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# Synthesis of 2-Arylamino-1,3,5-triazines from 2-Aminotriazines with Aryl Halides via CuI-Catalyzed Ullmann Coupling Reaction

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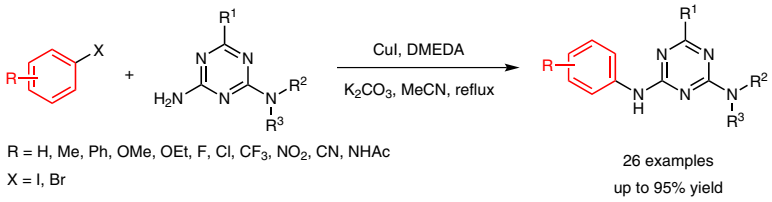


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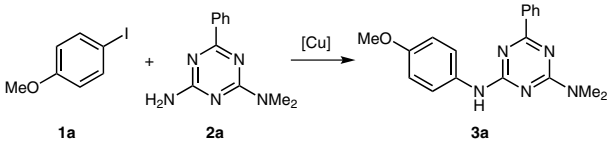
**Abstract** An efficient copper-catalyzed synthesis of 2-arylamino-1,3,5-triazines from 2-aminotriazines with aryl halides under mild conditions has been developed. The reaction occurred in moderate to good yields and tolerated aryl iodides containing functionalities such as nitriles, ethers, amides, and halogens. Aryl bromides were also well tolerated.

**Key words** aryl halides, 2-aminotriazines, 2-arylamino-1,3,5-triazines, copper catalyst, coupling reaction

A triazine fragment is a ubiquitous structure that occurs in a wide variety of naturally occurring and synthetic compounds exhibiting various important biological activities. Among the triazines derivatives reported, 1,3,5-triazine derivatives with arylamines substitution display several biological activities such as antibacterials, anti-HSV-1, anticancer and anti-HIV activities.[1] For this reason, the development of synthetic protocols for functionalized 1,3,5-triazines has always been an active area of research. Previous synthetic methods for such compounds mainly relied on two approaches. One involves the formation of triazinic ring by the reaction of substituted biguanides with carboxylates, acid chlorides, anhydrides or by cyclization of acylamidines with amidines or guanidines.[2] The most common synthetic methods for their preparation have been reported, fundamentally based on nucleophilic displacement of cyanuric chloride.[3] Although widely used, this route has some deficiencies: most notably, harsh conditions, and low reaction yields resulting from the poor reactivity of its third chlorine atom toward nucleophiles. Utilization of transition-metal-catalyzed cross-coupling reactions has been attracting much attention in recent years, and it has become one of the most versatile strategies for the synthesis of natural products, pharmaceuticals, organic functional materials, and so on.[4] Compared with other metals, the use of Cu(I) presents the major advantages of being inexpensive and easy to handle. Copper-catalyzed Ullmann-type C–N coupling has a history of more than one hundred years, and as a cost-effective and versatile C–N coupling, it is still actively used in the field of organic synthesis, including industrial processes.[5,6] Herein, we report a copper-catalyzed synthesis of 2-arylamino-1,3,5-triazines from 2-amino-1,3,5-triazines with aryl halides.[7]

We initially examined the reaction between 4-iodoanisole (**1a**) and $N^2$,$N^2$-dimethyl-6-phenyl-1,3,5-triazine-2,4-diamine (**2a**) in the presence of CuI (30 mol%), *N*,*N*′-dimethylethanediamine (DMEDA; 30 mol%) and $K_2CO_3$ (2 equiv) in MeCN at reflux. The reaction proceeded to give exclusively the 2-arylamino-1,3,5-triazine **3a** in 60% yield (Table 1, entry 1). Improving the amounts of DMEDA to 90 mol% increased the yield to 76% (Table 1, entry 7). Replacement of $K_2CO_3$ by KOH or $Cs_2CO_3$ led to a lower yield and $K_3PO_4$ gave satisfactory yield (Table 1, entries 9–11). Subsequently, we screened different organic solvents and identified dioxane also as the effective solvent for this C–N coupling reaction (Table 1, entry 6). While DMF and THF resulted in no product formation, DMSO and toluene as solvent only gave yields of 37% and 58%, respectively (Table 1, entries 2–5). We subsequently investigated the effect of various ligands on the reaction's yield. Both bipyridine and ethylenediamine ligands gave inferior results (Table 1, entries 12 and 13). Moderate yields were obtained when CuI was replaced by $Cu_2O$, CuBr or $Cu(OAc)_2$ resulting in slightly lower yields (Table 1, entries 14–16). Reducing the amount of CuI resulted in a slightly lower yield (Table 1, entry 8).

**Table 1** Optimization of the Reaction Conditions

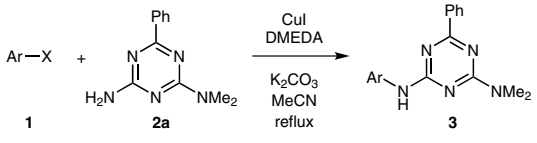



1a 2a 3a

| Entry | [Cu] | Base | Temp (°C) | Solvent | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | CuI | $K_2CO_3$ | reflux | MeCN | 60 |
| 2 | CuI | $K_2CO_3$ | 140 | DMF | trace |
| 3 | CuI | $K_2CO_3$ | 140 | DMSO | 37 |
| 4 | CuI | $K_2CO_3$ | reflux | toluene | 58 |
| 5 | CuI | $K_2CO_3$ | reflux | THF | N.R. |
| 6 | CuI | $K_2CO_3$ | 120 | dioxane | 60 |
| 7[b] | CuI | $K_2CO_3$ | reflux | MeCN | 76 |
| 8[c] | CuI | $K_2CO_3$ | reflux | MeCN | 43 |
| 9[b] | CuI | $K_3PO_4$ | reflux | MeCN | 73 |
| 10[b] | CuI | KOH | reflux | MeCN | 13 |
| 11[b] | CuI | $Cs_2CO_3$ | reflux | MeCN | 37 |
| 12[d] | CuI | $K_2CO_3$ | reflux | MeCN | 10 |
| 13[e] | CuI | $K_2CO_3$ | reflux | MeCN | 26 |
| 14[b] | CuBr | $K_2CO_3$ | reflux | MeCN | 46 |
| 15 | $Cu_2O$ | $K_2CO_3$ | reflux | MeCN | 51 |
| 16 | $Cu(OAc)_2$ | $K_2CO_3$ | reflux | MeCN | 52 |

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), catalyst (0.15 mmol), base (1.0 mmol), DMEDA (0.15 mmol), solvent (3 mL),10 h; isolated yields are shown.
[b] DMEDA (0.45 mmol).
[c] CuI (0.1 mmol).
[d] Bipyridine (0.45 mmol) was used in place of DMEDA.
[e] Ethylenediamine (0.45 mmol) was used in place of DMEDA.

**Table 2** Scope of the Synthesis of **3**[a]




1 2a 3

| Entry | 1 | Ar | X | Time (h) | 3 | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | **1a** | 4-$MeOC_6H_4$ | I | 10 | **3a** | 76 |
| 2 | **1b** | 2-$MeOC_6H_4$ | I | 10 | **3b** | 62 |
| 3 | **1c** | 4-$EtOC_6H_4$ | I | 10 | **3c** | 71 |
| 4 | **1d** | 4-$MeC_6H_4$ | I | 14 | **3d** | 71 |
| 5 | **1e** | Ph | I | 15 | **3e** | 52 |
| 6 | **1f** | 4-$PhC_6H_4$ | I | 30 | **3f** | 78 |
| 7 | **1g** | 4-$FC_6H_4$ | I | 11 | **3g** | 62 |
| 8 | **1h** | 4-$ClC_6H_4$ | I | 10 | **3h** | 71 |
| 9 | **1i** | 3-$ClC_6H_4$ | I | 9 | **3i** | 63 |
| 10 | **1j** | 4-$F_3CC_6H_4$ | I | 10 | **3j** | 62 |
| 11 | **1k** | 4-$NCC_6H_4$ | I | 7 | **3k** | 82 |
| 12 | **1l** | 4-$O_2NC_6H_4$ | I | 21 | **3l** | 90 |
| 13 | **1m** | 4-$AcNHC_6H_4$ | I | 18 | **3m** | 84 |
| 14 | **1n** | 4-$MeOC_6H_4$ | Br | 20 | **3a** | 76 |
| 15 | **1o** | 4-$MeC_6H_4$ | Br | 10 | **3d** | 68 |
| 16 | **1p** | Ph | Br | 10 | **3e** | 69 |
| 17 | **1q** | 3,4,5-$F_3C_6H_2$ | Br | 10 | **3n** | 71 |
| 18 | **1r** | Ph | Cl | 24 | **3e** | trace |
| 19 | **1s** | 4-$NCC_6H_4$ | Cl | 24 | **3k** | trace |

[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.5 mmol), CuI (0.15 mmol), $K_2CO_3$ (1.0 mmol), DMEDA (0.45 mmol), MeCN (3 mL), reflux; isolated yields are shown.

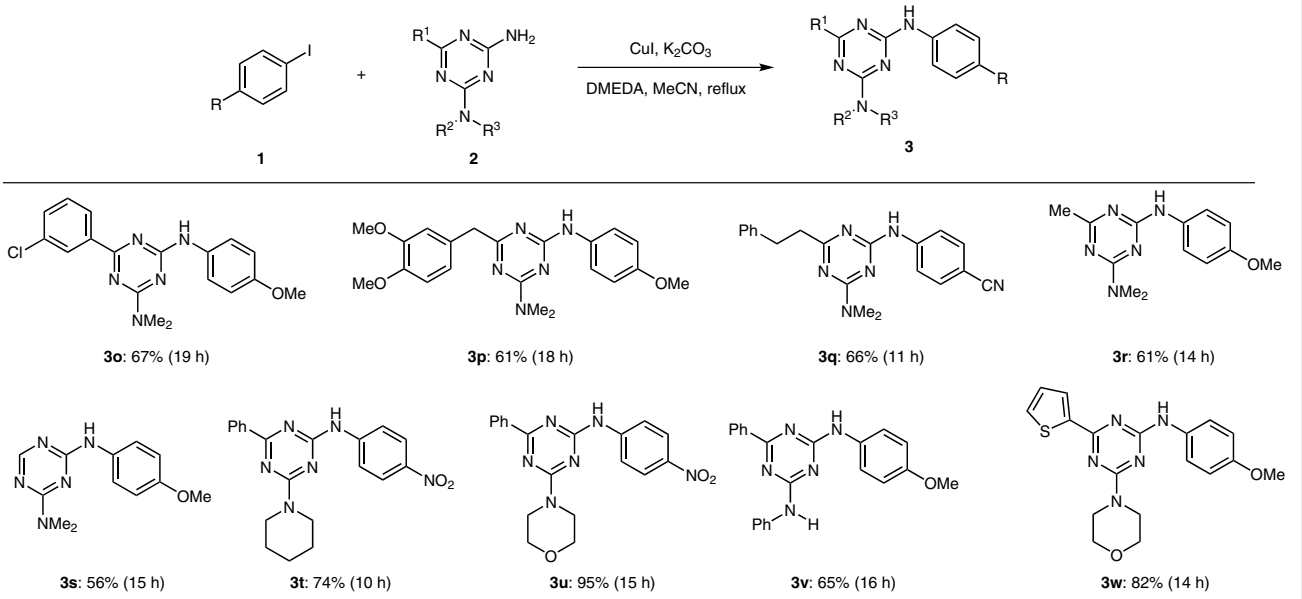
Having identified the optimal reaction conditions, the scope of the reaction was explored with different substituted aryl halides **1** (Table 2). Electron-donating substituents at the aryl iodides, such as *o*-methoxy, *p*-ethoxy, *p*-phenyl, and *p*-methyl groups, also provided 2-arylamino-1,3,5-triazines in good yields (Table 2, entries 1–4 and 6). In addition to electron-donating substitution, halogens such as Cl and F were also tolerated, leading to the desired products **3g–i** in 62–71% isolated yield (Table 2, entries 7–9). On the other hand, the more electron-withdrawing $CF_3$ group provided **3j** in 62% yield (Table 2, entry 10). Moreover, labile groups, such an AcNH, CN, and $NO_2$ were suitable in this reaction, with the corresponding 2-arylamino-1,3,5-triazines **3k–m** being delivered in 82–90% yield (Table 2, entries 11–13). In particular, a variety of aryl bromides, including those with MeO, Me, and F substituents, showed a great ability to react with 2-amino-1,3,5-triazines under these conditions, providing the corresponding coupling products in 68–76% yield (Table 2, entries14–17). Furthermore, aryl chlorides failed to undergo copper-catalyzed C–N coupling reaction (Table 2, entries 18 and 19).

Finally, we extended the newly developed coupling amination to 2-amino-1,3,5-triazines bearing various substituents. They worked well and afforded the corresponding products in good yields (Scheme 1).

In conclusion, we have successfully developed a new cross-coupling method for the synthesis of 2-arylamino-1,3,5-triazines using CuI as catalyst.[8] The method employs readily available reagents and has broad scope and high functional group tolerance. Further efforts to extend this catalytic system to the preparation of other useful heterocyclic compounds are currently underway in our laboratories.

## Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561632.




**Scheme 1** Scope of the synthesis of **3**

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(8) **Typical Experimental Procedure**: To a mixture of 1,3,5-triazine (0.5 mmol), aryl halide (0.5 mmol), DMEDA (0.45 mmol) and $K_2CO_3$ (1 mmol) in MeCN (3 mmol) was added CuI (0.15 mmol). The resulting mixture was stirred at reflux. After completion of the reaction, the reaction mixture was cooled to r.t., concd $NH_3$ (4 mL) and sat. NaCl (10 mL) were added, and the organic phase was then extracted with EtOAc (3 × 15 mL). The organic phase was dried over anhyd $Na_2SO_4$. The crude residue was obtained after evaporation of the solvent in vacuum, and the residue was purified by flash chromatography with petroleum and EtOAc as the eluent to give the pure product. ***N*²-(4-Methoxyphenyl)-*N*⁴,*N*⁴-dimethyl-6-phenyl-1,3,5-triazine-2,4-diamine (3a)**: white solid; mp 166–167 °C. $^1$H NMR (500 MHz, $CDCl_3$): δ = 8.43 (dd, *J* = 8.2, 1.4 Hz, 2 H), 7.58 (d, *J* = 9.0 Hz, 2 H), 7.46–7.53 (m, 3 H), 7.17 (br, 1 H), 6.91 (d, *J* = 9.0 Hz, 2 H), 3.83 (s, 3 H), 3.34 (s, 3 H), 3.23 (s, 3 H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 170.6, 165.9, 164.5, 155.6, 137.4, 132.4, 131.3, 128.4, 128.2, 121.8, 114.1, 55.6, 36.4. IR (KBr): 3353, 3066, 2944, 1604, 1506, 1211, 1039, 829, 778, 704 cm$^{-1}$. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{20}N_5O$: 322.1668; found: 322.1684. ***N*²-(4-Methoxyphenyl)-*N*⁴,*N*⁴-dimethyl-1,3,5-triazine-2,4-diamine (3s)**: white solid; mp 161–163 °C. $^1$H NMR (500 MHz, $CDCl_3$): δ = 8.40 (br, 1 H), 8.25 (s, 1 H), 7.50 (d, *J* = 8.2 Hz, 2 H), 6.88 (d, *J* = 8.2 Hz, 2 H), 3.80 (s, 3 H), 3.19 (s, 3 H), 3.16 (s, 3 H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 165.3, 164.5, 163.3, 155.8, 131.8, 122.3, 114.0, 55.5, 36.3. IR (KBr): 3434, 3195, 2951, 1613, 1512, 1197, 1037, 831, 805 cm$^{-1}$. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{16}N_5O$: 246.1355; found: 246.1377. **4-Morpholino-*N*-(4-nitrophenyl)-6-phenyl-1,3,5-triazin-2-amine (3u)**: yellow solid; mp 277–278 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): δ = 10.41 (s, 1 H), 8.39 (dd, *J* = 8.5, 1.5 Hz, 2 H), 8.23 (d, *J* = 9.2 Hz, 2 H), 8.05 (d, *J* = 9.2 Hz, 2 H), 7.57–7.61 (m, 1 H), 7.52–7.58 (m, 2 H), 3.95 (br, 2 H),

3.83 (br, 2 H), 3.68–3.76 (m, 4 H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): δ = 170.3, 164.5, 164.3, 146.5, 141.1, 136.2, 132.0, 128.5, 128.2, 124.9, 119.1, 65.9, 43.6. IR (KBr): 3310, 2950, 2858, 1606, 1497, 1332, 1270, 1215, 1107, 846, 779, 701 cm$^{-1}$. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{19}N_6O_3$: 379.1519; found: 379.1524.

***N*$^2$-(4-Methoxyphenyl)-*N*$^4$,6-diphenyl-1,3,5-triazine-2,4-diamine (3v)**: white solid; mp 143–145 °C. $^1$H NMR (500 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 7.3 Hz, 2 H), 7.65 (d, *J* = 6.4 Hz, 2 H), 7.49–7.58 (m, 5 H), 7.46 (br, 2 H), 7.35 (t, *J* = 7.3 Hz, 2 H), 7.11 (t, *J* = 7.4 Hz, 1 H), 6.92 (d, *J* = 8.4 Hz, 2 H), 3.84 (s, 3 H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 171.7, 164.9, 164.7, 156.2, 138.5, 136.5, 131.8, 131.3, 128.9, 128.4, 123.4, 123.0, 122.9, 120.5, 114.1, 55.6. IR (KBr): 3338, 3061, 2832, 1597, 1516, 1244, 1208, 1036, 826, 777, 756, 700 cm$^{-1}$. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{20}N_5O$: 370.1668; found: 370.1671.