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Perfluoroalkylations and perfluorooxaalkylations. Part 3. Chloro-substituted diazines as substrates in copper-mediated cross-coupling ☆

Grace J. Chen, Loomis S. Chen *

University of Dayton Research Institute, Dayton, OH 45469-0168, USA

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Abstract

The (perfluoroalkyl)- and (perfluorooxaalkyl)diazines, 2,4-bis(perfluorooctyl)pyrimidine (**3**), 2,4,6-tris(perfluorooctyl)pyrimidine (**6a**), 2,4,6-tris(perfluoro-6-methyl-5-oxaheptyl)pyrimidine (**6b**), 3,6-bis(perfluorooctyl)pyridiazine (**10**) and 2,6-bis(perfluorooctyl)-pyrazine (**13**), have been prepared in good yield. This was accomplished by using chloro-substituted diazines as substrates in copper-mediated cross-coupling reactions with perfluoroalkyl and perfluorooxaalkyl iodides. The yields of the cross-coupled products are influenced by the reaction conditions as well as by the structure of the fluoroaliphatic iodides and substrates.

Keywords: Perfluoroalkylations; Perfluorooxaalkylations; Chloro-substituted diazines; Cross-coupling; NMR spectroscopy; Mass spectrometry

1. Introduction

In previous communications [1,2], we have reported on the synthesis of fluoroalkyl- and fluorooxaalkyl-substituted aromatic compounds from bromoaromatic substrates involving fluoroalkyl- and fluorooxaalkyl-copper intermediates. Subsequently, this study was extended to the perfluoroalkylation of different di- and tri-chlorodiazines, and we now report the results.

Perfluoroalkylation via copper coupling reactions of the bromo- or iodo-pyridines and pyrimidine with perfluoroalkyl iodides gave good to excellent yields of perfluoroalkylated products [3–6]. Using similar experimental conditions as above, only low yields of the desired products were obtained from a chlorosubstituted triazine [3]. Since there are a greater variety of chloro-substituted diazines than the iodo or bromo analogs, the chloro-substituted diazines were selected as substrates in the present study (see Scheme 1).

2. Experimental details

All reactions were carried out in oven-dried glassware under an atmosphere of dry nitrogen. Copper bronze was purchased from Gallard Schlesinger Chemical Manufacturing Corporation, New York and used without activation. The chloro-substitued diazines, 2,2′-bipyridine, DMF (anhydrous) and dimethyl sulfoxide (DMSO, spectrographic grade) were commercial samples. The $(CF_3)_2CFO(CF_2)_4I$ was obtained from Allied Chemical Co. Hexafluorobenzene and perfluorooctyl iodide (**2**) were from PCR, Inc., FL. $C_3F_7OCF(CF_3)CF_2$-$OCF(CF_3)I$ was prepared by a reported procedure [2]. Gas chromatographic analyses were performed on a Perkin-Elmer Sigma I instrument with a 6 ft stainless-steel column (1/4 in i.d.) packed with 10% SE-30 on 80–100 mesh Supelcoport or on a HP 5890 Series II instrument with a 30 m, DB-1 capillary column. The GC–MS analyses were performed on a Finnigan 4021 mass spectrometer in the electron impact mode. Infrared spectra were recorded on a Perkin-Elmer 683 spectrometer. NMR spectra were obtained on an NT-300 spectrometer. All temperatures are uncorrected. Most compounds were characterized by a combination of analytical techniques, e.g., IR, GC–MS, NMR and elemental analyses (see Tables 1 and 2).

2.1. Synthesis of 2,6-bis(perfluorooctyl)pyrazine (13)

A mixture of 2,6-dichloropyrazine (**12**) (1.0 g, 6.71 mmol), n-$C_8F_{17}I$ (**2**) (11.0 g, 20.1 mmol), copper bronze (2.81 g, 44.3 mmol), 2,2′-bipyridine (0.22 g, 1.41 mmol)

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* Corresponding author.

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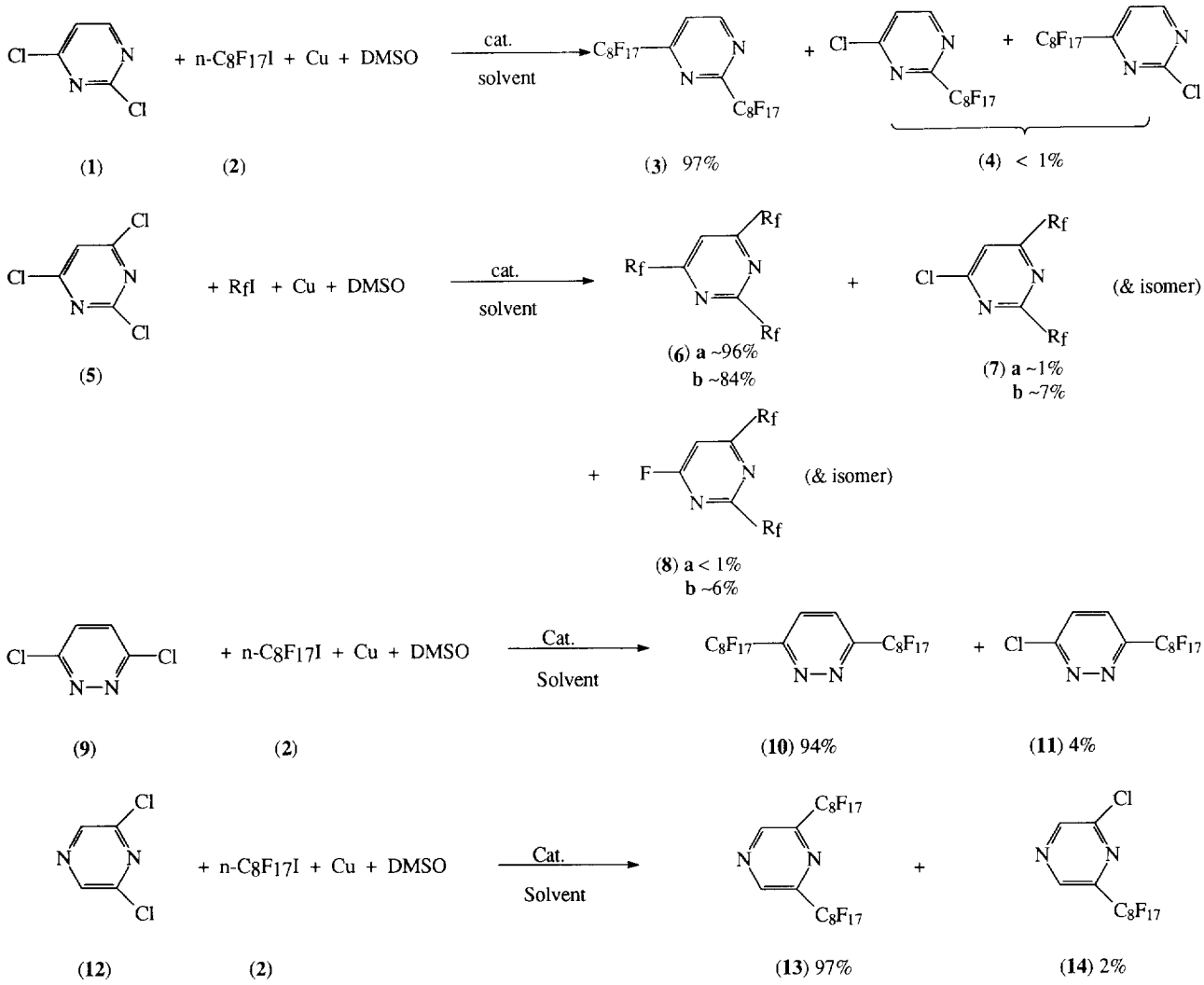


6, 7, 8: **a**, $R_f = R_f^1 = n\text{-}C_8F_{17}$; **b**, $R_f = R_f^2 = (CF_3)_2CFO(CF_2)_4$

Cat.: 2,2'-bipyridine

Solvent: C_6F_6

Structures of compounds **4**, **7**, **8**, **11** and **14** indicated by GC/MS alone.

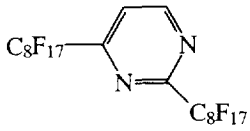
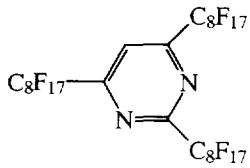
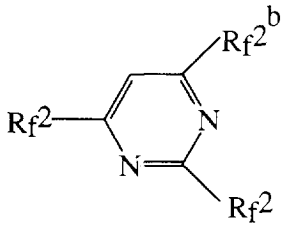
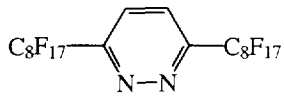
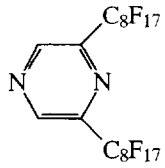
Scheme 1. The percentages shown are GC area %.

and DMSO (6.28 g, 80.5 mmol) in hexafluorobenzene (30 ml) was heated to reflux at ca. 85 °C. Samples were analyzed by GC for the reaction periods 2, 4, 23, 26 and 53 h. The results showed that the reaction mixture contained 2-chloro-6-perfluorooctylpyrazine (**14**) (28, 40, 11, 9 and 2%) and the expected disubstitution product, **13** (14, 37, 88, 90 and 97%), respectively. The reaction was terminated after 53 h. The reaction mixture was allowed to cool to ambient temperature. The solution was separated and solid extracted with Freon-113 (2×35 ml). The combined solution was washed with water (2×40 ml) and dried over anhydrous $MgSO_4$. On evaporation of the solvent, the crude product (9.9 g) was obtained. Distillation gave the pure product as a colorless liquid which solidified on cooling (5.5 g). Isolated yield, 89%; b.p. 112 °C/0.015 mmHg; m.p. 50–52 °C.

2.2. *Synthesis of 2,4-bis(perfluorooctyl)pyrimidine (3)*

Compound **3** was synthesized by a similar procedure as described above, except that the isolation procedure was different. The crude product was purified by passage through an alumina column (10 g) eluting with Freon-113. After removal of the solvent, the white crystals obtained were washed with petroleum ether (2×10 ml). Pure compound **3** was obtained in 70% yield, m.p. 87–88 °C.

Table 1
Physical properties and analysis of perfluoroalkyl and perfluorooxaalkyldiazines

Compounds		MS (EI) (*m/z*)	B.p. (°C/mmHg) [m.p. (°C)]	Elemental analysis (calc./found) (%)			
				C	H	N	F
	(**3**) (nc)	916 [M^+]	−[87–88]	26.22 25.97	0.22 0.38	3.06 3.32	70.50 69.99
	(**6a**) (nc)	965 [a] [$M-C_7F_{15}$]$^+$	132/0.07 [48–49]	25.21 25.03	0.08 0.06	2.10 2.21	72.62 70.16
	(**6b**) (nc)	897 [a] [$M-C_3F_7OC_3F_6$]$^+$	105/0.08	24.37 24.30	0.08 0.09	2.27 2.33	69.38 70.38
	(**10**) (nc)	916 [M^+]	−[185–188]	26.22 26.15	0.22 0.31	3.06 3.17	70.50 69.39
	(**13**) (nc)	916 [M^+]	112/0.015 [50–52]	26.22 26.04	0.22 0.22	3.06 3.01	70.50 68.81

[a] The parent ion peak (>1000) was beyond the limit of the spectrometer used. However, the fragmentation peaks were consistent with the structure.
[b] $R_f^2 = (CF_3)_2CFO(CF_2)_4-$.

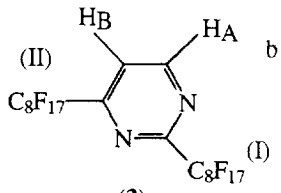
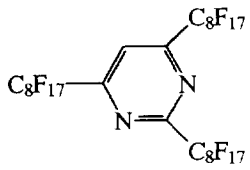
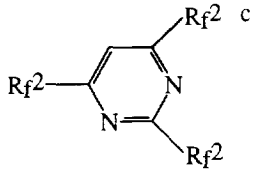
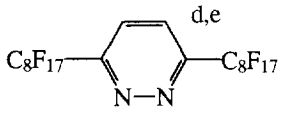
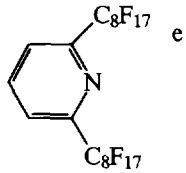
2.3. Synthesis of 3,6-bis(perfluorooctyl)pyridazine (10)

Compound **10** was prepared in the same manner as described for compound **13**. Due to the low solubility of the solid product **10** in the solvent mixture, the needle of syringe was warmed to ~60 °C while taking samples for GC analysis. A sample analyzed by GC after 27 h reaction showed 90% of the expected product **10** and 9% of the mono-substituted product, 2-chloro-6-perfluorooctylpyridazine (**11**). After this stage, the rate of reaction was very slow. At the end of 6 d, the yield of product **10** had increased to 94% while 4% of **11** and 2% of other unknown compounds were present. The reaction mixture was cooled to room temperature. The brown solid consisting of products and copper complexes was separated from the mixture and was washed with Freon-113 (2×30 ml) to remove the starting materials and by-products. The residual brown solid was sublimed at ~250 °C and atmosphere pressure to obtain the pure product as a white crystalline solid, **10** (yield 68%, m.p. 185–188 °C).

2.4. Synthesis of 2,4,6-tris(perfluorooctyl)pyrimidine (6a) and 2,4,6-tris(perfluoro-6-methyl-5-oxaheptyl)pyrimidine (6b)

Compounds **6a** and **6b** were synthesized by the same procedure as outlined above for compound **13**. At the end of 4 d, the results obtained by GC–MS analysis were as follows. For reaction between n-$C_8F_{17}I$ and 2,4,6-trichloropyrimidine: **6a** (96%), **7a** (~1%), **8a** (<1%) and by-products $C_8F_{17}CH_2SCH_3$ and $C_6F_5(C_8F_{17})$. For reaction between $(CF_3)_2CFO(CF_2)_4I$ and 2,4,6-trichloropyrimidine: **6b** (84%), **7b** (7%), **8b** (6%) and by-products $(CF_3)_2CFO(CF_2)_4Cl$, $(CF_3)_2CFO(CF_2)_4CH_2SCH_3$ and $[(CF_3)_2CFO(CF_2)_4]C_6F_5$.

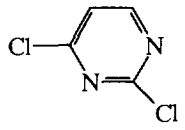
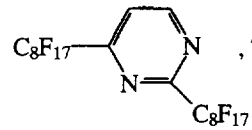
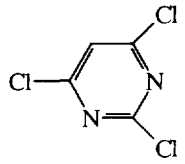
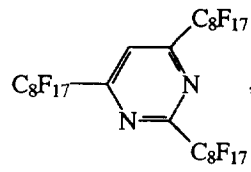
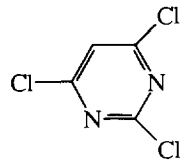
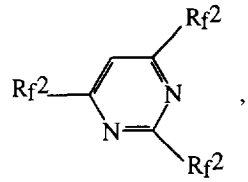
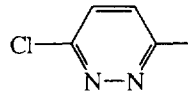
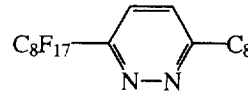
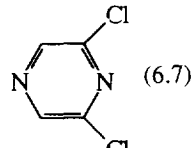
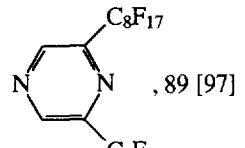
Table 2
NMR spectra of perfluoroalkyl and perfluorooxaalkyl diazines [a]

Compounds	^{1}H NMR δ (ppm)	^{19}F NMR δ (ppm)
 (3)	9.53 (ab, H_A); 8.39 (ab, H_B)	−81.9 (t, $2CF_3$); −115.3 (t, CF_2-I next to ring); −116.1 (t, CF_2-II next to ring); −121.5 (br, CF_2-I); −121.8 (br, CF_2-II); −122.5 (br, $6CF_2$-I and -II); −123.3 (br, $2CF_2$-I and -II); −126.9 (m, $2CF_2$-I and -II next to CF_3)
 (6a)	8.17 (s)	−81.6 (m, $3CF_3$); −115.3 (t, CF_2 next to ring); −115.9 (t, $2CF_2$ next to ring); −121.4 (br, $2CF_2$); −121.8 (br, CF_2); −122.3 (br, $3CF_2$); −122.5 (br, $2CF_2$); −122.7 (br, CF_2); −123.3 (br, $3CF_2$); −126.8 (br, $3CF_2$ next to CF_3)
 (6b)	8.14 (s)	−81.2 (br, $3CF_2O$); −81.4 (m, $6CF_3$); −115.4 (t, CF_2 next to ring); −116.1 (t, $2CF_2$ next to ring); −122.5 (m, $2CF_2$); −122.8 (m, CF_2); −125.0 (q, $2CF_2$); −125.5 (q, CF_2); −145.9 (m, 3CF)
 (10)	7.99 (s)	−81.7 ($2CF_3$); −114.1 ($2CF_2$ next to ring); −121.4, −121.7, −122.1, −122.3, −123.1, −126.7 ($12CF_2$)
 (13)	9.56 (s)	−80.8 (t, $2CF_3$); −114.0 (t, $2CF_2$ next to ring); −120.7, −121.4, −121.6, −121.8, −122.4 (br, $10CF_2$); −125.9 (m, $2CF_2$ next to CF_3)

[a] ^{1}H NMR (300 MHz), chemical shifts (ppm/TMS); ^{19}F NMR (282.3 MHz), chemical shifts (ppm/Freon-113); ab = half of AB pattern, br = broad, m = multiplet, q = quartet, t = triplet.
[b] Chemical shifts (H/ppm/acetone-d_6).
[c] $R_f^2 = (CF_3)_2CFO(CF_2)_4$.
[d] The solubility of the material was very low. The signals were so weak that areas and structure could not be meaningfully determined.
[e] ^{1}H NMR (499.8 MHz), chemical shifts (ppm/acetone); ^{19}F NMR (470.3 Mz), chemical shifts (ppm/Freon-113).

All experimental conditions, results and characterization data are listed in Scheme 1 and Tables 1, 2, and 3 and 4. IR spectra were obtained as neat liquids (capillary film) or KBr pellets. All compounds showed stretching vibrations (cm^{-1}): 3078–3101 (vw-m, CH on ring); 1407–1585 (w-m, C=N and C=C on ring); 990–1380 (s-vs, CF).

Table 3
Formation of perfluoroalkyl and perfluorooxaalkyldiazines [a]

Exp. No.	Chlorodiazines (mmol)	Iodofluoro compounds [b] (mmol)	Copper (mmol)	DMSO (mmol)	Reaction time (h)	Products, isolated yield (%) [c] [GC area %]
1	 (6.7) (1)	n-$C_8F_{17}I$ (20)	44	81	50	 , 70 [97] (3)
2	 (11) (5)	n-$C_8F_{17}I$ (37)	81	147	96	 , 59 [96] (6a)
3	 (5.4) (5)	R_f^2I (20)	43	78	96	 , 56 [84] (6b)
4	 (13) (9)	n-$C_8F_{17}I$ (40)	88	161	144	 , 68 [94] (10)
5	 (6.7) (12)	n-$C_8F_{17}I$ (20)	44	81	53	 , 89 [97] (13)

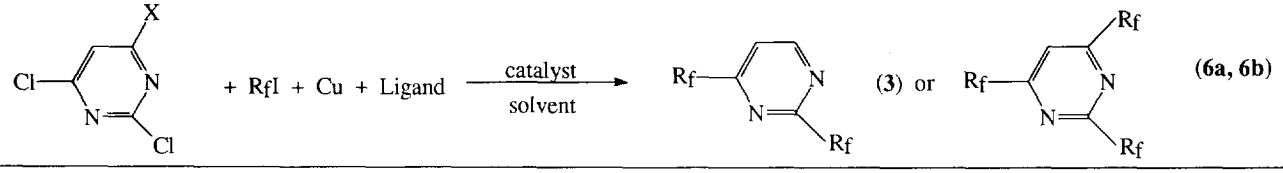
[a] Reaction temperature, ~85 °C; catalyst, 2,2′-bipyridine, 7 mol% of R_fI; solvent, C_6F_6.
[b] $R_f^2 = (CF_3)_2CFO(CF_2)_4-$.
[c] Yield based on chlorodiazines. By-products were products of partial substitution and reaction with DMSO and C_6F_6 (see Scheme 1 and Table 4).

3. Results and discussion

Perfluoroalkyl and perfluorooxaalkyl diazines (**3**, **6a**, **6b**, **10** and **13**) could readily be prepared by the reaction of chloro-substituted diazines (**1**, **5**, **9** and **12**), copper bronze and n-$C_8F_{17}I$ (**2**) or $(CF_3)_2CFO(CF_2)_4I$ according to Scheme 1. By controlling the reaction conditions, good-to-excellent yields of perfluoroalkylated or perfluorooxaalkylated products were obtained from chloro-substituted pyrimidines, pyridazines and pyrazines (see Table 3).

Our previous work [1,2] has shown that reaction conditions such as the reactant, solvent, polar aprotic ligand, catalyst, time and temperature play a critical role in determining the yield of the substitution products as well as by-products formation due to competing reactions. Without a suitable polar aprotic ligand such as DMSO or DMF, the activated fluoroalkylcopper

Table 4
Optimization of yield in the reaction [a]



Exp. No.	Reactants		Ligand	Solvent	Conditions		Yield of products (GC area %)	
	X	R_fI [b]			Temp. (°C)	Time (h)	Desired	By-products [c]
1	H	R_f^1I	–	C_6F_6	85	24	–	traces
2	H	R_f^1I	DMF	C_6F_6	85	96	**3** (59)	**4** (35) [d]
3	H	R_f^1I	DMSO	C_6F_6	50	24	**3** (traces)	traces
4	H	R_f^1I	DMSO	C_6F_6	85	25	**3** (90)	**4** (9)
5	H	R_f^1I	DMSO	C_6F_6	85	48	**3** (97)	**4** (<1)
6	H	R_f^3I	DMSO	C_6F_6	85	24	–	[e]
7	Cl	R_f^1I	DMSO	C_6F_6	85	24	**6a** (80)	**7a** (17) **8a** (~1)
8	Cl	R_f^1I	DMSO	C_6F_6	85	96	**6a** (96)	**7a** (~1) **8a** (~2)
9	Cl	R_f^2I	DMSO	C_6F_6	85	26	**6b** (52)	**7b** (10) **8b** (3)
10	Cl	R_f^2I	DMSO	C_6F_6	85	96	**6b** (84)	**7b** (6) **8b** (6)
11	Cl	R_f^2I	–	DMSO	85	24	**6b** (traces)	[f]
12	Cl	R_f^2I	–	DMSO	85	96	**6b** (25)	[f]

[a] Molar ratio of reactants: X = H, $C_4H_2N_2Cl_2/R_fI/Cu/ligand = 1:3:6:12$; X = Cl, $C_4HN_2Cl_3/R_fI/Cu/ligand = 1:4:8:16$. Catalyst, 2,2'-bipyridine, 0.07 mol% of R_fI.

[b] $R_f^1 = n\text{-}C_8F_{17}-$, $R_f^2 = (CF_3)_2CFO(CF_2)_4-$, $R_f^3 = C_3F_7OCF(CF_3)CF_2OCF(CF_3)-$.

[c] By-products included R_fH, $C_6F_5R_f$ and $R_fCH_2SCH_3$.

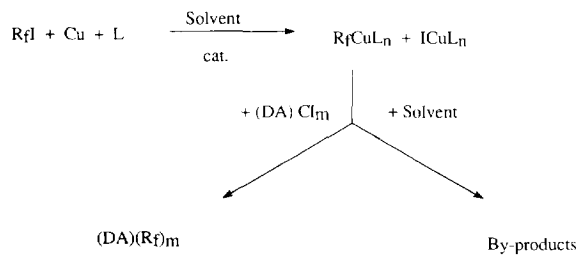
[d] By-products included R_f^1H, $C_6F_5R_f^1$ and $R_f^1C(O)N(CH_3)_2$.

[e] By-products included R_f^3H, $C_3F_7OCF(CF_3)H$, $C_6F_5R_f^3$, $R_f^3CH_2SCH_3$ and the decomposition product of 2,4-dichloropyrimidine.

[f] By-products included R_f^2H, R_f^2Cl, $R_f^2CH_2SCH_3$, $(CF_3)_2CFO(CF_2)_3CF=CHSCH_3$ and the decomposition product of 2,4,6-trichloropyrimidine.

complex is formed very slowly in hexafluorobenzene solvent (see Scheme 2). Hence, no desired product was formed at 85 °C within 24 h except a trace of by-products R_f^1H and $C_6F_5R_f^1$ (see Table 4, Exp. 1).

In previous studies [2], we reported that DMSO and DMF gave the highest yield of the product $C_3F_7O[CF(CF_3)CF_2O]_2CF(CF_3)C_6H_4F$. Hence, these



$R_f = n\text{-}C_8F_{17}$- (R_f^1), $(CF_3)_2CFO(CF_2)_4$- (R_f^2)
L = ligand:DMSO, DMF; n = 2,3
Solvent: C_6F_6, DMSO
Cat. = 2,2'-bipyridine
$(DA)Cl_m$ = chlorosubstituted diazines, m = 2,3

Scheme 2. Probable mode of formation of products.

two ligands were investigated in the present study. The reaction proceeded faster in DMSO than in DMF (Exp. 2, 4 and 5, Table 4). However, if DMSO was used as a solvent, the product **6b** decreased from 52 GC area % to traces and from 84 to 25 GC area % in 1 and 4 d of reaction, respectively (see Exp. 9–12, Table 4). In DMSO solvent, the $R_f^2CuL_n$, $R_f^2 = (CF_3)_2CFO(CF_2)_4$, reacted with DMSO faster than with the 2,4,6-trichloropyrimidine (**5**) (see Scheme 2). Hence, by-products R_f^2H, R_f^2Cl, $R_f^2CH_2SCH_3$ and $(CF_3)_2CFO(CF_2)_3CF=CHSCH_3$ were predominantly formed.

From Exp. 3 and 4, Table 4, it can be seen that product **3** increased from traces to 90 GC area % on increasing the reaction temperature from 50 °C to 85 °C (reflux). The rate of reaction was very slow towards the end of the reaction period. Hence, the best yield of reaction was a longer reaction time, i.e. 2–4 d, and a higher reaction temperature, ~85 °C (see Exp. 5 and 8, Table 4).

The secondary perfluorooxaalkyl iodide, $R_f^3I[R_f^3 = C_3F_7OCF(CF_3)CF_2OCF(CF_3)]$, was allowed to react with 2,4-dichloropyrimidine (**1**) in the presence of copper bronze, 2,2'-bipyridine (catalyst), DMSO

(ligand) and hexafluorobenzene (solvent) (see Exp. 6, Table 4). After 24 h reaction at ~85 °C, no substitution product was formed. GC–MS showed that the reaction mixture consisted of unreacted reactants, R_f^3H, $C_3F_7OCF(CF_3)H$, $C_6F_5R_f^3$, $R_f^3CH_2SCH_3$ and the decomposition product of compound **1**. Similar results were reported in our previous studies [2].

The optimum experimental conditions for the cross-coupling reaction of primary R_fI and the chloro-substituted diazines **1**, **5**, **9** and **12** were C_6F_6 as solvent at ~85 °C for ~3 d using the ratio of diazines $(Cl_nC_4H_{4-n}N_2)/R_fI/Cu/DMSO/2,2'$-bipyridine = 1:3:6:12:0.21, for $n=2$; and 1:4:8:16:0.28, for $n=3$. All the reactions are listed in Table 3. The physical properties, analysis and NMR spectra of (perfluoroalkyl) and (perfluorooxaalkyl)diazines are presented in Tables 1 and 2.

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References

[1] Part 1: G.J. Chen, L.S. Chen and K.C. Eapen, *J. Fluorine Chem., 63* (1993) 113.
[2] Part 2: G.J. Chen, L.S. Chen and K.C. Eapen, *J. Fluorine Chem., 65* (1993) 59.
[3] V.C.R. McLoughlin and J. Thrower, *Tetrahedron, 25* (1969) 5921.
[4] G.J. Chen and C. Tamborski, *J. Fluorine Chem., 46* (1990) 137.
[5] Y. Kobayashi and I. Kumadaki, *J. Chem. Soc., Perkin Trans. 1,* (1980) 661.
[6] J. Leroy, M. Rubinstein and C. Wakelman, *J. Fluorine Chem., 27* (1985) 291.