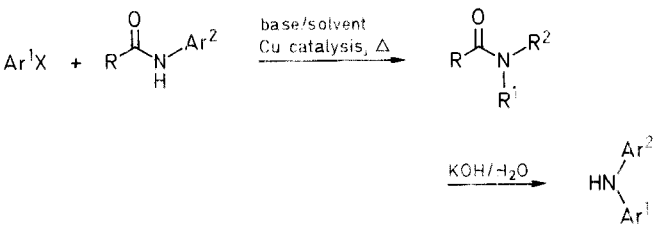
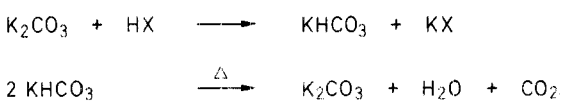


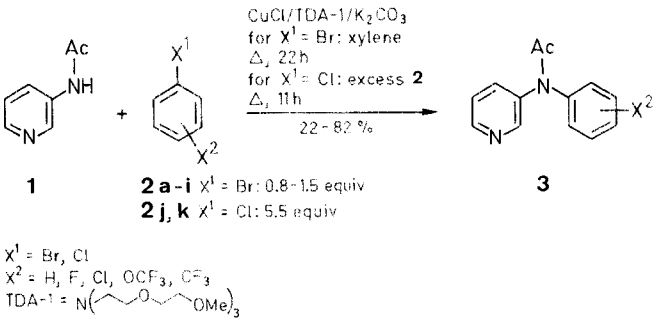
Aromatic halides (often iodides, less commonly bromides) are used as reaction solvents[7] or in an aprotic polar solvent.[8] Most authors also stress that it is essential to use strictly anhydrous reagents, particularly potassium carbonate (the base commonly used in the Goldberg reaction). In fact, these precautions are unnecessary since water is formed during the reaction by the thermal decomposition of potassium hydrogen carbonate:

The conversion of the aromatic halide can be followed by measuring the amount of water produced which is separated by azeotropic distillation.



This observation, together with the outstanding solubilizing effect of tris(3,6-dioxaheptyl)amine (TDA-1) on copper salts,[10] has enabled us to simplify the operating conditions. In this way, the catalytic copper species which is essential for the reaction to proceed is available in the reaction medium at a higher concentration as compared to the usual heterogeneous system. The removal of water permits this copper species to survive, and diminishes the amount of copper salt required to complete the reaction.

We have applied these conditions to the synthesis of 3-(*N*-acetyl-*N*-arylamino)pyridines **3** in good yields from substituted bromobenzenes **2a–i** and 3-acetylaminopyridine **(1)**. The use of the arylating agent in quasi-stoichiometric quantities (Table, entries 1–9) is of special interest, as the work-up of the reaction mixture is considerably simplified, especially when high-boiling aryl halides are used.



The reaction was also applied to chloroarenes **2j,k** (X^1 = Cl), excess **2** being used as reaction solvent (Table, entries 10–11). The general utility of this method is demonstrated by an inverse preparation of product **3l** using 3-bromopyridine **(4)** as agent for the arylation of the substituted acetanilide **5** (example 12).

The synthesis of related structures such as *N*,*N*-diphenylamides, has also been performed in our laboratory by this method.

An Improvement of the *N*-Arylation of Amides; Application to the Synthesis of Substituted 3-(*N*-Acetyl-*N*-phenylamino)-pyridines

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In the presence of catalytic quantities of tris(3,6-dioxaheptyl)amine (TDA-1) and of copper(I) chloride, with azeotropic separation of the reaction water, the *N*-arylation of carboxamides has been simplified and can now be performed under rather mild conditions, using substituted bromobenzenes as arylating agents in quasi-stoichiometric quantities in boiling xylene, or using chlorobenzenes as arylating agents and as reaction solvents at reflux. The general applicability of the reaction to the preparation of various diarylamines is demonstrated.

Copper as well as its salts and oxides are known for catalyzing the substitution of aromatic halogen by various nucleophiles.[1] For nitrogen nucleophiles, two related reactions are known:

- the Ullmann amine arylation,[2] and its variant,
- the Goldberg amide arylation.[3]

The latter readily produces (after hydrolysis) various diarylamines, some of which are more difficult to obtain by other methods.[4]

However, the reaction generally requires the use of the stoichiometric quantity of a copper derivative,[5] often copper(I) iodide or a copper catalyst requiring special preparation, and an acid neutralization system.[6]

Table. 3-(*N*-Acetyl-*N*-arylamino)pyridines **3** Prepared

Entry	Starting Materials	X^1 in **2**	X^2 in **2**, **3**	Product	Yield[a] (%)	mp (°C) and/or bp (°C)/Torr[b]	Molecular Formula[c] or Lit. mp (°C)
1	**1** + **2a**	Br	H	**3a**	74	85 (*i*-Pr_2O)	47.5–50[11]
2	**1** + **2b**	Br	4-F	**3b**	66	87 (*i*-Pr_2O)	$C_{13}H_{11}FN_2O$ (230.2)
3	**1** + **2c**	Br	4-OCF_3	**3c**	53	oil[d]	$C_{14}H_{11}F_3N_2O_2$ (296.3)
4	**1** + **2d**	Br	2-CF_3	**3d**	22	78 (*i*-Pr_2O)	$C_{14}H_{11}F_3N_2O$ (280.3)
5	**1** + **2e**	Br	3-CF_3	**3e**	69	85 (*i*-Pr_2O) 170/0.03	$C_{14}H_{11}F_3N_2O$ (280.3)
6	**1** + **2f**	Br	4-CF_3	**3f**	73	165/0.04	$C_{14}H_{11}F_3N_2O$ (280.3)
7	**1** + **2g**	Br	4-Cl	**3g**	73	67 (*i*-Pr_2O)	$C_{13}H_{11}ClN_2O$ (246.7)
8	**1** + **2h**	Br	3-F	**3h**	68	50 (*i*-Pr_2O/Et_2O) 155/0.03	$C_{13}H_{11}FN_2O$ (230.2)
9	**1** + **2i**	Br	2-F	**3i**	44	76 (*i*-Pr_2O)	$C_{13}H_{11}FN_2O$ (230.2)
10	**1** + **2j**	Cl	3-Cl	**3j**	56	67 (*i*-P_2O/Et_2O) 167/0.04	$C_{13}H_{11}ClN_2O$ (246.7)
11	**1** + **2k**	Cl	2-Cl	**3k**	82	64 (*i*-Pr_2O/Et_2O) 165/0.03	$C_{13}H_{11}ClN_2O$ (246.7)
12	**4** + **5**	–	3,4-di-Cl	**3l**	62	61 (*i*-Pr_2O/Et_2O)	$C_{13}H_{11}Cl_2N_2O$ (282.2)
13	**1** + **2m**	Br	2,3,4,5,6-penta-F	–[e]			

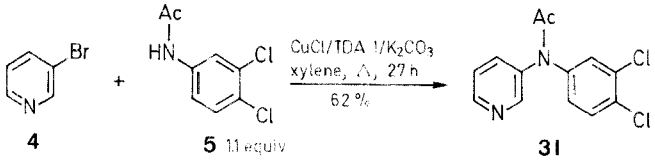
[a] Yield of isolated pure product (purified by distillation, chromatography, and/or recrystallization); impurities were not detectable by ^{1}H-NMR spectrometry. The yields have not been optimized.

[b] Uncorrected. Melting points were determined with a Mettler FP 61 apparatus.

[c] Satisfactory microanalyses: C ±0.36, H ±0.13, N ±0.17.

[d] Purified by column chromatography on silica gel using, consecutively, toluene and EtOAc/hexane (1:1) as eluents.

[e] Reaction failed.



Under our reaction conditions, the reactivities of aromatic Br- and Cl-atoms are clearly different and the stoichiometry of the reagents prevents further reactions which, for the arylation with bromochlorobenzenes, have been reported[9] to lead to the formation of complex mixtures. Condensation with bromopentafluorobenzene failed (Table, entry 13).

Another advantage of our method is that the products can be simply purified by crystallization or distillation.

All reagents were of commercial quality. TDA-1 and CuCl were purchased from Prolabo. 4-Bromo(trifluoromethoxy)benzene was obtained from Rhone Poulenc Fine Chemicals Division, 3-aminopyridine and all other bromoarenes were purchased from Janssen. 3-Acetylaminopyridine (**1**) was prepared in 93% yield (recrystallized product) by heating 3-aminopyridine and Ac_2O in boiling toluene. ^{1}H-NMR spectra were recorded on a Bruker AC 250 MHz spectrometer.

3-[*N*-Acetyl-*N*-(4-fluorophenyl)amino]pyridine (3b); Typical Procedure:
A mixture of 3-acetylaminopyridine (**1**; 95 g, 700 mmol), 1-bromo-4-fluorobenzene (**2b**; 100 g, 570 mmol), K_2CO_3 (193 g, 1.4 mol), CuCl (7 g, 70 mmol), and TDA-1 (5 g, 15 mmol) in xylene (400 mL) is heated to reflux for 22 h with azeotropic removal of the water formed. The volume of H_2O recovered is 5.5 mL. The mixture is filtered and the residue on the filter is washed with toluene (200 mL). The organic phase is washed with H_2O (2 × 300 mL), diluted aqueous NH_3 (200 mL), and then H_2O until neutral. The organic phase is concentrated to give **3b** as a beige solid which is recrystallized from *i*-Pr_2O; yield: 86 g (66%); mp 87 °C.

^{1}H-NMR ($CDCl_3$ + TFAD/TMS): δ = 2.10 (s, 3H); 7.24–7.40 (m, 4H); 7.86 (dd, 1H, J = 8.7, 5.6 Hz); 8.29 (dd, 1H, J = 8.7, 2.5 Hz); 8.65 (d, 1H, J = 5.6 Hz); 9.11 (d, 1H, J = 2.5 Hz).

3-[*N*-Acetyl-*N*-(2-chlorophenyl)amino]pyridine (3k):
A mixture of 3-acetylaminopyridine (**1**; 54.4 g, 400 mmol), K_2CO_3 (110 g, 800 mmol), CuCl (4 g, 40 mmol), and TDA-1 (3.9 g, 12 mmol) in *o*-dichlorobenzene (250 mL, 2.2 mol) is heated to reflux with azeotropic removal of the water formed.

The progress of the reaction is monitored by GLC. After heating for 11 h, the mixture is evaporated under reduced pressure, diluted with toluene (300 mL), filtered, and concentrated. The oily residue is vacuum-distilled to give **3k** as a pale yellow oil which solidifies; yield: 81.3 g (82%); bp 165 °C/0.03 Torr; mp 64 °C (*i*-Pr_2O/Et_2O).

^{1}H-NMR ($CDCl_3$ + TFAD/TMS): δ = 2.17 (s, 3H); 7.50–7.69 (m, 4H); 7.97 (dd, 1H, J = 8.7, 5.7 Hz); 8.37 (dd, 1H, J = 8.7, 2.5 Hz); 8.71 (d, 1H, J = 5.7 Hz); 9.13 (d, 1H, J = 2.5 Hz).

3-[*N*-Acetyl-*N*-(3,4-dichlorophenyl)amino]pyridine (3l):
A mixture of *N*-(3,4-dichlorophenyl)acetamide (**5**; 81.6 g, 400 mmol), 3-bromopyridine (**4**; 69.5 g, 440 mmol), K_2CO_3 (110 g, 800 mmol), CuCl (1 g, 10 mmol), and TDA-1 (5 g, 15 mmol) in xylene (300 mL) is heated to reflux for 27 h, during which time further portions of CuCl (3 × 1 g, 3 × 10 mmol) are added at regular intervals. The volume of H_2O recovered is 5 mL. The mixture is diluted with $CHCl_3$ (200 mL), filtered, washed successively with H_2O (2 × 300 mL), diluted aqueous NH_3 (200 mL), and then H_2O until neutral. The dark residue (100 g) obtained by evaporation of solvents is dissolved in Et_2O (500 mL) and this solution is stirred with conc. aqueous HCl (50 mL) and acetone (100 mL). The resultant cream-colored crystals (78 g) are isolated by suction and redissolved in H_2O (700 mL). This solution is neutralized with $NaHCO_3$. Extraction with EtOAc (2 × 250 mL), drying (Na_2SO_4), and evaporation of the solvent gives **3l** as a solid which is recrystallized from *i*-Pr_2O/Et_2O; yield: 70 g (62%); mp 61 °C.

^{1}H-NMR ($CDCl_3$ + TFAD/TMS): δ = 2.23 (s, 3H), 7.30 (dd, 1H, J = 8.5, 2.5 Hz); 7.54 (d, 1H, J = 2.5 Hz); 7.70 (d, 1H, J = 8.5 Hz); 7.94 (dd, 1H, J = 8.6, 5.7 Hz); 8.28 (dd, 1H, J = 8.6, 2.5 Hz); 8.73 (d, 1H, J = 5.7 Hz); 9.25 (d, 1H, J = 2.5 Hz).

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