100°C under concentration and catalyst loadings described in Table 1. In alcoholic solvents, a significant amount of alkoxy pyridine **6a** was also formed in the reaction. In an attempt to avoid this by-product, several polar, aprotic solvents, including THF, acetonitrile, 1-methyl-2-pyrrolidinoe (NMP) and DMF (entries 6–9) were studied. In THF, acetonitrile and DMF, very low conversion to products was observed while moderate (50%) conversion was seen in NMP. The latter reaction (NMP) proceeded cleanly; however, the pressure generated during the reaction was too high and it could not be scaled up. The low conversion and high reaction pressure are attributed to the poor solubility of ammonia in these solvent systems. The use of MeOH (entries 2 and 3) instead of water as solvent improved the selectivity slightly and the combination of Cu/CuCl was demonstrated to be more effective than $CuCl_2$ as the catalyst. Interestingly, in EtOH and *i*PrOH (entries 4, and 5), the amination reaction only proceeded with low conversion and the pressure inside the reaction vessel during the reaction was much higher than with water or MeOH.

Ethylene glycol (entries 10, and 11) was found to be the best solvent to date for the amination reaction; the reaction proceeded to completion affording aminopyridine **5a** in 91% yield and the product ratio of **5a**:**6a** was 16:1. Both Cu_2O and Cu/CuCl promote the transformation. Most importantly, the solubility of ammonia in ethylene glycol even at high temperature, is sufficient to allow the reaction to proceed at an appreciable rate with moderate pressure build up. Cu_2O is generally preferred over Cu/CuCl as the catalyst of choice due to the practical simplicity of operation and cleanliness of the reaction profile. The reaction in ethylene glycol was further studied in order to look at and hence optimize the correlation between the N versus O selectivity and the reaction pressure. The results are summarized in Table 2. A saturated solution of ammonia in ethylene glycol was prepared at 10°C and was determined to be 8 M by titration. At this concentration, the pressure generated during the reaction at 100°C was ca 100 psi. A small decrease in the ammonia concentration only modestly reduced the selectivity and yield of the reaction while the pressure in the reaction vessel was reduced substantially. Even with the ammonia at 2 M concentration, the reaction proceeded smoothly at low pressure, affording the desired amination product **5a** in respectable yield. Thus, the transformation has been achieved in good yield and selectivity under pressures which can easily be implemented in the laboratory or at pilot scale. It is also worth noting that

Table 2. Study of amination reaction of **4a** under different pressures

Entry	Conc. of NH_3	**5a**:**6a**	Pressure (psi)	Assay yield (%)
1	8 M	94:6	100	91
2	6 M	92:8	50	89
3	4 M	91:9	30	88
4	2 M	89:11	20	86

Table 3. Applications of amination protocol[a]

Entry	Substrate	Product	Yield (%)	Selectivity
1	2-Bromopyridine	2-Aminopyridine	65	80:20
2	2-Bromo-6-picoline	2-Amino-6-picoline	70	86:14
3	2-Bromo-6-methoxypyridine	2-Amino-6-methoxypyridine	75	92:8
4	2-Bromo-5-nitropyridine	2-Amino-5-nitropyridine	99	100:0
5	2-Chloropyridine	2-Aminopyridine	0	N/A
6	2-Chloro-5-nitropyridine	2-Amino-5-nitropyridine	85	100:0
7	3-Bromopyridine	3-Aminopyridine	85	95:5
8	4-Bromopyridine	4-Aminopyridine	81	97:3
9[b]	2,5-Dibromopyridine	2-Amino-5-bromopyridine	62	91:9
10	4′-Bromoacetophenone	4′-Aminoacetophenone	65	91:9
11	1-Bromo-4-trifluoromethylbenzene	4-Trifluromethylaniline	72	75:25
12	Iodobenzene	Aniline	74	86:14
13	2-Bromothiazole	2-Aminothiazole	94	100:0
14	3-Bromoquinoline	3-Aminoquinoline	84	91:9

[a] Reaction conditions: in a stainless steel vessel were mixed 1.0 g aryl bromide, 5.0 mg Cu_2O, and 10 mL 8 M NH_3 solution in ethylene glycol. The vessel was sealed and the reaction mixture heated at 80°C for 16 h

[b] The amination of 2,5-dibromopyridine was done at 60°C for 40 h to give mono-amination product. Under the normal conditions, the major product is 2,5-diaminopyridine.

the catalyst (Cu_2O) loading can be as low as 0.5 mol%, which makes the process very environmentally friendly.

A typical experimental procedure is as follows: A 1 liter pressure tested autoclave was charged with Cu_2O (0.25 g), then 50 g of bromide **4b** as a slurry in ethylene glycol (450 mL). The mixture was cooled to 0°C and liquid ammonia (75 g) was added over 30 min. The temperature was kept below 10°C during the addition. The autoclave was then sealed and the reaction mixture was heated to 80°C for 16 h. The pressure in the autoclave during the reaction is about 50 psi. The reaction mixture was cooled to 10°C and drained into a 3 liter flask for workup. The reaction mixture was adjusted to pH 10.5 with 2 M H_2SO_4 and extracted with 900 mL EtOAc. The extract was solvent switched to *i*PrOH (total volume 900 mL), then a solution of PTSA monohydrate (53.92 g) in 600 mL *i*PrOH was added over 2 h at 15°C. The slurry was stirred for 4 h and the solid collected: 74.7 g (85%) product (99.9% purity as determined by HPLC analysis) as its bis-TsOH salt. It is noteworthy that the Boc protecting group in **4b** survived the amination conditions.

The success of this amination reaction protocol prompted us to explore the scope of the amination conditions. The results are summarized in Table 3.

As shown in Table 3, a series of 2-bromopyridine substrates (entries 1–4, and 9) were investigated. With an electron withdrawing substituent, the amination reaction proceeded with better yield and selectivity. Interestingly, while piperidine derivative **4** is similar electronically to 2-bromopyridine and 2-bromo-6-picoline (entries 1 and 2), the amination of **4** gave much higher yield and selectivity. Our hypothesis is that the bidentate complexation of **4** with Cu facilitates the delivery and insertion of Cu to the carbon–bromine bond, resulting in improved selectivity. The good selectivity for the amination of 2-bromo-6-methoxypyridine (entry 3) also relies significantly on complexation, as opposed to an electronic factor. With careful control of reaction conditions, selective mono-amination is achieved (entry 9) and the amination takes place preferentially at the 2-position rather than the 5-position of the pyridine ring. Aryl chlorides generally are inert toward the amination conditions (entry 5). However, with proper activation they can be converted to the desired product under the same reaction conditions (entry 6) in good yield. For bromobenzene derivatives with electron-withdrawing substituents (entries 10 and 11), the reaction proceeds smoothly while the ketone functionality is compatible with the amination conditions. Iodobenzene (entry 12) was converted successfully to aniline in 74% yield. Several other heterocyclic bromides can also be converted to the corresponding amines with good N versus O ratios and useful yields (entries 13 and 14).

In summary, we have found general, practical amination reaction conditions that use Cu catalysts in a solution of ammonia in ethylene glycol to convert aryl halides into aryl amines in good yields and selectivities.

Acknowledgements

We thank Mr. A. L. Houck and Mr. C. Bazaral for their support during high pressure laboratories and Dr. T. Wang, Ms. J. T. Wu and Dr. X. Jia for their expertise in metal analysis. We also want to thank Dr. J. Z. Song and Dr. D. Tschaen for helpful suggestions and we acknowledge the continuing modification and development work by Drs. T. Wada and T. Iida of Banyu Pharmaceutical Company, Japan.

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