A Facile Copper-Catalyzed Ullmann Condensation: *N*-Arylation of Heterocyclic Compounds Containing an -NHCO- Moiety

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***N*-Aryl heterocyclic compounds were synthesized from aryl halides and heterocyclic compounds containing an -NHCO- moiety by using a catalytic amount (1—10 mol%) of a commercially available copper catalyst in satisfactory yields. This catalytic reaction was applicable to the synthesis of *N*-aryl-2-pyridone, -2-pyrrolidone, -1(2*H*)-isoquinolone, -1(2*H*)-phthalazinone, -4(3*H*)-quinazolinone and -1,2,3-benzotriazin-4(3*H*)-one derivatives.**

Key words Ullmann condensation; *N*-arylation; catalytic reaction

N-Aryl heterocyclic compounds have attracted synthetic organic chemists because of their intriguing biological activities.[1] Conventional methods for the preparation of *N*-aryl heterocyclic compounds include reaction of anilines with lactones,[2] palladium-catalyzed amino arylation,[3] *N*-arylation of amide by aryllead triacetates[4] and Ullmann condensation of aryl halides with cyclic amines[5] or lactams.[6,7] In the last reaction, the use of a stoichiometric amount of copper catalyst is generally required,[6,8] though a catalytic process, in which freshly prepared Cu/SiO_2 is essential, has been reported by Renger.[7] In spite of numerous studies on Ullmann condensation, the utilization of heterocyclic compounds as substrates has been limited to lactams,[6,7] pyridones[7] and imides.[8,9]

We report here a facile Ullmann condensation in the presence of a catalytic amount of a commercially available copper catalyst together with K_2CO_3[6] (used to neutralize the released acid, HX) for the synthesis of various types of *N*-aryl heterocyclic compounds containing an -NHCO- moiety. The scope and limitations of the reaction are also discussed.

Results and Discussion

To find an effective copper catalyst, Ullmann condensation of iodobenzene (**1a**) (547 mg, 2.68 mmol) with 2-hydroxypyridine (**2a**) (127 mg, 1.34 mmol) was carried out in the presence of K_2CO_3 (185 mg, 1.34 mmol) in *N*,*N*-dimethylformamide (DMF) (2 ml) at 150 °C for 6 h under a nitrogen atmosphere (Table 1). When the reaction was carried out in the presence of 10 mol% of various copper catalysts (CuI, CuBr, Cu_2O, $CuBr_2$, Cu), 1-phenyl-2-pyridone (**3a**) was obtained in satisfactory yields. Next we investigated the effect of the amount of copper catalyst on the yield of **3a**. It became obvious that the reaction proceeded fast enough to give **3a** in satisfactory yield even if the amount of copper catalyst was reduced to 1 mol%. Table 2 shows the solvent effect on this reaction. DMF and dimethyl sulfoxide (DMSO) were effective, but the reaction was sluggish in other solvents. We consequently chose 1 mol% of CuI as a catalyst and DMF as a solvent (Table 1, run 6), and subsequently carried out the reaction under these conditions.

The results for the reaction of aryl (heteroaryl) halides (**1a—j**) with 2-hydroxypyridine (**2a**) are shown in Table 3. Aryl halides (**1c**, **e**, **f**), having either electron-withdrawing or electron-donating substituents, provided *N*-aryl-2-pyridones (**3c**, **e**, **f**) in satisfactory yields (entries 3, 5 and 6). 2,4,6-Trimethylbromobenzene (**1d**) afforded only

Table 1. Influence of Catalyst on Reaction of Iodobenzene (**1a**) with 2-Hydroxypyridine (**2a**)

Run	Catalyst	mol%	Yield (%)
1	CuI	10	83
2	CuBr	10	75
3	Cu_2O	10	79
4	$CuBr_2$	10	68
5	Cu	10	82
6	CuI	1	72
7	CuBr	1	72
8	Cu_2O	1	71
9	$CuBr_2$	1	67
10	Cu	1	56

Table 2. Effect of Solvent on Reaction of Iodobenzene (**1a**) with 2-Hydroxypyridine (**2a**)

Run	Solvent	Yield (%)
1	DMF	72
2	DMSO	71
3	NMP[a]	54
4	DMI[b]	19
5	Ethylene glycol	0
6	Mesitylene	0
7	1,1,2,2-Tetrachloroethane	0

a) 1-Methyl-2-pyrrolidinone. *b*) 1,3-Dimethyl-2-imidazolidinone.

Table 3. Reaction of Aryl (Heteroaryl) Halides **1a—j** with 2-Hydroxypyridine (**2a**)

Entry	**1**	Product **3** (Yield, %)
1	Iodobenzene (**1a**)	**3a** (72)
2	Bromobenzene (**1b**)	**3a** (71)[a]
3	4-Methyliodobenzene (**1c**)	**3c** (86)[a]
4	2,4,6-Trimethylbromobenzene (**1d**)	**3d** (0)
5	4-Bromobenzaldehyde (**1e**)	**3e** (54)
6	4-Nitroiodobenzene (**1f**)	**3f** (70)
7	2-Bromopyridine (**1g**)	**3g** (83)[b]
8	3-Bromopyridine (**1h**)	**3h** (0)
9	3-Bromoquinoline (**1i**)	**3i** (90)
10	3-Bromothiophene (**1j**)	**3j** (73)[a]

a) CuI (0.134 mmol). *b*) Reaction at 120 °C.

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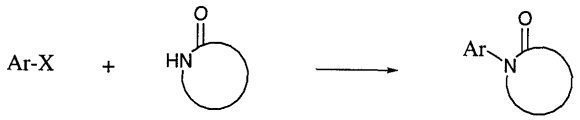
Table 4. Reaction of Iodobenzene (**1a**) with Heterocyclic Compounds **2a—k**

Entry	2	Product **3**, **4** (Yield, %)
1	2-Hydroxypyridine (**2a**)	**3a** (72)
2	2-Hydroxy-4-methylpyridine (**2b**)	**4b** (87)
3	4(3*H*)-Pyrimidone (**2c**)	**4c** (0)
4	2-Pyrrolidone (**2d**)	**4d** (89)
5	1(2*H*)-Phthalazinone (**2e**)	**4e** (78)
6	4(3*H*)-Quinazolinone (**2f**)	**4f** (32)[a]
7	1(2*H*)-Isoquinolone (**2g**)	**4g** (91)
8	1,2,3-Benzotriazin-4(3*H*)-one (**2h**)	**4h** (14)[a]
9	2-Hydroxyquinoline (**2i**)	**4j** (0)
10	1,5-Isoquinolinediol (**2j**)	**4j** (32)
11	Phthalimide (**2k**)	**4k** (0)

a) CuI (0.134 mmol).



1a-j **2a-k** **3a-j, 4a-k**

Chart 1

a trace amount of **3d** because of steric hindrance (entry 4). These results indicated that Ullmann condensation was not affected by the electronic effect of substituents, but was influenced by steric hindrance. Heteroaryl halides (**1g**, **i**, **j**) also provided moderate yields of **3g**, **i** and **j**, respectively (entries 7, 9 and 10), but 3-bromopyridine (**1h**) gave only a trace amount of **3h** (entry 8).

Table 4 shows the results for the reaction of iodobenzene (**1a**) with heterocyclic compounds (**2a—k**) containing an -NHCO- moiety. While 2-hydroxypyridine derivatives (**2a**, **b**), 2-pyrrolidone (**2d**), 1(2*H*)-phthalazinone (**2e**) and 1(2*H*)-isoquinolone (**2g**) provided **3a**, **4b**, **4d**, **4e** and **4g** in good yields, respectively (entries 1, 2, 4, 5 and 7), both 2-hydroxyquinoline (**2i**) and phthalimide (**2k**) afforded only trace amounts of **4i** and **4k**, presumably because of steric hindrance and the low nucleophilicity of nitrogen (entries 9 and 11). The reaction of iodobenzene (**1a**) with 1,5-isoquinolinediol (**2j**) proceeded chemoselectively to give only the *N*-arylated product (**4j**), not the 5-*O*-arylated product, in 32% yield.

In summary, we have developed a facile copper-catalyzed Ullmann condensation, which is applicable to *N*-arylation of various heterocyclic compounds containing an -NHCO- moiety (*e.g.*, 2-pyridone, 2-pyrrolidone, 1(2*H*)-isoquinolone, 1(2*H*)-phthalazinone, 4(3*H*)-quinazolinone and 1,2,3-benzotriazin-4(3*H*)-one).

Experimental

Melting points were measured using a Büchi 535 melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 1640 infrared spectrophotometer. NMR spectra were recorded on a Bruker AC-200 spectrometer with Me_4Si as an internal standard. Mass spectra (MS) were recorded on a Hitachi M-2000A spectrometer. Column chromatography was carried out on silica gel (Kieselgel 60, 70—230 mesh, E. Merck). CuI, CuBr and Cu (purchased from Aldrich Chemical Company, Inc.), Cu_2O and $CuBr_2$ (purchased from Wako Pure Chemical Industries, Ltd.) were used without purification.

General Procedure A mixture of an aryl (heteroaryl) halide (**1a—j**, 2.68 mmol), a heterocyclic compound (**2a—k**, 1.34 mmol), K_2CO_3 (1.34 mmol), and CuI (0.0134—0.134 mmol) in DMF (2 ml) was stirred at 150 °C for 6 h under a nitrogen atmosphere. Then diluted aqueous NH_3 was added, and the aqueous solution was extracted twice with AcOEt. The combined organic layer was washed with brine, and dried over $MgSO_4$. The organic layer was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel. All purified compounds were characterized as follows:

1-Phenyl-2-pyridone (**3a**): mp 129 °C (recrystallized from iso-Pr_2O) (lit.[7] mp 118 °C). IR (KBr): 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.50—7.31 (7H, m), 6.69—6.63 (1H, m), 6.24 (1H, dt, J=1.3, 6.7 Hz). MS *m/z*: 171 (M^+). *Anal.* Calcd for $C_{11}H_9NO$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.08; H, 5.35; N, 8.37.

1-(4-Methylphenyl)-2-pyridone (**3c**): mp 136 °C (iso-Pr_2O). IR (KBr): 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.43—7.22 (m, 6H), 6.68—6.62 (m, 1H), 6.22 (dt, 1H, J=1.3, 6.7 Hz), 2.40 (s, 3H). MS *m/z*: 185 (M^+). *Anal.* Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.53; H, 5.94; N, 7.73.

1-(4-Formylphenyl)-2-pyridone (**3e**): mp 129 °C (AcOEt). IR (KBr): 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 10.08 (s, 1H), 8.05—8.00 (m, 2H), 7.61 (d, 2H, J=8.4 Hz), 7.48—7.39 (m, 1H), 7.35 (dd, 1H, J=1.6, 6.9 Hz), 6.68 (d, 1H, J=9.3 Hz), 6.30 (dt, 1H, J=1.2, 6.7 Hz). MS *m/z*: 199 (M^+). *Anal.* Calcd for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.27; H, 4.50; N, 6.90.

1-(4-Nitrophenyl)-2-pyridone (**3f**): mp 192 °C (AcOEt). IR (KBr): 3068, 1666, 1577, 1533 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.40—8.33 (m, 2H), 7.67—7.59 (m, 2H), 7.49—7.32 (m, 2H), 6.71—6.65 (m, 1H), 6.33 (dt, 1H, J=1.2, 6.7 Hz). MS *m/z*: 216 (M^+). *Anal.* Calcd for $C_{11}H_8N_2O_3$: C, 61.11; H, 3.73; N, 12.96. Found: C, 61.22; H, 3.74; N, 13.14.

1-(2-Pyridyl)-2-pyridone (**3g**): mp 55—57 °C (cyclohexane) (lit.[7] mp 45—48 °C). IR (KBr): 1670 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.59—8.56 (1H, m), 7.98—7.84 (3H, m), 7.44—7.27 (2H, m), 6.67—6.63 (1H, m), 6.30 (1H, dt, J=1.3, 7.1 Hz). MS *m/z*: 172 (M^+). *Anal.* Calcd for $C_{10}H_8N_2O$: C, 69.75; H, 4.68; N, 16.27. Found: C, 69.55; H, 4.68; N, 16.35.

1-(3-Quinolyl)-2-pyridone (**3i**): mp 145—146 °C (AcOEt). IR (KBr): 1662 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.97 (d, 1H, J=2.4 Hz), 8.23 (d, 1H, J=2.3 Hz), 8.18 (d, 1H, J=8.4 Hz), 7.90—7.41 (m, 5H), 6.75—6.70 (m, 1H), 6.34 (dt, 1H, J=1.2, 6.7 Hz). MS *m/z*: 222 (M^+). *Anal.* Calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.61. Found: C, 75.47; H, 4.63; N, 12.50.

1-(3-Thiophenyl)-2-pyridone (**3j**): mp 112—113 °C (AcOEt) (lit.[7] mp 119.5 °C).

1-Phenyl-4-methyl-2-pyridone (**4b**): mp 115 °C (iso-Pr_2O). IR (KBr): 1675 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.53—7.34 (m, 5H), 7.23 (d, 1H, J=7.0 Hz), 6.46 (s, 1H), 6.09 (dd, 1H, J=1.8, 7.0 Hz), 2.23 (s, 3H). MS *m/z*: 185 (M^+). *Anal.* Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.70; H, 6.15; N, 7.41.

1-Phenyl-2-pyrrolidone (**4d**): mp 70 °C (iso-Pr_2O) (lit.[7] mp 65—67 °C).

2-Phenyl-1(2*H*)-phthalazinone (**4e**): mp 109 °C (iso-Pr_2O) (lit.[10] mp 104—105 °C).

3-Phenyl-4(3*H*)-quinazolinone (**4f**): mp 139 °C (iso-Pr_2O) (lit.[11] mp 135—137 °C).

2-Phenyl-1(2*H*)-isoquinolone (**4g**): mp 115—116 °C (iso-Pr_2O) (lit.[12] mp 103.5—105 °C). IR (KBr): 1662 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.48 (1H, d, J=7.9 Hz), 7.68 (1H, dt, J=1.3, 6.8 Hz), 7.57—7.38 (7H, m), 7.19 (1H, d, J=7.4 Hz), 6.56 (1H, d, J=7.4 Hz). MS *m/z*: 221 (M^+). *Anal.* Calcd for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.13; H, 5.00; N, 6.21.

3-Phenyl-1,2,3-benzotriazine-4(3*H*)-one (**4h**): mp 150—151 °C (iso-Pr_2O) (lit.[13] mp 149—150 °C).

2-Phenyl-5-hydroxy-1(2*H*)-isoquinolone (**4j**): mp 246—248 °C (EtOH). IR (KBr): 3152, 1645 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 10.29 (s, 1H), 7.70 (d, 1H, J=7.8 Hz), 7.58—7.31 (m, 7H), 7.15 (dd, 1H, J=1.1, 7.8 Hz), 6.82 (d, 1H, J=7.5 Hz). MS *m/z*: 237 (M^+). *Anal.* Calcd for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90. Found: C, 75.68; H, 4.77; N, 5.99.

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