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A ligand-free and base-free copper catalyzed reaction: arylation of ammonia and primary amines as their acetate salts

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ABSTRACT

A ligand-free, base-free copper catalyzed arylation of ammonia and primary amines as their corresponding acetate salts are established. The Carboxylate group is believed to be catalyzing the arylation of ammonia. This reaction is specific for primary amines.

Metal catalyzed reactions of amines are very well documented in the literature[1] which are part of industrially and academically important strategies. Ammonia, a primary source of nitrogen is an abundant and inexpensive source of nitrogen.[2] Substituted ammonia has great importance in pharmaceutical industry and other branches of industry.[3] Hence, there is great interest in using ammonia as a reagent for transformations leading to alkyl/aryl amines. Generally, reactions that use ammonia employ high pressures for successful completion of the reaction. Recently, several catalysts have been designed to overcome this problem.[4] Though, copper and palladium catalyzed amination are very well documented in the literature, their utility in arylation of ammonia is reported recently.[5] Due to the continued importance of arylation of ammonia, several modifications and improvisations in the copper and palladium catalyzed arylation of amines have been published over a period of several decades. In copper catalyzed reactions, generally copper or copper salts like CuI,[6] $Cu(OAc)_2$,-CuBr/Cu/Cu_2O[7,8] have been used as catalyst in the presence of inorganic bases such as potassium phosphate,[6a] potassium carbonate,[9] or cesium carbonate.[5b] Normally, ligands such as aminoacids,[6a] diamines,[7,8] or thio ligands[9b] have been used as catalyst. However, palladium catalyzed reactions have been carried out in the presence of phosphine ligands[5c] and bases such as sodium *tert*-butoxide, potassium carbonate, potassium phosphate etc. In these transformations solvents such as DMF,[5b] DMSO,[6a] water, alcohols[10] etc. have been used. Although these reactions work very well for organic amines, they are not successful for the arylation of ammonia. Recently, Taillefer and coworkers documented the utility of aqueous ammonia,[5b] which provides a new direction for the copper catalyzed arylation of ammonia.[5b] In this CuI catalyzed reaction, diketones are used as the ligand in the presence of cesium carbonate and is selective for aromatic bromides and iodides to furnish the corresponding anilines in moderate yield. Another recent paper by Stradiotto[5c] presents an interesting improvisation of arylation of ammonia using palladium catalyst. Unlike copper catalyzed reactions, palladium catalyzed reactions work well for many aromatic chloro compounds. Further, Wan[11] and coworkers reported an interesting reaction, wherein copper oxide and *N_2,N_2*-diisopropyloxalohydrazide have been successfully used for the arylation of ammonia. Apart from these literature precedence, the use of ammonia as a reagent has also been reviewed recently.[12] There are several attempts to directly convert aromatic halides to anilines using many reagents. For example, trifluoroacetamide,[13] sodium hexamethyldisilazane, and[14] $TMSN_3$-CuF_2[15] have been used as a source of ammonia for the direct arylation of aromatic halides. Despite the success of these initial reports, there are a number of limitations concerning the scope and utility of this metal catalyzed cross coupling of aryl halides with ammonia.

Copper catalyzed reaction of aniline with 2-halobenzoic acid under reflux condition was first reported by Ullmann almost a

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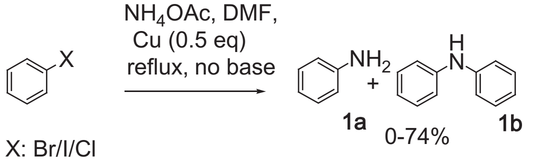
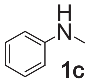
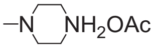
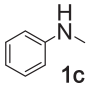
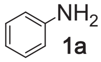
Table 1
Alkylation of ammonium salts in the absence of base



Entry[a]	Amine source[b]	Product/s	Yield[c]
1	NH_4OAc	**1a:1b**(2:1)	74
2	NH_4OAc	**1a:1b**(1:2)	57[d]
3	NH_4OAc	**1a:1b**(1.6:1)	70[e]
4	NH_4OAc	**1a:1b**(1:8)	54[f]
5	NH_4OBz	**1a:1b** (1.3:1)	35
6	CH_3NH_3OAc	 **1c**	55
7	$(CH_3)_2NH_2OAc$	No reaction	0
8		No reaction	0
9	NH_2HPO_4	No reaction	0
10	NH_4Cl	No reaction	0
11	NH_4OAc	**1a:1b** (2.2:1)	58
12	NH_4OBz	**1a:1b** (0.8:1)	45
13	CH_3NH_3OAc	 **1c**	60
14	$(CH_3)\ _2NH_2OAc$	No reaction	0
15	NH_4OAc	 **1a**	Trace

[a] Entries 1–10 with bromobenzene, entries 11–14 with Iodobenzene, entry 15 with chlorobenzene.

[b] Along with amine source, 0.5 at equiv of copper, DMF used as solvent. Ratio of substrate/ammonium acetate (1:2).

[c] Yield refers to isolated yield.

[d] C_6H_5Br/NH_4OAc (1:1).

[e] C_6H_5Br/NH_4OAc (1:5).

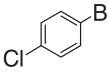
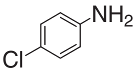
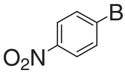
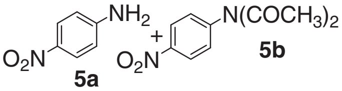
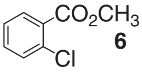
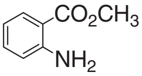
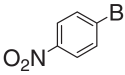
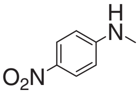
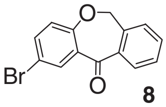
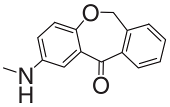
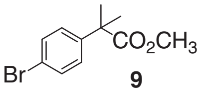
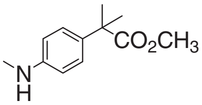
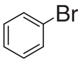
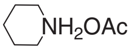
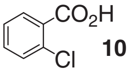
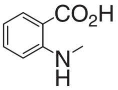
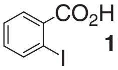
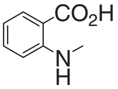
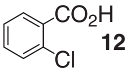
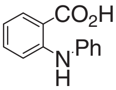
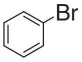
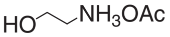
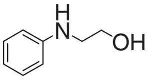
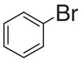
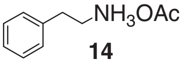
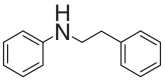
[f] C_6H_5Br/NH_4OAc (5:1).

century ago.[1b] This reaction requires harsh conditions and is usually catalyzed by copper or its salts in the presence of inorganic bases. Several ligands have been found to accelerate this reaction.[6–8] A recent report on the mild Ullmann reaction by Pellon[16] attracted our attention, wherein 2-chlorobenzoic acid is reacted with aqueous methylamine in the presence of copper catalyst and K_2CO_3 to furnish *N*-methlyanthranilic acid in good yield. This facile copper catalyzed amination of 2-chlorobenzoic acid cannot be explained by the electron withdrawing effect of the carboxylic acid group alone. This prompted us to think whether the carboxylic group present in the molecule is catalyzing the reaction. If this is true, such reaction should also be catalyzed by external carboxylates such as acetates/benzoates. To test this hypothesis, we decided to use the ammonium salt of carboxylic acid, wherein the carboxylic group acts as ligand and the amine counterpart as amine source. The results are presented in Table 1. When bromobenzene (1 equiv) is reacted with ammonium acetate (2 equiv), copper (0.5 at equiv), and DMF, the reaction proceeded smoothly to afford aniline as the major product and diphenylamine as the minor product (Table 1, entry 1). Varying the ratio of substrate to ammonium acetate did not give exclusive aniline/diphenylamine (Table 1, entries 2–4). However, with an excess of bromobenzene (5 equiv) diphenylamine is obtained as the major product (Table 1, entry 4) and with an excess of ammonium acetate (5 equiv), aniline is obtained as the major product. Similarly, the reaction of bromobenzene with ammonium benzoate also furnished moderate yield of aniline (Table 1, entry 5). Further, it was noticed that methyl ammonium acetate reacted smoothly with bromobenzene to give *N*-methyl aniline in moderate yield (55%, Table 1, entry 6). However, secondary amine salts such as dimethylamine acetate or *N*-methyl piperazenium acetate (Scheme 1, Table 1, entries 7–8) did not react with bromobenzene under the reaction conditions. Interestingly, in these experiments neither external base nor external ligand has been used for the reaction. Reaction of iodobenzene with ammonium acetate, ammonium benzoate, and methyl ammonium acetate gave comparable results (Table 1, entries 11–13). Under the similar condition chlorobenzene almost did not react (Table 1, entry 15). To find out whether the reaction is catalyzed by carboxyl moiety, the reaction was carried with bromobenzene, diammonium phosphate, and ammonium chloride (Table 1, entries 9, 10). As expected, there was no reaction under identical reaction conditions. These results clearly indicate that the carboxylic acid group is catalyzing the arylation of amines.

To study the scope of the reaction, a variety of aromatic halides[17] were reacted with ammonium acetate/methyl ammonium acetate to furnish the corresponding aniline or *N*-methylaniline (Table 2, entries 1–5) in good to moderate yields. 4-Bromo chlorobenzene (Table 2, entry 1) reacted with ammonium acetate, to furnish 4-chloro aniline in moderate yield (Table 2, entry 1). 4-Nitro bromobenzene gave a mixture of 4-nitro aniline and corresponding *N*,*N*-diacetate (Table 2, entry 2). 2-Chloro methyl benzoate furnished methyl anthranilate in moderate yield (Table 2, entry 3). 4-Nitro bromobenzene reacted with methyl ammonium acetate to give 4-nitro-*N*-methyl aniline in good yield. Similarly 3-bromo doxepinone and 4-bromo-2,2-dimethyl phenyl acetic acid methyl ester furnished the corresponding *N*-methyl anilines in moderate yield (Table 2, entries 5–6). However, piperidine acetate failed to react under the present reaction condition (Table 2, entry 7). Further, for substrates having internal carboxyl group, corresponding amine salts were prepared in situ and reacted with copper in DMF. Thus, 2-halo benzoic acid is converted to their methylamine salt and then reacted with copper in DMF to afford *N*-methyl anthranilic acid in good yield (Table 2, entries 8–9). In the entries 8–9, no external carboxylate was used. As a control, these substrates were also reacted with 2 equiv of external ammonium/methyl ammonium acetate to see whether it has any effect on yield. However, we obtained comparable yields in these experiments too (see the yield in the bracket). Further, this strategy has been extended for other primary amines such as aniline (Table 2, entry 10), amino ethanol (Table 2, entry 11), and phenyl ethylamine(Table 2, entry 12). When aniline is reacted with 2-chloro benzoic acid, a moderate yield of *N*-phenyl anthranilic acid is obtained (Table 2, entry 10). When 2-amino ethanol acetate was reacted with bromobenzene under similar condition, *N*-phenylamino ethanol is obtained as a major product (Table 2, entry 11). Similarly, phenyl ethyl ammonium acetate furnished *N*-phenyl phenyl ethylamine in moderate yield (Table 2, entry 12). From these experiments we have shown that it is possible to carry out ligand-free, base-free copper catalyzed arylation of ammonia and primary amines as their corresponding carboxylic acid salts.

In a nutshell, we have shown that ammonia and primary amines can be arylated by converting them into their acetate salts in the presence of copper as catalyst. To the best of our knowledge, this is the first example of arylation of ammonia using copper catalyst under ligand-free and base-free conditions. In these reactions, carboxyl anion is believed to be acting as ligand and also as a base for the reaction. This reaction is specific for primary amines. Secondary amines fail to react under the reaction condition. Efforts are underway to explore the mechanism of the reaction.

Table 2
Alkylation of ammonium salts in the absence of base

Entry	Substrates	Amine source[a]	Products	Yield[b]
1	 **4**	NH_4OAc	 **4a**	40
2	 **5**	NH_4OAc	 **5a** **5b**	73 (6:4) **5a:b**
3	 **6**	NH_4OAc	 **6a**	42
4	 **7**	CH_3NH_3OAc	 **7a**	78
5	 **8**	CH_3NH_3OAc	 **8a**	24
6	 **9**	CH_3NH_3OAc	 **9a**	55
7	 **1**		No reaction	–
8	 **10**	CH_3NH_2	 **10a**	74(65)[c]
9	 **11**	CH_3NH_2	 **11a**	79(74)[c]
10	 **12**	$C_6H_5NH_2$	 **12a**	60(56)[c]
11	 **1**		 **13a**	46
12	 **1**	 **14**	 **14a**	35

[a] Along with amine source, 0.5 at equiv of copper, DMF used as solvent.

[b] Yield refers to isolated yield.

[c] Substrate ammonium salts were made before the reaction. Yield in the bracket with 2 equiv of external ammonium acetate for entry 8 and 9 and aniline acetate for entry 10.

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Supplementary data

Supplementary data (spectral data and ^1H and ^{13}C NMR of amines and corresponding products) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.07.048.

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17. *General procedure for Aryl amines – with ammonium acetate:* A mixture of iodobenzene (5 g, 24.5 mmol), ammonium acetate (3.778 g, 49 mmol), Cu powder (0.778 g), and DMF (15 mL) was heated at reflux in a 100 mL round bottom flask for 9 h. The reaction mixture was cooled to rt, dichloromethane (200 mL) was added and then, filtered to remove Cu powder. The filtrate was washed with water (200 mL) and dried over sodium sulphate and concentrated under reduced pressure. Crude sample thus obtained was purified by column chromatography (silica gel, ethyl acetate/petroleum ether, 2:98) to give aniline and diphenylamine (58%, **1a**:**1b**, 2.2:1). *General procedure for aryl amines – with methylamine acetate*: A mixture of bromobenzene (10 g, 63.6 mmol), acetic acid (5.76 g, 96 mmol), methylamine (3.0 g-100% basis, 95.5 mmol) of 40% solution, and Cu powder (2.01 g) followed by DMF (20 mL) was heated at reflux in a 100 mL round bottom flask for 9 h. The mixture was cooled to rt, dichloromethane (200 mL) was added and then filtered to remove Cu powder. The filtrate was washed with water (200 mL) and dried over sodium sulphate and concentrated under reduced pressure. Crude sample thus obtained was purified by column chromatography (silica gel, ethyl acetate/petroleum ether, 5:95) to give *N*-methyl aniline (3.74 g, 55%, **1c**). *Procedure for N-methyl anthranillic acid:* A mixture of *o*-chloro benzoic acid (5.0 g, 31.9 mmol), methylamine (1.98 g, 64 mmol, calculated to 100%) of 40% solution and Cu powder (1.01 g) followed by DMF (15 mL) was heated to reflux in a 100 mL round bottom flask for 9 h. Cooled to RT, added dichloromethane (200 mL), filtered to remove Cu powder. Filtrate was washed with water (200 mL) and dried over sodium sulphate and concentrated under reduced pressure. Crude sample thus obtained was purified by column chromatography (silica gel, ethyl acetate/petroleum ether, 5:95) to give the product *N*-methyl anthranillic acid (3.62 g, 74%, **10a**).