Cobalt-Catalyzed Arylation or Benzylation of 2-Chloro-4,6-dimethoxy-1,3,5-triazine

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Abstract: A variety of functionalized aryl bromides or benzyl chlorides were coupled with 2-chloro-4,6-dimethoxy-1,3,5-trazine in good yields by a one-step procedure via cobalt catalysis.

Key words: cobalt, catalysis, cross-coupling, arylation, azo compounds

1,3,5-Triazines have emerged as versatile heterocycles finding applications either as ligand in the palladium-catalyzed Suzuki–Miyaura cross-coupling[1] or in material[2] as well as in medicinal chemistry. In the latter field, 1,3,5-triazines constitute the pharmacophore of therapeutic agents used to treat cancer,[3] diabetes,[4] dyslipidaemia,[5] microbial and bacterial infections[6] or inflammatory diseases.[7] More specifically, recent studies have shown promising activities for 2,4,6-tris(*N*,*N*-dialkylamino)-1,3,5-triazines against cancer which stressed the need for developing efficient access to other 2-aryl- (or benzyl)-substituted 1,3,5-triazines. Then, classical cross-coupling processes such as the Kumada, Corriu, Negishi, Stille, or Suzuki reactions are of utmost importance to create C–C bonds for modern organic synthesis and are heavily dominated by the use of palladium or nickel complexes, presenting an excellent compatibility with many functional groups.[8] In this manner, Menicagli et al.[9] have worked on the cross-coupling of various organometallic reagents with chlorotriazines using Pd or Ni catalysis. However, these catalysts have some disadvantages resulting from the high price of palladium precursors, the toxicity of nickel salts and the need for ancillary ligands to stabilize and activate these catalytic species. Fortunately, inexpensive, stable and toxicologically benign iron or cobalt salts as catalyst under 'ligand-free' conditions are commercially available. The elegant iron methodology is essentially limited to cross-coupling of Grignard, organomanganese or recently organozinc reagents with various compounds.[10] In these cross-coupling protocols, the major difficulty lies in the preparation of functionalized organometallics. Moreover, sometimes cobalt catalysts can present a higher reactivity for various C–C bond-forming reactions that has been demonstrated by different groups and ours.[11] Recently, we have reported a very efficient Co(II)-mediated cross-coupling reaction devoted to the direct synthesis of 2-aryldiazines such as 2-arylpyrimidines or 2-arylpyrazines.[12] The key step of this procedure is the formation of aromatic organozinc reagents and their coupling with 2-chlorodiazines using the same cobalt catalyst. However, this last protocol cannot be applied to 2-chloropyridines as coupling partners.[13]

In the course of our work on the cobalt-catalyzed cross-coupling of nitrogen heteroaromatic compounds, the current paper deals with a method of coupling of organozinc compounds with a halotriazine. It seems interesting to develop a convenient method for the one-step synthesis of various 2-aryl (or benzyl)-4,6-dimethoxy-1,3,5-triazines. To the best of our knowledge, this is the first cobalt-catalyzed reductive coupling of aryl or benzyl halides with 2-chloro-4,6-dimethoxy-1,3,5-trazine. Stemming from our previous results concerning the reactivity of aryl zinc species obtained under cobalt catalysis,[14] we were convinced that 2-chloro-4,6-dimethoxy-1,3,5-trazine could be cross-coupled in the same way with these arylzinc species. Therefore, we first investigated a two-step coupling involving formation of 4-(ethoxycarbonyl)phenyl zinc bromide from ethyl 4-bromobenzoate using cobalt catalysis and subsequent coupling with 2-chloro-4,6-dimethoxy-1,3,5-triazine without further addition of cobalt catalyst (Scheme 1).

The coupling product was detected in 79% GC yield. Then, we tried to develop a simple Barbier-type procedure and applied this method to various aromatic bromides (Scheme 2).

As shown in Table 1, this reaction was successful with various aryl bromides and the resulting products were isolated in good to excellent yields. As described for the other Barbier-type procedures using cobalt catalysis, the major by-product was the reduction one, whereas the homocoupling product was detected in small amounts. Contrary to the coupling with 2-chlorodiazines, coupling in the *ortho*, *meta* or *para* position led to good yields at room temperature. Under these standard conditions described for aromatic bromides, the reaction with 3-thienyl bromide was particularly longer due to its lower reactivity and its coordination to the cobalt catalyst as previously reported.[15]

We have extended this cross-coupling of 2-chloro-4,6-dimethoxy-1,3,5-triazine with various functionalized ben-

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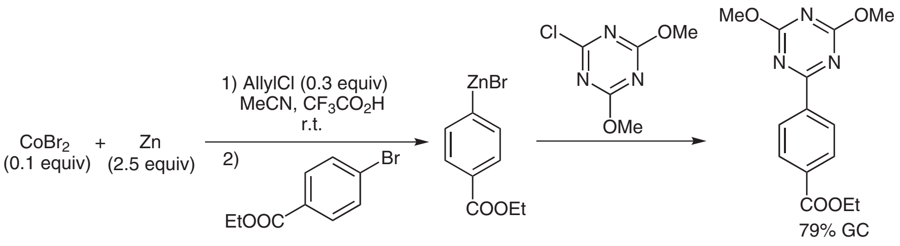
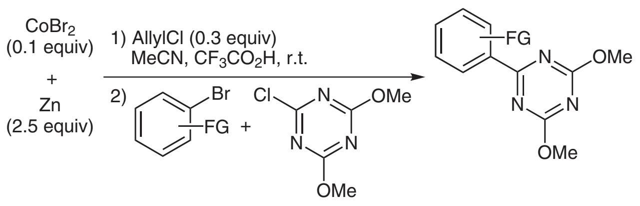


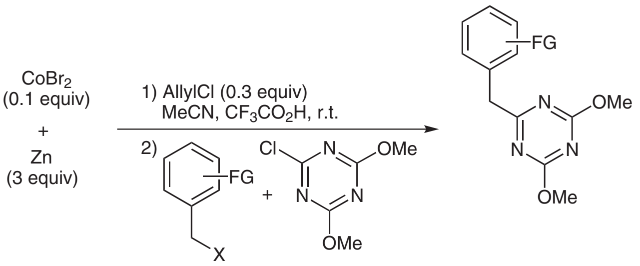
Scheme 1 Two-step procedure for the reductive cross-coupling of 4-$EtO_2CC_6H_4Br$ with 2-chloro-4,6-dimethoxy-1,3,5-triazine



Scheme 2 $CoBr_2$-catalyzed synthesis of 2-aryl-4,6-dimethoxy-1,3,5-triazines

Table 1 Cross-Coupling between 2-Chloro-4,6-dimethoxy-1,3,5-triazine and Various Aryl Bromides

Entry	FG	Time	Product	Yield (%)
1	3-F	3 h	**1**	84
2	4-F	1 h	**2**	68
3	4-EtO_2C	1 h	**3**	80
4	2-EtO_2C	1 h	**4**	51
5	4-NC	1 h	**5**	70
6	4-F_3C	30 min	**6**	92
7	4-Cl	4 min	**7**	73
8	4-MeO	1.5 h	**8**	67
9	2-MeO	30 min	**9**	89
10	3-MeO	30 min	**10**	88
11	3-Br-thiophene	5 h	**11**	73



Scheme 3 $CoBr_2$-catalyzed synthesis of 2-benzyl-4,6-dimethoxy-1,3,5-triazines

zyl halides via the Barbier procedure described earlier (Scheme 3).

The results are reported in Table 2. Good to excellent yields were obtained with various benzyl chlorides. On the other hand, this Barbier-type procedure applied to benzyl bromide led to a lower yield (Table 2, entry 2).

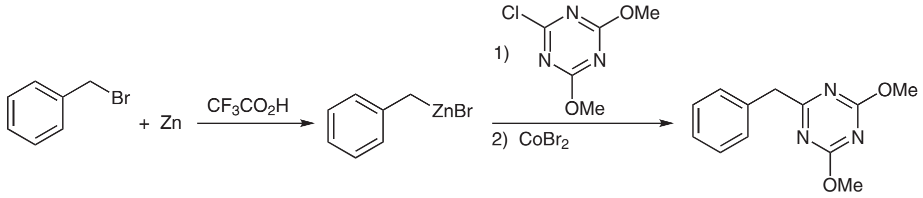
Table 2 Cross-Coupling between 2-Chloro-4,6-dimethoxy-1,3,5-triazine and Various Benzyl Halides

Entry	FG-$C_6H_4CH_2X$	Product	Yield (%)
1	$C_6H_5CH_2Cl$	**12**	80
2	$C_6H_5CH_2Br$	**12**	50
3	4-$ClC_6H_4CH_2Cl$	**13**	67
4	3-$MeC_6H_4CH_2Cl$	**14**	67
5	4-$FC_6H_4CH_2Cl$	**15**	85
6	4-$F_3CC_6H_4CH_2Cl$	**16**	65
7	4-$MeO_2CC_6H_4CH_2Cl$	**17**	77
8	4-$NCC_6H_4CH_2Cl$	**18**	54

In order to examine the role of cobalt catalyst in this reaction, we decided to use a benzylzinc species synthesized without cobalt. In fact, these last compounds can be obtained without cobalt catalyst in acetonitrile unlike arylzinc bromides. Thus, we synthesized the benzylzinc bromide in acetonitrile by using zinc dust activated by trifluoroacetic acid and the 2-chloro-4,6-dimethoxy-1,3,5-trazine was added in the solution. The resulting mixture was stirred for one hour at ambient temperature and no cross-coupling occurred. On the other hand, when we added a catalytic amount of $CoBr_2$ (10 mol%) in the second step, cross-coupling product was immediately formed. By this experience, we have demonstrated that cobalt catalyst plays an important role in the subsequent reaction with 2-chloro-4,6-dimethoxy-1,3,5-triazine (Scheme 4).

However, the yield was lower (30% GC yield) than that in the Barbier protocol described previously in Scheme 3 with benzylzinc bromide (Table 2, entry 2). In fact, more homocoupling and reduction products from benzylzinc bromides were obtained decreasing the cross-coupling yield.

In conclusion, we have devised an expedient route to various functionalized 2-aryl (or benzyl)-4,6-dimethoxy-1,3,5-triazines in a Barbier-fashion for more convenience, using mild reaction conditions.[16] The tolerance of our protocol toward a variety of functional groups enables the synthesis of a broad spectrum of valuable compounds from commercially available aryl bromides or benzyl



Scheme 4 Role of the cobalt catalyst in the cross-coupling

halides. This catalytic process involves a simple, inexpensive and environmentally friendly cobalt halide salt without ligand. Finally, this procedure compares favorably and makes an excellent complement to palladium- or nickel-catalyzed methods.

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(16) **Representative Experimental Procedure for the Synthesis of 2-Aryl-4,6-dimethoxy-1,3,5-triazines and 2-Benzyl-4,6-dimethoxy-1,3,5-triazines from Aryl Bromides or Benzyl Chlorides**; *Zinc Insertion and Cross-Coupling*: To a solution of $CoBr_2$ (10 mol%, 0.75 mmol, 165 mg) and zinc powder (19 mmol, 1.2 g) in MeCN (6 mL) were successively added at r.t. allyl chloride (2.25 mmol, 190 μL) and trifluoroacetic acid (100 μL), causing an immediate rise in temperature and color change to dark grey. After stirring the resulting mixture for 3 min, aryl bromide or benzyl chloride (7.5 mmol) and 2-chloro-4,6-dimethoxy-1,3,5-triazine (10 mmol, 1.7 g) were added. The medium was then stirred at r.t. until aryl or benzyl halide was consumed. The amount of the corresponding coupling product was measured by GC (by addition of iodine) using an internal reference (dodecane, 100 μL). The reaction mixture was poured into a sat. aq solution of NH_4Cl and extracted with CH_2Cl_2. The organic layer was washed with a sat. aq solution of NaCl and dried over $MgSO_4$. Evaporation of the solvent and purification by column chromatography on silica gel (pentane–Et_2O) afforded the coupling product characterized by NMR (^1H, ^{13}C, ^{19}F), mass spectrometry and elementary analysis for new products.