Insertion of Arynes into Carbon–Chlorine Bonds of Chlorotriazines

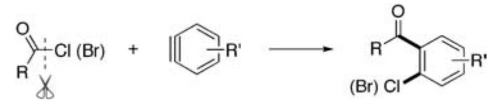
Hiroto Yoshida,* Yasuhiro Mimura, and Joji Ohshita
Department of Applied Chemistry, Graduate School of Engineering, Hiroshima University,
Higashi-Hiroshima 739-8527

(Received September 16, 2009; CL-090835; E-mail: yhiroto@hiroshima-u.ac.jp)

A variety of chlorotriazines were found to undergo insertion of arynes at their carbon–chlorine bonds, leading to formation of triarylated triazines in a straightforward manner.

In view of a considerable demand for efficacious methods for synthesizing complex organic halides that can be transformed into diverse molecules via cross-coupling reaction etc., development of insertion reactions of unsaturated carbon–carbon compounds into a carbon–halogen σ-bond, which enable a carbon–carbon and a carbon–halogen bonds to be constructed simultaneously, has been an essential subject in synthetic organic chemistry (eq 1).[1] In this context, we have already disclosed that a carbonyl carbon–chlorine (or bromine) σ bond of acid chlorides (or bromides) is facilely added across a carbon–carbon triple bond of arynes, demonstrating that a carbon and a halogen functional groups can be installed into neighboring positions of aromatic rings all at once (eq 2).[2–4] Since six-membered nitrogen-heteroaromatic compounds bear marked electronic and structural resemblances to carbonyl compounds, we envisaged that those with a halogen substituent should participate in the reaction with arynes, providing a new method for constructing aryl–heteroaryl bonds. Herein we report on the insertion reaction of arynes into carbon–chlorine bonds of chlorotriazines, which offers a direct approach to triaryltriazines.

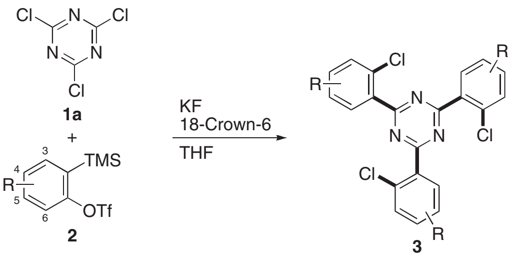
(1)



(2)

A reaction of cyanuric chloride (2,4,6-trichloro-1,3,5-triazine, **1a**) with in situ-generated benzyne (from **2a**[5] and KF/18-crown-6) was initially carried out in THF at 0 °C to afford a 35% yield of 2,4,6-tris(2-chlorophenyl)-1,3,5-triazine (**3aa**), in which three aryl–heteroaryl bond forming processes took place via benzyne insertion into all of the carbon–chlorine bonds of **1a** (Entry 1, Table 1). Substituted arynes such as 3,6-dimethylbenzyne (from **2b**) or 4,5-dimethylbenzyne (from **2c**) could also take part in the reaction, giving the respective products (**3ab** or **3ac**) in 33 or 27% yield (Entries 2 and 3), and furthermore, **1a** underwent the insertion of three molar equivalents of cycloalkane-condensed arynes (from **2d** or **2e**) or 2,3-naphthalyne (from **2f**) (Entries 4–6). In some cases, *ortho*-chloro(trimethylsilyl)arenes and bis(2-chloroaryl)triazines[6] arising from the insertion of two molar equivalents of arynes were produced as by-products (Figure 1).

Table 1. Insertion of arynes into cyanuric chloride[a]



Entry	R	Temp/°C	Time/h	Yield/%[b]	3
1	H (**2a**)	0	8	35	**3aa**
2	3,6-Me$_2$ (**2b**)	0	23	33	**3ab**
3	4,5-Me$_2$ (**2c**)	50	2	27	**3ac**
4	4,5- –(CH$_2$)$_3$– (**2d**)	50	6	31	**3ad**
5	4,5- –(CH$_2$)$_4$– (**2e**)	50	3	20	**3ae**
6	4,5- –(CH)$_4$– (**2f**)	50	6.5	14	**3af**

[a]The reaction was carried out in THF (2 mL) using **1a** (0.1 mmol), **2** (0.3 mmol), KF (0.6 mmol), and 18-crown-6 (0.6 mmol). [b]Isolated yield based on **1a**.

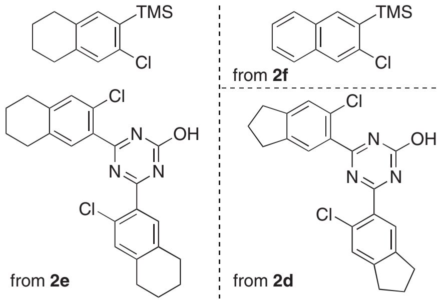
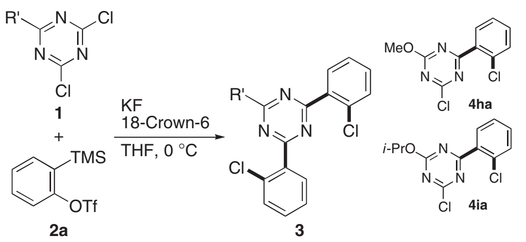


Figure 1. By-products formed in the reaction of **1a** with arynes.

Next we investigated the reaction of dichlorotriazines as shown in Table 2. Similarly to the case of **1a**, both of the carbon–chlorine bonds of 2-(2-chlorophenyl)-4,6-dichloro-1,3,5-triazine (**1b**) were added to benzyne to furnish **3aa** as the sole product in 58% yield (Entry 1). Dichlorotriazines having 3-cyanophenyl (**1c**) or 4-(trifluoromethyl)phenyl moiety (**1d**) reacted with two molar equivalents of benzyne as well, offering moderate yields of the respective products (**3ca** or **3da**) (Entries 2 and 3), and the insertion of benzyne also occurred with aryldichlorotriazines **1e**–**1g**, although the yields were rather low (Entries 4–6). Treatment of alkoxydichlorotriazines (**1h** or **1i**) with benzyne gave a mixture of diarylated (**3ha** or **3ia**) and monoarylated triazines (**4ha** or **4ia**) in approximately equal ratios (Entries 7 and 8), and moreover, no trace of the insertion product was formed in the reaction of aminodichlorotriazine **1j** (Entry 9), which implies that introduction of an electron-donating group into the triazine ring retards the reaction.

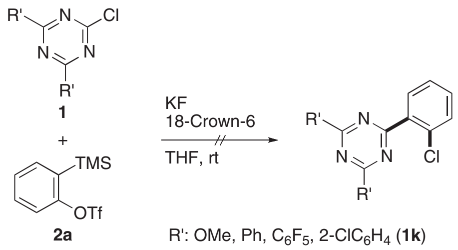
In marked contrast to the above results, monochlorotriazines did not undergo the insertion of benzyne at all (Scheme 1).[7] In particular, it should be noted that 2,4-bis(2-chlorophenyl)-6-

Table 2. Insertion of benzyne into dichlorotriazines[a]



Entry	R′	Time/h	Yield/%[b]	3
1[c]	$\text{2-ClC}_6\text{H}_4$ (**1b**)	15	58	**3aa**
2	$\text{3-NCC}_6\text{H}_4$ (**1c**)	8	43	**3ca**
3[c]	$\text{4-F}_3\text{CC}_6\text{H}_4$ (**1d**)	8	39	**3da**
4	$\text{4-ClC}_6\text{H}_4$ (**1e**)	9	30	**3ea**
5	$\text{4-NCC}_6\text{H}_4$ (**1f**)	11	21	**3fa**
6	$\text{3,5-(F}_3\text{C)}_2\text{C}_6\text{H}_3$ (**1g**)	7	20	**3ga**
7[d,e]	MeO (**1h**)	8	37	**3ha**
8[f]	*i*-PrO (**1i**)	10	29	**3ia**
9	(i-Pr)$_2$N (**1j**)	24	—	—

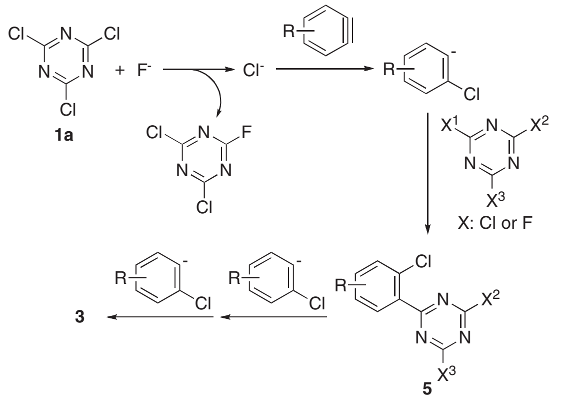
[a]The reaction was carried out in THF (2 mL) at 0 °C using **1** (0.1 mmol), **2a** (0.2 mmol), KF (0.4 mmol), and 18-crown-6 (0.4 mmol). [b]Isolated yield based on **1**. [c]**2a**: 0.4 mmol, KF: 0.8 mmol, 18-crown-6: 0.8 mmol. [d]**2a**: 0.3 mmol, KF: 0.6 mmol, 18-crown-6: 0.6 mmol. [e]2-(2-Chlorophenyl)-4-chloro-6-methoxy-1,3,5-triazine (**4ha**) was also produced in 49% yield. [f]2-(2-Chlorophenyl)-4-chloro-6-isopropoxy-1,3,5-triazine (**4ia**) was also produced in 38% yield.



Scheme 1. Reaction of monochlorotriazines.

chloro-1,3,5-triazine (**1k**) was absolutely inert toward the reaction, which shows that **1k** is definitely not an intermediate in the formation of **3aa** from **1a** or **1b**.[8]

A plausible pathway for the insertion reaction, which commences with generation of a chloride ion by nucleophilic substitution of cyanuric chloride with a fluoride ion, is depicted in Scheme 2. Subsequent nucleophilic attack of the chloride ion to an aryne produces a 2-chloroaryl anion, which then adds to a trihalogenated triazine (X: Cl or F) to give a mono(2-chloroaryl)triazine **5**. Finally, successive addition of the 2-chloroaryl anion to **5** and the resulting bis(2-chloroaryl)triazine leads to the formation of tris(2-chloroaryl)triazine **3**. The inertness of aminodichlorotriazine **1j** and monochlorotriazines toward the present reaction can rationally be explained by diminished electrophilicity of the triazine rings compared with those of **1a**–**1i**, which inhibits the generation of a chloride ion via the nucleophilic substitution with a fluoride ion. According to the proposed reaction pathway, formation of *ortho*-chloro(trimethylsilyl)arenes would be ascribable to the reaction of a 2-chloroaryl anion with Me_3Si–X′ (X′: Cl, F, or OTf).



Scheme 2. A pathway for the insertion reaction.

In conclusion, we have demonstrated that arynes are facilely inserted into carbon–chlorine bonds of dichlorotriazines of sufficient electrophilicity or cyanuric chloride, which enables multiple aryl–heteroaryl bonds to be constructed all in one pot.[9] Further studies on insertion reactions of arynes into other carbon–halogen σ bonds are in progress.

We thank Central Glass Co., Ltd. for a generous gift of trifluoromethanesulfonic anhydride.

References and Notes

1 For recent examples, see: G. R. Cook, R. Hayashi, *Org. Lett.* **2006**, *8*, 1045; T. Kashiwabara, K. Fuse, R. Hua, M. Tanaka, *Org. Lett.* **2008**, *10*, 5469; K. Oh, H. Kim, F. Cardelli, T. Bwititi, A. M. Martynow, *J. Org. Chem.* **2008**, *73*, 2432; T. Iwai, T. Fujihara, J. Terao, Y. Tsuji, *J. Am. Chem. Soc.* **2009**, *131*, 6668; Z. Liu, J. Wang, Y. Zhao, B. Zhou, *Adv. Synth. Catal.* **2009**, *351*, 371.

2 H. Yoshida, Y. Mimura, J. Ohshita, A. Kunai, *Chem. Commun.* **2007**, 2405.

3 We have also reported on insertion reactions of arynes into other nucleophilic–electrophilic σ bonds: H. Yoshida, E. Shirakawa, Y. Honda, T. Hiyama, *Angew. Chem., Int. Ed.* **2002**, *41*, 3247; H. Yoshida, T. Terayama, J. Ohshita, A. Kunai, *Chem. Commun.* **2004**, 1980; H. Yoshida, T. Minabe, J. Ohshita, A. Kunai, *Chem. Commun.* **2005**, 3454; H. Yoshida, M. Watanabe, J. Ohshita, A. Kunai, *Chem. Commun.* **2005**, 3292; H. Yoshida, M. Watanabe, J. Ohshita, A. Kunai, *Tetrahedron Lett.* **2005**, *46*, 6729; H. Yoshida, M. Watanabe, J. Ohshita, A. Kunai, *Chem. Lett.* **2005**, *34*, 1538; H. Yoshida, M. Watanabe, T. Morishita, J. Ohshita, A. Kunai, *Chem. Commun.* **2007**, 1505; H. Yoshida, T. Kishida, M. Watanabe, J. Ohshita, *Chem. Commun.* **2008**, 5963.

4 For a review on insertion reactions of arynes into element–element σ bonds, see: D. Peña, D. Pérez, E. Guitián, *Angew. Chem., Int. Ed.* **2006**, *45*, 3579.

5 Y. Himeshima, T. Sonoda, H. Kobayashi, *Chem. Lett.* **1983**, 1211.

6 These products were isolated as hydroxytriazines probably via the hydrolysis of the unreacted carbon–chlorine bond.

7 The reaction of other nitrogen-heteroaromatic compounds including 2-chloropyridine, 2-bromopyridine, 2-bromo-3-nitropyridine, and 2-bromopyrimidine with benzyne did not afford the desired insertion products at all.

8 This result also indicates that the common pathway for the aryne insertion reactions into nucleophilic–electrophilic σ bonds, which starts with the formation of zwitterions, would not be operative in the present reaction. For the detailed pathway, see Refs. 3 and 4.

9 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

Published on the web (Advance View) October 31, 2009; doi:10.1246/cl.2009.1132