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Organometallic alkylation of 2-chloro-4,6-dimethoxy-1,3,5-triazine: a study

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Abstract—The reactivity of 2-chloro-4,6-dimethoxy-1,3,5-triazine (**1**) has been investigated in Pd- or Ni-catalyzed cross-coupling processes with organostannanes, Grignard reagents, organoalanes and organozinc halides. All organometallic reagents considered form new C–C bonds on the heteroaromatic ring and afford the corresponding 2-alkyl-4,6-dimethoxy-1,3,5-triazines in moderate to very good yields. The collected data allows the choice of the alkylating agent as well as the experimental conditions depending on the residue to transfer.

1. Introduction

During the last few years the potential of 1,3,5-triazine derivatives in molecular recognition, agrochemical and medicinal properties has been subject to investigation.[1] Our studies pointed out that 2-alkyl-4,6-dihetero(*N*,*O*)alkyl-1,3,5-triazines (Fig. 1) show interesting antitumor properties.[1c–e] Among the structures studied, 2-(alk-1′-ynyl)-4,6-dimethoxy-1,3,5-triazines were the most promising compounds. In order to gain an insight into the structure–activity relationship, the synthesis of 2-aryl (alkyl or alk-1′-enyl or benzyl or allyl)-4,6-dimethoxy-1,3,5-triazines was necessary.

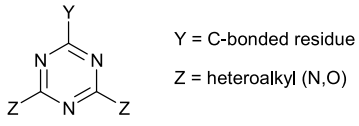
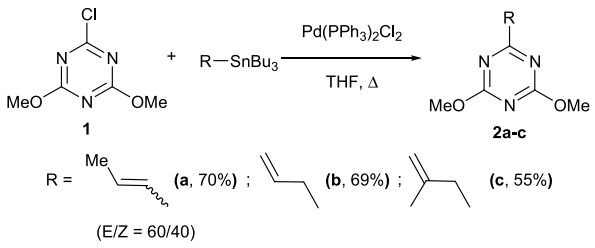


Figure 1.

The use of transition metal-catalyzed cross-coupling reactions, between 2-chloro-4,6-dimethoxy-1,3,5-triazine (**1**) and different organometallic reagents, is hereby reported and critically discussed in order to provide the most convenient procedures for the synthesis of the desired compounds.

2. Results and discussion

Since the 1990s, transition metal catalyzed cross-coupling reactions have been described for the preparation of symmetrical and non-symmetrical 1,3,5-triazine systems, starting from 2,4,6-trichloro-1,3,5-triazine or its derivatives.[2] Recently we used Sonogashira cross-coupling to prepare 2-(alk-1′-ynyl)-4,6-dialkoxy-1,3,5-triazines.[3] The good results obtained in the Sonogashira[3] and in the Stille[1e] cross-couplings prompted us to extend this last approach to the transfer of other unsaturated residues onto the heteroaromatic ring (Scheme 1). The use of tributylalk-1-enylstannanes in Pd-catalyzed cross-coupling procedures is well known,[4] and in our case the introduction of prop-1-enyl residue was successfully achieved, affording (*E*,*Z*)-**2a** (Scheme 1). The diastereomeric composition (glc) of the product was the same as the starting organotin derivative. In turn, when Stille cross-couplings are carried out with allyl stannanes, a process of isomerization of the double bond is often observed,[4,5] which can sometimes be prevented by using tri(2-furyl)phosphine as the palladium ligand.[5d] Nevertheless, the description of Stille non-isomerized allyl products under more usual conditions is frequent.[4,5b,6]



Scheme 1.

Keywords: 2-Chloro-4,6-dimethoxy-1,3,5-triazine; Organometallics; Coupling reactions; Palladium and nickel catalysts.
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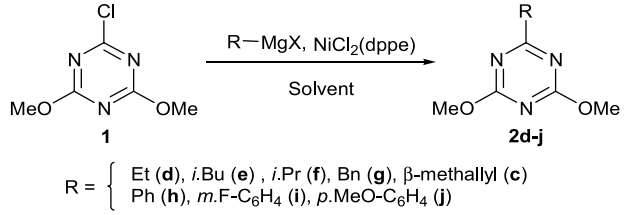
Therefore, the synthesis of 2-allyl-4,6-dimethoxy-1,3,5-triazine was attempted under the same conditions allowing the preparation of the other derivatives (Scheme 1). It was found that the structure of the product was strongly affected by the work-up procedure: as a matter of fact, when the usual hydrolysis sequence was carried out [Procedure A: (1) KF_{aq} (60% wt); (2) filtration on Florisil®/silica gel], only (*E*)-2-prop-1′-enyl-4,6-dimethoxy-1,3,5-triazine [(*E*)-**2a**] was obtained. It has to be underlined that only 2-allyl-4,6-dimethoxy-1,3,5-triazine had been detected (glc and GC/ms) in the reaction mixture prior to hydrolysis.

In order to understand if the formation of (*E*)-**2a** was a base- and/or Pd-mediated process, in a further experience the reaction mixture was (1) filtered on Florisil®/silica gel, to remove most of the catalyst and (2) treated with the KF solution (Procedure B). Under these conditions no traces of (*E*)-**2a** were detected and **2b** was obtained in good yield (69%). Moreover, the quantitative isomerization of **2b** into (*E*)-**2a** was achieved when a pure sample of **2b** was treated with both a 60% KF aqueous solution and a catalytic amount of Pd/C. In turn, **2b** was recovered unreacted when it was treated with the same basic solution in the absence of the Pd catalyst. The observed base- and Pd-catalyzed isomerization process conveniently afforded 2 (2′,2′-dialkylalk-1′-enyl)-4,6-dimethoxy-1,3,5-triazines, whose synthesis would otherwise need the tedious preparation of the necessary 2-alkyl-1-haloalk-1-enes. In order to verify this possibility, a cross-coupling reaction was carried out between **1** and 2-methylprop–2-enyltributylstannane (β-methallyltributyltin, Scheme 1), following the work-up Procedure A. The reaction was much slower and no isomerization was observed; eventually, **2c** was recovered with a moderate (55%) isolated yield.

Although tetraalkyltin compounds are sometimes used as cross-coupling alkylating agents,[4] their use for the preparation of 2-alkyl-4,6-dialkoxy-1,3,5-triazines seemed rather expensive. To overcome this problem, the use of readily available Grignard reagents under the Kumada reaction conditions was investigated (Scheme 2). In this context, arylation and allylation processes, previously carried out via Stille reaction, were repeated and compared under the Kumada protocol. A preliminary experiment, carried out in the presence of $PdCl_2(PPh_3)_2$, afforded only by-products arising from decomposition of **1**. Although recently iron-catalyzed cross-couplings between RMgBr (R=*n*.$C_{14}H_{29}$ and Ph) and **1** were described,[2e] the availability of $NiCl_2$(dppe) in our laboratory prompted us to use this catalyst, which is widely employed in Kumada cross-couplings.[7] The main results obtained are collected in Table 1: while the reaction failed in the cases of Bn- and β-MethallylMgCl (Table 1, entries 4 and 5), **1** reacted



Scheme 2.

Table 1. Kumada cross-coupling between **1** and Grignard reagents[a]

Entry	*t* (h), *T* (°C)	R	Et_2O/THF	**2** % Yield[b]
1	2, 25	Et (**d**)	100/0	74
2	1, 25	*i*.Bu (**e**)	100/0	60
3	4, 25	*i*.Pr (**f**)	100/0	68
4	76, 25	Bn (**g**)	100/0	35
5	48, 60	β-Methallyl (**c**)	80/20	0
6	14, 25	Ph (**h**)	95/5	75
7	3, 25	*m*.F-C_6H_4 (**i**)	50/50	65
8	28, 25	*p*.MeO–C_6H_4 (**j**)	50/50	30[c]

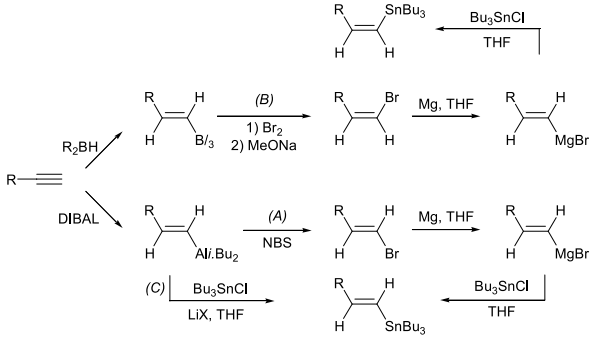
[a] Reactions carried out in the presence of $NiCl_2(dppe)_2$, **1**/RMgX/cat=1/1.3/0.05.
[b] Isolated yield.
[c] 50% conversion (glc).

smoothly with primary, α-branched primary and secondary Grignard reagents (Table 1, entries 1–3) and afforded the corresponding products **2d–f** in good isolated yields (60–74%).

As far as arylmagnesium halides are concerned, the outcome of the reaction was strongly affected by the nature of the aromatic Grignard reagent used. In particular, good results were obtained in the preparation of **2h–i** (Table 1, entries 6 and 7), while repeated experiments carried out in the presence of *p*-methoxyphenylmagnesium bromide always afforded **2j** in modest yield, due to the partial conversion of **1** (Table 1, entry 8).

Moreover, it should be noted that, under the reaction conditions, minor amounts of by-products (7–10%) arising from the di- and trialkylation of **1** were observed (GC/ms).

In a further step and with the aim of comparing the use of organotin and organomagnesium derivatives in the alkenylation of **1**, the possible synthetic pathways to the necessary unsaturated organometallic reagents were critically considered (Scheme 3). A common and convenient synthetic procedure for the preparation of 1-haloalk-1-enes, precursors of both organometals, is the halolysys of C–B[8] or C–Al[9] bonds, arising from hydroboration[10] or hydroalumination[11] processes (Scheme 3, sequences *A*, *B*). An alternative, more recent procedure (Scheme 3, Sequence *C*) allows the direct transmetallation of the unsaturated residue from organoalane to organotin.[12] Unfortunately, this rather attractive approach is not general, since the obtained yields are satisfactory only in the case of non-α-substituted organoalanes.[12] Moreover, the preparation of vinylic



Scheme 3.

Grignard reagents has been recently achieved by Mn-promoted carbomagnesiation of acetylenic linkages.[13]

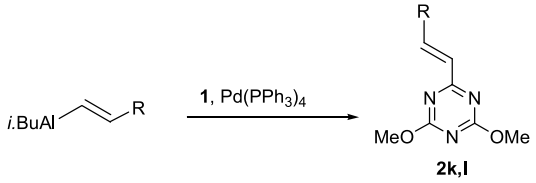
Taking into account that (i) alk-1-enyldialkylalanes are often key intermediates in the preparation of the corresponding halides and that (ii) these organometallic reagents have been known for years as alkenylating agents in Pd or Ni catalysed cross-coupling reactions,[14] their use for the alkenylation of **1** was considered.

In order to verify the reactivity of alkenylalanes with **1** under the usual cross-coupling conditions, **1** was reacted with di-isobutyl(hex-1-enyl)alane in CH_2Cl_2, using $PdCl_2(PPh_3)_2$ as catalyst. Since only decomposition products were observed, the reaction was repeated in THF (Table 2, entry 1). In this case, the analysis of the reaction mixture revealed the formation of the expected 2-(hex-1′-enyl)-4,6-dimethoxy-1,3,5-triazine (**2k**). Nevertheless, **2k** was recovered in modest yield (38%) due to the competitive formation of an equimolar amount of 2-(2′-methylpropyl)-4,6-dimethoxy-1,3,5-triazine (**2e**). In a further experiment the lack of selectivity in the chain transfer was solved (Table 2, entry 2) by replacing $PdCl_2(PPh_3)_2$ with $Pd(PPh_3)_4$. In the presence of this catalyst the conversion of **1** into **2k** was completely chemoselective and the desired derivative was recovered in 60% yield (Table 2, entry 2). Although the yield obtained in the synthesis of **2k** was lower than that obtained in the preparation of **2a** by the Stille cross-coupling (70%, see Scheme 1), it has to be underlined that the synthesis of alkenylalanes via hydroalumination is more convenient than the preparation of alkenylstannanes. This observation suggested the use of unsaturated alanes in the synthesis of other triazine derivatives. Thus, in a further experiment, phenylethyne was used as precursor of the organoaluminium reagent and afforded the expected **2l** in moderate (51%) yield (Table 2, entry 3). In this case, a significant (21%) amount of 2-phenylethynyl-4,6-dimethoxy-1,3,5-triazine[3b] was observed due to the competitive metallation of phenylethyne. The cases reported in entries 4–6 of Table 2 were considered to verify if β-branched unsaturated residues as well as internal alkenyl chaines could be transferred. The reactions were carried out in the presence of $ZnCl_2$, to enhance the reactivity of sterically hindered alkenylalanes.[14b] In none of the examples appreciable amounts of the corresponding 2-alkenyl-4,6-dimethoxy-1,3,5-triazines were isolated, but **2e** was always present in the reaction mixtures.

On the basis of these results it seems reasonable to conclude that alk-1-enyldi-isobutylalanes can be successfully used to prepare 2-(alk-1′-enyl)-4,6-dialkoxy-1,3,5-triazines only when the unsaturated chain is not hindered.

Although it is well-known that ethereal solvents can sometimes inhibit the reactivity of organoalanes,[15] the cross-couplings of **1** with unsaturated organoalanes (Table 2, entries 1–3) were successfully carried out in the presence of THF. These results suggested the in situ

Table 2. Cross-coupling reactions between **1** and alkenyldiisobutylalanes[a]

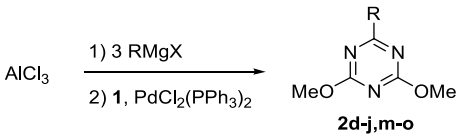


2k,l

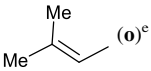
Entry	*t* (h)	THF/*n*.Hexane	R	**2** % Yield[b]
1[c]	15 (rt), 5[d]	50/50	*n*.Bu (**k**)	38[e]
2[f]	13 (rt), 4[g]	60/40	*n*.Bu (**k**)	60
3[h]	5 (rt), 30[d]	60/40	Ph (**l**)	51[i]
4[j]	48 (rt)	50/50	Et, Me	—[k]
5[j]	20 (rt), 4[l]	75/25	*t*.Bu	—[m]
6[j]	4 (rt), 15[g]	45/55	Et, Et	—[m]

[a] **1**/Organometal/cat = 1/1.15/0.03.
[b] Isolated yield.
[c] Reaction carried out in the presence of $PdCl_2(PPh_3)_2$.
[d] $T = 40$ °C.
[e] From the reaction mixture 2-*i*.butyl-4,6-dimethoxy-1,3,5-triazine (**2e**) was recovered (45%).
[f] 90% conversion (glc).
[g] $T = 50$ °C.
[h] 100% conversion (glc).
[i] A sample (21%) of 2-(2′-phenylethynyl)-4,6-dimethoxy-1,3,5-triazine[3b] was isolated.
[j] 0.5 equiv of $ZnCl_2$ were added.
[k] In the reaction mixture the main product was **2e** (30%) along with traces of the desired product (GC/ms).
[l] At reflux.
[m] In the reaction mixture only **2e** was detected (glc).

Table 3. Cross-coupling reactions between **1** and in situ prepared organoalanes[a]



2d-j,m-o

Entry	*t* (h)	Et_2O/THF	R	**2** % Yield[b]
1	4	100/0	Et (**d**)	81
2	4	100/0	*n*.Hex (**m**)	75
3	2	100/0	*i*.Bu (**e**)	70
4	2	100/0	(*S*)-(2Me)Bu (**n**)	70
5[c]	18	65/35	*i*.Pr (**f**)	43[d]
6[e]	6	60/40	 (**o**)[e]	62
7	3[f]	100/0	Bn (**g**)	74
8	12	70/30	Ph (**h**)	75
9	200	50/50	*m*.F-C_6H_4 (**i**)	—[g]
10	2[f]	65/35	*p*.MeO-C_6H_4 (**j**)	88

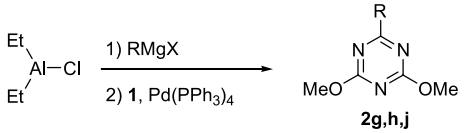
[a] **1**/AlR_3/$PdCl_2(PPh_3)_2$ = 1/1.15/0.03; reactions carried out at reflux if not otherwise stated; quantitative conversion was observed if not otherwise stated.
[b] Isolated yield.
[c] 82% conversion (glc).
[d] In the reaction mixture 2-*n*.propyl-4,6-dimethoxy-1,3,5-triazine was also recovered (21%).[17]
[e] When β-methallylMgCl was used 2-(2′-methylprop-1′-enyl)-4,6-dimethoxy-1,3,5-triazine (**2o**) was obtained.
[f] Reaction carried out at room temperature.
[g] Repeated experiences never afforded more than 10% conversion (glc) of **1**.

preparation of trialkyl (aryl or allyl or benzyl) alanes by a transmetallation reaction between $AlCl_3$ and the suitable Grignard reagent[15] (Table 3). This approach, which was not a priori predictable, due to the possible interaction between Lewis acids and the catalytic system used,[16] would simplify the procedure, avoiding the rather cumbersome isolation of the organoalanes.

The collected data (Table 3) shows that **1** can be conveniently alkylated by organoalanes prepared in situ, and that the presence of magnesium salts does not affect the activity of the catalytic system.[16] In particular: (i) the yield of **2** was very good (70–81%) when aliphatic primary (Table 3, entries 1 and 2) as well as α-branched primary (Table 3, entries 3 and 4) alanes were used. (ii) The partial isomerization of the transferred chain was observed when tri-isopropylalane was used (Table 3, entry 5) and, in repeated experiments, carried out under different reaction conditions (solvent, temperature, catalyst), the formation of 2-*n*-propyl-4,6-dimethoxy-1,3,5-triazine[17] could never be avoided. Anyway, chemically pure **2f** was recovered in 43% yield. (iii) When β-methallylmagnesium chloride was used for the preparation of the corresponding alane, the cross-coupling yielded 2-(2′-methylprop-1′-enyl)-4,6-dimethoxy-1,3,5-triazine (**2o**), isolated in 62% yield. (iv) Tribenzylalane was particularly reactive and afforded the desired **2 g** in 74% yield (Table 3, entry 7). (v) Eventually, triarylalanes could be employed in the cross-coupling reaction with **1**, although the outcome of the reaction seemed to depend on the nature of the transferred aryl residue. As a matter of fact, while triphenylalane and tri(4-methoxyphenyl)alane afforded **2h** and **2j** in very good yields (Table 3, entries 8 and 10, respectively), it was not possible to obtain 2-(3′-fluorophenyl)-4,6-dimethoxy-1,3,5-triazine (**2i**, Table 3, entry 9), contrary to what was observed with Grignard reagents (see Table 1, entries 6–8).

The results concerning trialkyl (or aryl) alanes showed that these organometallic reagents are complementary to the previously studied ones. In fact, they allowed the benzylation of **1** as well as the synthesis of **2o** via the isomerization of the corresponding methallyl residue. Moreover, while Grignard reagents had afforded minor amounts of di- and trialkylated products (Table 1), no appreciable amounts (glc) of these byproducts were observed when trialkylalanes were used. Nevertheless, the protocol seemed rather expensive, because only one out of the three residues could be transferred from the organoalane to the heteroaromatic ring.[15] Further efforts were thus made to use mixed organoalanes (REt_2Al) for the one-pot transfer of non-aliphatic residues. These organometallic reagents can be readily obtained by reaction between chlorodiethylalane and a suitable Grignard reagent.[15] While the cross-coupling between **1** and benzyldiethylalane gave unsatisfactory results in the presence of both $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$ (Table 4, entries 1 and 2), the reaction of 4-methoxyphenyl- as well as diethylphenylalane afforded **2j** and **2h** in 71 and

Table 4. Cross-coupling reaction between **1** and benzyl(aryl)diethylalanes REt_2Al[a]

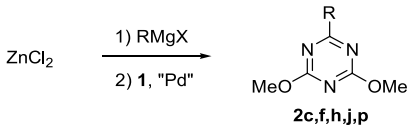


2g,h,j

Entry	*t* (h)	Et_2O/THF	R	**2** % Yield[b]
1	68	70/30	Bn (**g**)	35[c]
2[d]	3	100/0	Bn (**g**)	35[c]
3	25	0/100	*p*.$MeOC_6H_4$ (**j**)	71
4	10	70/30	Ph (**h**)	65[e]

[a] Reactions carried out in the presence of $Pd(PPh_3)_4$ in refluxing solvent, **1**/REt_2Al/cat = 1/1.15/0.03; 100% conversion (glc).
[b] Chromatographic yield.
[c] 2-Ethyl-4,6-dimethoxy-1,3,5-triazine (**2d**) was also detected (glc).
[d] Reaction carried out in the presence of $PdCl_2(PPh_3)_2$.
[e] Isolated yield.

Table 5. Cross-coupling reaction between **1** and in situ prepared organozinc halides[a]



2c,f,h,j,p

Entry	*t* (h)	Et_2O/THF	R	**2** % Yield[b]
1[c,d]	3	0/100	*p*.$EtOOCC_6H_4$ (**p**)	78
2	2	90/10	*p*.$MeOC_6H_4$ (**j**)	80[e]
3	2	65/35	Ph (**h**)	91
4	1.5	100/0	*i*.Pr (**f**)	64[f]
5[d]	4	0/100	β-Methallyl (**c**)	42

[a] Reactions carried out at room temperature, in the presence of prereduced (*i*.PrMgCl) $PdCl_2(PPh_3)_2$, **1**/RZnX/cat = 1/1.15/0.03, 100% conversion if not otherwise stated.
[b] Isolated yield.
[c] The organozinc reagent was commercially available.
[d] 90% conversion (glc).
[e] Chromatographic yield.
[f] 5% of 2-*n*.propyl-4,6-dimethoxy-1,3,5-triazine was also present.[17]

65% yields, respectively (Table 4, entries 3 and 4), thus showing that aryldiethylalanes are at least comparable with aryltributyltin reagents in this type of cross-coupling reactions.[1e]

After investigation of the experimental conditions suitable for the selective transfer of alkyl, aryl, alkenyl residues, the synthesis of some functionalized derivatives was considered. The inspection of the literature would suggest use of organotin reagents, which tolerate most functional groups well, nevertheless the long and often expensive procedures necessary for their preparation prompted us to test the reactivity of **1** towards organozinc reagents.[18–21]

Commercial 4-carbethoxyphenylzinc iodide was reacted with **1** in the presence of $PdCl_2(PPh_3)_2$, after the reduction of the catalyst by iso-propylmagnesium chloride (Table 5, entry 1) and afforded the expected product **2p** in very good (78%) yield. This encouraging result suggested the use of organozinc reagents as alternative alkylating agents with respect of Grignard reagents.

Some organozinc derivatives were thus prepared by transmetallation,[21] starting from the corresponding organomagnesium compound and were used under the same reaction conditions affording **2p**.

The yields in the expected products, after generally short reaction times, were very good and polyalkylation byproducts were never observed in the reaction mixtures (Table 5, entries 2–5).

It has to be underlined that, when iso-propylzinc chloride was used, the reaction was not optimized to avoid the isomerization product (Table 5, entry 4) and that the cross-coupling with β-methallylzinc chloride afforded **2c** in moderate (42%) yield (Table 5, entry 5). Anyway, the simplicity of the whole one-pot cross-coupling process make it undoubtedly interesting in the planning of 2-alkyl-4,6-dialkoxy-1,3,5-triazines.

3. Conclusions

In the search for a general, simple approach to the synthesis of 2-alkyl (alk-1′-enyl- or aryl or allyl or benzyl)-4,6-dialkoxy-1,3,5-triazines, the reactivity of commercially available **1** has been investigated in Pd- or Ni-catalyzed cross-coupling processes with organostannanes, Grignard reagents, symmetrical and non-symmetrical organoalanes and organozinc halides. It has been found that all the organometallic reagents studied can be used to form new C–C bonds on the heteroaromatic ring and that the choice of the alkylating agent and/or the experimental conditions can be modulated in dependence on the residue to transfer. In particular: (i) according to what previously observed in the case of aryltin derivatives,[1e] alk-1-enyl- and allylstannanes afforded good results and, at least in the case of allyl derivative **2b**, suitable work-up conditions have been found to avoid double bond migration. (ii) Kumada cross-coupling proved a very simple, convenient and economical process for the transfer of saturated chains. Unfortunately, the same methodology was not synthetically useful to transfer benzyl and β-methallyl residues. In the case of aryl Grignard reagents, the yield seems to be affected by the nature of the substituents, although further experiments are necessary to account for this. (iii) Critical observations concerning the synthesis of alk-1-enyl organometallic reagents suggested the use of alk-1-enyldialkylalanes for the preparation of 2-(alk-1′-enyl)-4,6-dimethoxy-1,3,5-triazines. Unfortunately the reaction fails, even in the presence of $ZnCl_2$,[14b] in the case of α-branched and/or β-hindered residues. On the other hand, organoalanes (R_3Al) were found to be efficient agents in the alkylation, benzylation and arylation of **1**. This last process can be carried out also by using the economically more convenient aryldiethylalanes, which, at least in the case of **2j**, afforded the product in even better yield than using organotin derivatives.[1e] Moreover, the easy in situ preparative protocol of these organometallic reagents has to be underlined. (iv) The cross-coupling reactions between **1** and organozinc halides were also very interesting, not only for the synthesis of functionalized **2p**, but also in the case of **2c**,**f**, **h–j**

Our results provide useful guidelines to choose the suitable organometallic reagent (Sn, Mg, Al, Zn), as well as the catalytic system (Pd or Ni) for a direct, time-saving preparation of 2-alkyl (aryl or alk-1′-enyl or allyl)-4,6-dimethoxy-1,3,5-triazines.

4. Experimental

4.1. General procedures and materials

Solvents were purified and dried by standard methods.[22] 2-Chloro-4,6-dimethoxy-1,3,5-triazine (CDMT, **1**) was prepared according to a reported procedure.[23] Benzyl- and allylmagnesium chlorides (1 and 2 M, respectively in diethylether) and 4-carbethoxyphenylzinc iodide (0.5 M in THF) were purchased from Aldrich; the other Grignard reagents used were prepared from the corresponding alkyl halides according to reported procedures.[24,25] (*S*)-2-methylbutylmagnesium chloride was prepared from (*S*)-2-methyl-1-chlorobutane (optical purity 97.5%[26]). Hydroalumination

of alk-1-ynes was performed according to described protocols.[11a,27] Chlorotributyltin (Aldrich) and chlorodiethylalane (Schering) were distilled before use (bp 93–95 °C/0.2 mmHg[28] and 90 °C/10 mmHg[15]); aluminium trichloride was sublimed (194 °C)[29] under nitrogen; zinc dichloride (Aldrich) was dried at 140 °C/0.03 mmHg (15 h);[30] the catalysts $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$ and $NiCl_2$-(dppe) were prepared according to literature.[31–33] GLC analyses were performed on a Perkin–Elmer 8500 instrument [ZB1 capillary column (15 m×0.25 mm), film 0.25 μm] equipped with a flame ionization detector and a split–splitless injector, with He as carrier gas. The evaluation (glc) of conversions and yields was carried out by using suitable hydrocarbons as internal standards. Thin layer chromatography (TLC) analyses were performed on silica gel 60 plates (Fluka) and flash chromatography purifications were carried out on silica gel 60 (Fluka, 230–400 mesh) using the eluting mixtures (v/v) reported for each case. Melting points were determined using a Kofler hot-stage apparatus and are not corrected. Optycal rotatory power was measured by a Perkin–Elmer 142 polarimeter. ^1H and ^{13}C NMR (200 and 50 MHz, respectively) spectra were recorded on a Varian Gemini 200 spectrometer; all NMR data were obtained using $CDCl_3$ solutions if not otherwise stated. Chemical shifts (δ ppm) are referred to tetramethylsilane (TMS) (^1H NMR) or $CDCl_3$ (^{13}C NMR) as internal standard. Mass spectra (*m/z*, I%) were taken on a Perkin–Elmer Q-Mass 910 instrument.

4.2. Synthesis of organotin compounds

Chlorotributyltin (0.8 equiv) in THF was slowly added to a solution of the suitable Grignard reagent in the same solvent, and the reaction mixture was refluxed until complete conversion of the chlorotributyltin (GLC, GC/ms). The mixture was hydrolysed (NH_4Cl_{aq}) extracted with diethyl ether and dried; after removal of the solvent (20 mmHg) the crude product was purified by distillation. The pure organotin derivatives, obtained with the reported yield, showed: (*E*,*Z*)-prop-1-enyltributyltin (77%, bp 86–88 °C/1 mmHg, *E*/*Z*=60/40, glc); prop-2-enyltributyltin (81%, bp 84–87 °C/0.05 mmHg, lit.[34] 106 °C/0.1 mmHg); 2-methylprop-2-enyltributyltin (77%, bp 119–120 °C/1 mmHg, lit.[35] 110 °C/0.3 mmHg).

4.3. In situ preparation of symmetrical organoalanes

In a typical procedure, an ethereal solution of freshly sublimed $AlCl_3$ (0.400 g, 3.00 mmol) was slowly added to the suitable Grignard reagent (3 equiv) and the mixture was stirred for 1–12 h at room temperature.

4.4. In situ preparation of diethylbenzyl (or aryl) organoalanes

In a typical procedure, the suitable Grignard reagent (1 equiv) was added to a cooled (0 °C) ethereal solution of freshly distilled Et_2AlCl (0.2 ml, 1.6 mmol), and the reaction mixture was stirred at room temperature for 8 h.

4.5. In situ preparation of organozinc halides

In a typical procedure, the suitable Grignard reagent (1 equiv) was slowly added to a cooled (0 °C) diethyl ether solution of dry $ZnCl_2$ (0.615 g, 4.60 mmol) and the mixture was stirred at 0 °C for 15 min.

4.6. Reaction of 1 with organotin compounds (Scheme 1)

In a typical procedure, a THF (20 ml) solution of **1** (0.500 g, 2.85 mmol) was treated, under nitrogen, with $PdCl_2(PPh_3)_2$ (0.03 equiv) and the suitable organotin compound (1.1 equiv); the mixture was refluxed (12–40 h) until satisfactory conversion of **1** (TLC and glc) was achieved. The reaction mixture was cooled and treated according to one of the following procedures: Procedure A: (1) treatment with 60% KF aqueous solution; (2) filtration on Florisil®/silica gel; Procedure B: (1) filtration on Florisil®/silica gel; (2) treatment with 60% KF aqueous solution. The recovered organic phase was dried over Na_2SO_4 and, after removal of solvents, the crude products were purified by flash chromatography. Chemically pure **2a–c** (for the characterizations see below) were isolated in 70, 69 and 55% yields, respectively.

4.7. Reaction of 1 with RMgX (Table 1)

In a typical procedure, the suitable Grignard reagent (1.15 equiv) was quickly added to a cooled (0 °C) solution of **1** (0.500 g, 2.85 mmol) and $NiCl_2$(dppe) (0.05 equiv) in diethyl ether. The mixture was stirred at room temperature until a satisfactory conversion of **1** (TLC and glc) was achieved. After hydrolysis with a saturated solution of NH_4Cl, the reaction mixture was extracted in $CHCl_3$, dried over Na_2SO_4 and, after removal of the solvent, the crude products were purified by flash chromatography. Chemically pure **2d–j** (for the characterizations see below) were isolated in 30–75% yields.

4.8. Reaction of 1 with alk-1-enyldi-isobutylalanes (Table 2)

The hexane solution of alkenylalane was diluted with THF (THF/hexane see Table 2) and treated with **1** (0.500 g, 2.85 mmol) and $Pd(PPh_3)_4$ (0.03 equiv); the reaction mixture was stirred at the temperature and for the time reported in Table 2 and was monitored by TLC and glc. After hydrolysis with a saturated aqueous solution of NH_4Cl, the reaction mixture was extracted with $CHCl_3$, dried over Na_2SO_4 and, after removal of the solvent, the crude products were purified by flash chromatography. Chemically pure **2k** and **l** (for the characterizations see below) were isolated in 58 and 51% yields, respectively.

4.9. Reaction of 1 with symmetrical organoalanes (Table 3)

A mixture of solid **1** (0.500 g, 2.85 mmol) and $PdCl_2(PPh_3)_2$ (0.03 equiv) was added to the white suspension of AlR_3 and the mixture was stirred under the experimental conditions described in Table 3 until the maximum conversion of **1** (TLC and glc) was achieved. After hydrolysis with a saturated aqueous solution of NH_4Cl, the reaction mixture was extracted with $CHCl_3$, dried over Na_2SO_4 and, after removal of the solvent, the crude products were purified by flash chromatography. Chemically pure **2d–j**,**m–o** (for the

characterizations see below) were isolated in 43–88% yields.

4.10. Reaction of 1 with benzyl (or aryl) diethylalanes (Table 4)

Following the same protocol as 4.9, compound **1** (0.500 g, 2.85 mmol), $Pd(PPh_3)_4$ (0.03 equiv) and the organoalanes were reacted under the experimental conditions specified in Table 4. The reaction mixture was stirred until the complete conversion of **1** (TLC and glc) was achieved. After hydrolysis with a saturated solution of NH_4Cl, the reaction mixture was extracted with $CHCl_3$, dried over Na_2SO_4 and, after removal of the solvent, the crude products were purified by flash chromatography. The reaction afforded **2g**,**h**,**j** in 35, 65 and 71% yields, respectively.

4.11. Reaction of 1 with RZnX (Table 5)

To the suspension of organozinc halide, **1** (0.500 g, 2.85 mmol) and the catalyst, prepared immediately before use by addition of 2 equiv of *i*-PrMgCl to $PdCl_2(PPh_3)_2$, were added. The reaction mixture was stirred at room temperature until the complete conversion of **1** (TLC and glc) was achieved (Table 5). After hydrolysis with a saturated aqueous solution of NH_4Cl, the reaction mixture was extracted with $CHCl_3$, dried over Na_2SO_4 and, after removal of the solvent, the crude products were purified by flash chromatography. The reaction afforded **2c**,**f**,**h**,**j**,**p** in 42–91% yields (Table 5).

4.12. Characterization of products 2a–p

For each of the prepared products the flash chromatography conditions, as well as the chemical-physical and spectroscopic characterization are reported.

4.12.1. (*E*/*Z*) 2-(1′-Propenyl)-4,6-dimethoxy-1,3,5-triazine ((*E*/*Z*)-2a). Hexane/acetone 75/25 v/v, pale yellow oil; diastereoisomeric ratio *E*/*Z* (glc): 60/40; GC/ms (*m*/*z*, I%) for Z isomer: 181 ($M^{+\cdot}$, 12), 166 (100), 151 (36), 109 (52), 82 (9), 66 (18), 58 (49); for *E* isomer see 4.12.2; ^{1}H NMR: 1.98, 2.35 (2dd, J=7.0 Hz, J'=1.2 Hz, J=7.0 Hz, J'=1.7 Hz, 3H), 4.05 (s, 6H), 6.27–6.53, 7.43 (m and dq, J=16.0 Hz, J'=7.0 Hz, 2H); ^{13}C NMR: 26.7, 27.7, 54.0, 54.9, 127.3, 129.2, 142.3, 172.4, 174.5, 175.3. Anal. Calcd for $C_8H_{11}N_3O_2$: C 53.03, H 6.12, N 23.19%; found: C 53.09, H 6.14, N 23.15%.

4.12.2. (*E*)-2-(1′-Propenyl)-4,6-dimethoxy-1,3,5-triazine ((*E*)-2a). Hexane/ethyl acetate 70/30 v/v, pale yellow oil; GC/ms (*m*/*z*, I%): 181 ($M^{+\cdot}$, 100), 166 (43), 151 (34), 136 (47), 126 (14), 109 (26), 93 (21), 82 (18), 69 (41), 58 (60); ^{1}H NMR: 1.98 (dd, J=7.0 Hz, J'=1.6 Hz, 3H), 4.04 (s, 6H), 6.37 (dq, J=16.0 Hz, J'=1.6 Hz, 1H), 7.43 (dq, J=15.0 Hz, J'=7.0 Hz, 1H); ^{13}C NMR: 29.6, 54.8, 129.2, 142.5, 172.4, 174.5. Anal. Calcd for $C_8H_{11}N_3O_2$: C 53.03, H 6.12, N 23.19%; found: C 53.09, H 6.14, N 23.15%.

4.12.3. 2-(2′-Propenyl)-4,6-dimethoxy-1,3,5-triazine (2b). Hexane/ethyl acetate 70/30 v/v, pale yellow oil; GC/ms (*m*/*z*, I%): 181 ($M^{+\cdot}$, 15), 180 (99), 155 (7), 108 (4), 82 (6), 69 (4), 41 (73), 39 (100); ^{1}H NMR (C_6D_6): 3.44 (dt, J=6.9 Hz, J'=1.5 Hz, 2H), 3.61 (s, 6H), 5.03–5.16 (m, 2H), 6.20 (ddt, J=17.2 Hz, J'=10.1 Hz, J''=6.9 Hz, 1H), ^{13}C NMR (C_6D_6): 43.3, 54.5, 117.4, 133.5, 173.0, 181.2. Anal. Calcd for $C_8H_{11}N_3O_2$: C 53.03, H 6.12, N 23.19%; found: C 53.00, H 6.15, N 23.23%.

4.12.4. 2-(2′-Methyl-2′-propenyl)-4,6-dimethoxy-1,3,5-triazine (2c). Petroleum spirit/ethyl acetate 85/15 v/v, pale yellow oil; GC/ms (*m*/*z*, I%): 195 ($M^{+\cdot}$, 22), 194 (100), 181 (6), 180 (67), 155 (25), 126 (6), 125 (5), 123 (8), 122 (6), 109 (9), 96 (9), 95 (7), 82 (8), 80 (7), 72 (14), 70 (13), 69 (10), 58 (11); ^{1}H NMR: 1.47 (s, 3H), 3.50 (s, 2H), 4.09 (s, 6H), 4.92 (d, J=1.5 Hz, 1H), 4.96 (d, J=1.5 Hz 1H); ^{13}C NMR: 22.8, 47.4, 55.2, 114.4, 140.9, 172.8, 181.4. Anal. Calcd for $C_9H_{13}N_3O_2$: C 55.37, H 6.71, N 21.52%; found: C 55.33, H 6.75, N 21.50%.

4.12.5. 2-Ethyl-4,6-dimethoxy-1,3,5-triazine (2d). Petroleum spirit/ethyl acetate 70/30 v/v; white solid mp 67 °C; GC/ms: (*m*/*z*, I%): 170 (4), 169 ($M^{+\cdot}$, 100), 168 (67), 154 (41), 101 (30), 83 (10), 70 (55), 69 (54), 68 (19), 58 (6), 56 (14); ^{1}H NMR: 1.38 (t, J=7.7 Hz, 3H), 2.83 (q, J=7.6 Hz, 2H), 4.10 (s, 6H); ^{13}C NMR: 11.5, 32.1, 55.3, 172.7, 184.5. Anal. Calcd for $C_7H_{11}N_3O_2$: C 49.70, H 6.55, N 24.84%; found: C 49.73, H 6.57, N 24.80%.

4.12.6. 2-(2′-Methylpropyl)-4,6-dimethoxy-1,3,5-triazine (2e). Hexane/ethyl acetate 70/30 v/v, yellow oil; GC/ms (*m*/*z*, I%): 197 ($M^{+\cdot}$, 1), 196 (4), 182 (36), 155 (100), 126 (10), 101 (4), 82 (14), 72 (16), 69 (12), 58 (46), 55 (23); ^{1}H NMR: 0.79 (d, J=6.6 Hz, 6H), 2.12 (sept, J=6.8 Hz, 1H), 2.44 (d, J=7.2 Hz, 2H), 3.87 (s, 6H); ^{13}C NMR: 22.3, 27.4, 47.4, 54.8, 172.2, 182.6. Anal. Calcd for $C_9H_{15}N_3O_2$: C 54.81, H 7.67, N 21.30%; found: C 54.84, H 7.69, N 21.28%.

4.12.7. 2-*iso*Propyl-4,6-dimethoxy-1,3,5-triazine (2f). Hexane/ethyl acetate 80/20 v/v, yellow oil; GC/ms (*m*/*z*, I%): 183 ($M^{+\cdot}$, 13), 182 (10), 169 (10), 168 (100), 72 (10), 70 (14), 69 (13), 68 (24), 58 (13); ^{1}H NMR: 1.19 (d, J=13.2 Hz, 6H), 2.86 (sept, J=13.3 Hz, 1H), 3.92 (s, 6H); ^{13}C NMR: 20.5, 36.8, 54.8, 172.3, 187.4. Anal. Calcd for $C_8H_{13}N_3O_2$: C 52.45, H 7.15, N 22.94%; found: C 52.48, H 7.11, N 22.90%.

4.12.8. 2-Benzyl-4,6-dimethoxy-1,3,5-triazine (2g). Hexane/acetone 80/20 v/v, dark yellow oil; GC/ms: (*m*/*z*, I%): 231 ($M^{+\cdot}$, 38), 230 (100), 216 (14), 201 (6), 159 (9), 158 (9), 132 (23), 117 (12), 116 (12), 91 (18), 69 (4); ^{1}H NMR: 4.06 (s, 6H), 4.08 (s, 2H), 7.20–7.50 (m, 5H); ^{13}C NMR: 45.0, 54.8, 126.6, 128.3, 129.2, 136.3, 172.4, 181.3. Anal. Calcd for $C_{12}H_{13}N_3O_2$: C 62.33, H 5.67, N 18.17%; found: C 62.35, H 5.70, N 18.13%.

4.12.9. 2-Phenyl-4,6-dimethoxy-1,3,5-triazine (2h). Petroleum spirit/ethyl acetate 85/15 v/v, white solid mp 66 °C; GC/ms: 218 (M^{+}+1, 13), 217 ($M^{+\cdot}$, 100), 216 (33), 187 (45), 186 (27), 172 (49), 104 (49), 103 (19), 77 (17), 69 (28); ^{1}H NMR: 4.21 (s, 6H), 7.52–7.66 (m, 3H), 8.56–8.60 (m, 2H); ^{13}C NMR: 55.4, 128.7, 129.3, 133.0, 135.3, 173.2, 175.2. Anal. Calcd for $C_{11}H_{11}N_3O_2$: C 60.82, H 5.10, N 19.34%; found: C 60.84, H 5.07, N 19.36%.

4.12.10. 2-(3′-Fluorophenyl)-4,6-dimethoxy-1,3,5-triazine (2i). Chemical–physical and spectroscopic properties were in agreement with the previously reported characterization.[1e]

4.12.11. 2-(4′-Methoxyphenyl)-4,6-dimethoxy-1,3,5-triazine (2j). Hexane/ethyl acetate 80/20 v/v; white solid mp 93–95 °C; GC/ms (*m/z*, I%): 247 ($M^{+\cdot}$, 100), 217 (20), 202 (35), 176 (18), 159 (10), 134 (54), 90 (12), 69 (13); ^{1}H NMR: 3.88 (s, 3H), 4.11 (s, 6H), 6,97 (d, J=9.1 Hz, 2H), 8,46 (d, J=9.1 Hz, 2H), ^{13}C NMR: 55.0, 55.4, 113.8, 127.5, 130.9, 163.6, 172.7, 174.4. Anal. Calcd for $C_{12}H_{13}N_3O_3$: C 58.29, H 5.30, N 16.99%; found: C 58.32, H 5.27, N 16.96%.

4.12.12. 2-(Hex-1′-enyl)-4,6-dimethoxy-1,3,5-triazine (2k). Hexane/acetone 85/15 v/v; yellow oil; GC/ms (*m/z*, I%): 223 ($M^{+\cdot}$, 29), 208 (55), 194 (100), 180 (66), 166 (37), 155 (31), 151 (7), 122 (11), 108 (9), 94 (14), 80 (28), 69 (21), 58 (73); ^{1}H NMR: 0.86 (t, J=7.0 Hz, 3H), 1.17–1.50 (m, 4H), 2.25 (qd, J=7.3 Hz, J'=1.5 Hz, 2H), 3.99 (s, 6H), 6.28 (dt, J=15.2 Hz, J'=1.8 Hz, 1H), 7.23 (dt, J=15.6 Hz, J'=7.0 Hz, 1H); ^{13}C NMR: 14.0, 22.5, 30.5, 32.6, 55.1, 128.0, 147.9, 172.7, 175.0. Anal. Calcd for $C_{11}H_{17}N_3O_2$: C 59.17, H 7.67, N 18.82%; found: C 59.20, H 7.68, N 18.80%.

4.12.13. 2-(2′-Phenylethenyl)-4,6-dimethoxy-1,3,5-triazine (2l). Petroleum spirit/ethyl acetate 70/30 v/v; white solid mp 82–84 °C; GC/ms (*m/z*, I%): 243 ($M^{+\cdot}$, 32), 242 (100), 228 (19), 185 (25), 171 (10), 170 (32), 128 (32), 77 (12), 69 (9); ^{1}H NMR: 4.15 (s, 6H), 7.08 (d, J=15.7 Hz, 1H), 7.46 (m, 3H), 7.68 (m, 2H), 8.24 (d, J=15.7 Hz, 1H); ^{13}C NMR: 55.2, 125.5, 128.4, 129.1, 130.2, 135.5, 142.8, 172.8, 175.1. Anal. Calcd for $C_{13}H_{13}N_3O_2$: C 64.19, H 5.39, N 17.27%; found: C 64.21, H 5.42, N 17.24%.

4.12.14. 2-*n*-Hexyl-4,6-dimethoxy-1,3,5-triazine (2m). Hexane/ethyl acetate 80/20 v/v; yellow oil; GC/ms (*m/z*, I%): 224 ($M^{+\cdot}-1$, 1), 210 (5), 182 (30), 168 (39), 155 (100), 87 (7), 72 (9), 69 (6); ^{1}H NMR: 0.68 (t, J=6.9 Hz, 3H), 1.06–1.20 (m, 6H), 1.59 (tt, J=J'=7.6 Hz, 2H), 2.53 (t, J=7.6 Hz, 2H) 3.84 (s, 6H); ^{13}C NMR: 13.8, 22.3, 27.1, 28.7, 31.3, 38.4, 54.7, 172.2, 183.4. Anal. Calcd for $C_{11}H_{19}N_3O_2$: C 58.64, H 8.50, N 18.65%; found: C 58.67, H 8.46, N 18.67%.

4.12.15. 2-[(*S*)-2′-Methylbuthyl]-4,6-dimethoxy-1,3,5-triazine (2n). Hexane/ethyl acetate 70/30 v/v; yellow oil, $[\alpha]_{589}^{26}$ +4.04° (*c* 0.99, $CHCl_3$); GC/ms (*m/z*, I%): 211 ($M^{+\cdot}$, 0.3), 210 (0.8), 196 (17.5), 182 (20), 155 (100), 72 (11), 69 (6), 58 (34), 41 (45); ^{1}H NMR: 0.72–0.77 (d and t, J_d= 6.6 Hz, J_t=7.3 Hz, 6H), 1.11 (m, 1H), 1.25 (m, 1H), 1,92 (m, 1H), 2.35 (dd, J=13.5 Hz, J'=8.1 Hz, 1H), 2.58 (dd, J=13.5 Hz, J'=6.3 Hz, 1H), 3.9 (s, 6H); ^{13}C NMR: 11.1, 18.9, 29.2, 33.6, 45.4, 54.8, 172.2, 182.9. Anal. Calcd for $C_{10}H_{17}N_3O_2$: C 56.85, H 8.11, N 19.89%; found: C 56.84, H 8.09, N 19.92%.

4.12.16. 2-(2′-Methylprop-1′-enyl)-4,6-dimethoxy-1,3,5-triazine (2o). Petroleum spirit/ethyl acetate 90/10 v/v; yellow oil; GC/ms (*m/z*, I%): 195 ($M^{+\cdot}$, 3), 181 (10), 180 (100), 165 (24), 123 (29), 122 (13), 80 (14), 69 (3), 58 (10); ^{1}H NMR: 1.98 (m, 3H), 2.34 (m, 3H), 3.99 (s, 6H), 6.18 (m, 1H); ^{13}C NMR: 21.5, 28.8, 55.2, 123.5, 155.0, 172.6, 175.6. Anal. Calcd for $C_9H_{13}N_3O_2$: C 55.37, H 6.71, N 21.52%; found: C 55.39, H 6.74, N 21.49%.

4.12.17. 2-(4′-Ethoxycarbonylphenyl)-4,6-dimethoxy-1,3,5-triazine (2p). Hexane/ethyl acetate 70/30 v/v; white solid, mp 89–91 °C; GC/ms (*m/z*, I%): 289 ($M^{+\cdot}$, 75), 261 (11), 259 (26), 245 (16), 244 (100), 231 (11), 216 (18), 186 (44), 176 (27), 159 (33), 148 (16), 144 (27), 132 (10), 130 (28), 116 (12), 107 (12), 104 (10), 103 (20), 102 (44), 100 (26), 99 (15), 90 (10), 84 (12), 76 (27), 75 (25), 72 (48), 70 (14), 69 (66); ^{1}H NMR: 1.40 (t, J=7.1 Hz, 3H), 4.11 (s, 6H), 4.39 (q, J=7.1 Hz, 2H), 8.12 (d, J=8.7 Hz, 2H), 8.53 (d, J=8.7 Hz, 2H); ^{13}C NMR: 14.3, 55.3, 61.5, 128.9, 129.6, 134.1, 138.9, 166.1, 173.0, 174.1. Anal. Calcd for $C_{14}H_{15}N_3O_4$: C 58.13, H 5.23, N 14.53%; found: C 58.15, H 5.20, N 14.57%.

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