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Selective and efficient fluorination of chlorodiazines under solvent-free phase transfer catalysis

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Abstract

3-Chloro-6-phenylpyridazine, 2,3-dichloroquinoxaline and 1,4-dichlorophthalazine were reacted with KF under solvent-free conditions in the presence of a phase transfer agent, with or without microwave irradiation. The chlorine–fluorine exchanges were obtained with enhanced yields and selectivities when compared with previous methods.

Keywords: Chlorodiazines; Fluorination; Microwave activation; Solvent-free conditions

1. Introduction

Diazines (*x*,*y*-diazabenzenes) are important compounds having biological activity [1–3]. Among interesting derivatives, fluorodiazines present the usual advantages of introduction of fluorine atoms in terms of increased therapeutic and agrochemical activities. They are involved in some catalytic cross-coupling reactions of Kharash [4,5] type reagents. They also constitute substrates of choice for directed *ortho*-metallation reactions of diazines [6]. They are accessible from chlorodiazines by nucleophilic aromatic substitutions (S_NAr) using fluorine as the nucleophile.

They were usually prepared by reacting KF in polar aprotic solvents such as DMF or DMSO at 150 °C [7], or in neat reaction conditions at 290–480 °C [8–10] for 8–20 h, and leading to rather limited yields. Phase transfer catalysis (PTC) was used in the case of S_NAr reaction with chloroquinoxalines by reacting CsF in the presence of 18-crown-6 in THF with low to good yields (20–90%) [11]. Tetrabutylphosphonium hydrogendifluoride (Bu_4P^+, HF_2^-) was shown to give satisfactory yields (70–90%) when used under solvent-free conditions at 80–140 °C for 2–100 h [12]. Finally, a mild and efficient reagent was recently advocated comprising a combination of proton sponge (PS = bis α,α′-dimethylaminonaphthalene)-triethylamine-hydrogen fluoride. This mixture appeared capable of selective halogen exchange or complete substitution of chlorine atoms in (poly)chlorodiazines [13]. However, its drawbacks are its high cost (PS), the handling of hazardous compounds (HF), the extended delay for the preparation of this reagent and the large reaction times from 2 to 7 days.

We describe here an improvement in conditions and selectivities by using the solvent-free PTC technique, whose potential was shown in some S_NAr reactions on halopyridines [14]. We have also checked the microwave activation as especially efficient when coupled with solvent-free PTC conditions [15], and yet tested in some fluorinations by S_NAr reactions in halopyridines [16,17].

As selected reactions have to be improved, we chose to tackle the reactivity problem presented by the fluorination of

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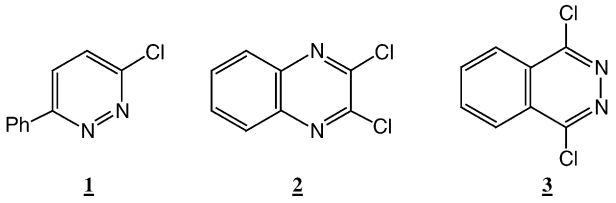


1 2 3

Scheme 1.

3-chloro-6-phenylpyridazine **1** and the reactivity and selectivity aspects (mono and difluorination) characteristic of 2,3-dichloroquinoxaline **2** and 1,4-dichlorophthalazine **3** (Scheme 1).

2. Results and discussion

All the reactions were carried out under solvent-free PTC conditions, i.e. the chlorinated compound plays the dual role of electrophilic reagent and organic phase for the reaction. Cheap, safe and easy-to-handle KF was used as the nucleophilic species in combination with a phase transfer agent catalyst (PTA). Preliminary experiments without a PTA failed completely; the conversion was less than 5% and the yield negligible.

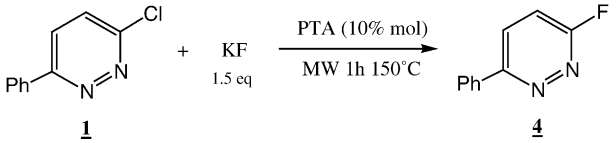
For the sake of experimental simplification (no necessity to preheat an oil or sand bath), reactions were carried out using a monomode microwave (MW) reactor [18] at a fixed temperature by modulation of emitted power. Results are compared with those obtained with conventional heating under similar conditions (vessels, time, temperature and profiles of temperature rise).

All experiments were repeated at least twice and by different workers.

2.1. Fluorination of **1**

This fluorination was twice described in the literature [11,13], at 100 °C, using:

(i) PS + $Et_3N{\cdot}3HF$ within 144 h, isolated yield = 63% [13];
(ii) Bu_4P^+, HF_2^- within 2 h, g.c. yield = 89% [12].



1 KF 1.5 eq PTA (10% mol) MW 1h 150°C **4**

Scheme 2.

Table 1
Fluorination of **1** (5 mmol) under solvent-free PTC conditions and MW activation

Entry	PTA[a]	Conversion[b]	Yield[c] (%) in **4**
1	18-crown-6	53	20
2	NBu_4 HSO_4	63	29
3	NBu_4 Br	41	12
4	NBu_4 Cl	28	20

[a] Phase transfer agent (10% mol.equiv.).
[b] Based on consumption of **1**.
[c] g.c. yields using an internal standard (dibutyl phthalate).

We first studied the influence of the PTA, fixing the temperature at 150 °C, the reaction time at 1 h and using 1.5 eq. of KF (Scheme 2). The results are given in Table 1.

The best results were obtained with $[n\text{-}Bu_4]^+[HSO_4]^-$ and 18-crown-6 (entries 1 and 2), but ammonium salts are prone to the decomposition at elevated temperature (Hoffmann reaction); so, the influence of temperature and reaction time using 18-crown-6 as the catalyst were determined. The results are given in Table 2.

The best set of conditions is KF (1.3 eq.) for 1 h at 200 °C (PTA: 18-crown-6). Using a simple solvent-free procedure involving simple conditions (KF and 18-crown-6) [19], we got a quantitative yield avoiding thus any further purification. We have therefore improved noticeably the published yields and conditions.

The reaction was also performed under conventional heating, and we also obtained a quantitative yield.

2.2. Fluorination of **2**

The fluorination of **2** is shown in Scheme 3.

2.2.1. Conditions for selective monofluorination

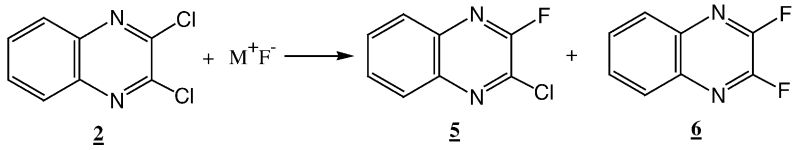
In the literature [13], this reaction was performed using the mixture PS + $NEt_3{\cdot}3HF$ in acetonitrile at 80 °C for 105 h with a 57% conversion of **2**, a 35% yield of **5** + **6** and with a selectivity **5**/**6**: 71/29.

We studied the monofluorination under solvent-free PTC conditions using 1 eq. KF and 18-crown-6 or TDA-1 [20] as catalyst. The main results are given in Table 3.

Two sets of conditions led to satisfactory yields and selectivities. They involved either 18-crown-6 or TDA-1 as catalyst within 1 h at 150 and 200 °C, respectively (entries

Table 2
Fluorination of **1** (5 mmol) according to reaction time and temperature PTA = 18-crown-6 (10%)

Entry	KF (eq.)	Time (min)	Temperature (°C)	Conversion	Yield (%) in **4**
5	1.5	60	150	53	20
6	1.5	60	170	77	77
7	**1.3 or 1.5**	**60**	**200**	**100**	**100**
8	1.3	30	200	83	83
9	1.3	60	210	99	75



2 5 6

Scheme 3.

Table 3
Monofluorination of **2** (5 mmol) with KF (5 mmol) under solvent-free PTC conditions and MW activation

Entry	PTA (10%)	Temperature (°C)	Time (min)	Conversion[a]	Yield[b] (%) in **5** + **6**	**5**/**6**
10	**18-crown-6**	**150**	**60**	**40**	**40**	**93/7**
11	18-crown-6	150	180	71	58	66/34
12	18-crown-6	200	60	53	50	73/27
13[c]	18-crown-6	200	60	57	44	91/9
14	TDA-1	150	60	27	20	70/30
15	**TDA-1**	**200**	**60**	**53**	**52**	**90/10**
16	TDA-1	200	180	72	9	96/4

[a] Based on consumption of **2**.
[b] g.c. yields using an internal standard (diethyl phthalate).
[c] Using 50% of catalyst.

10 and 15). With respect to mono/difluorination (**5/6**), selectivity was very good (≥90/10) and yields acceptable for such kind of reactions (40–52%). They constitute a large improvement over previous experiments.

In order to compare the results of MW irradiation versus conventional heating (Δ), the same reactions were performed inside a thermostated oil bath under similar conditions. Using 1 eq. KF and 10% TDA-1 for 1 h at 200 °C, the yields obtained under Δ and MW were respectively 34 and 52%; the selectivity remained identical.

Specific (not purely thermal) MW effects were thus highlighted in this special case and related to mechanistic considerations [21]. An enhancement in the polarity of the system from the ground state (GS) towards the transition state (TS) was responsible for the observation of a specific MW effect. It is consistent with the extension of anionic charge delocalization in TS [22]. This implies an increase in the polarity of the reaction system from GS to TS and subsequent decrease in the energy of activation due to better dipole–dipole coulombic interactions with TS.

2.2.2. *Conditions for difluorination*

This reaction has been studied twice in the literature [11,13]:

(i) PS (4 eq.)-NEt_3·3HF (1.33 eq.) without solvent for 75 h at 90 °C (**5**/**6** = 12/88, total yield = 50%) [13];
(ii) CsF (8 eq.) + 18-crown-6 (1 eq.) in THF for 4 h at 65 °C (**5**/**6** = 0/100, yield = 64%) [11].

We studied the effect of excess KF under solvent-free PTC conditions. The results are given in Table 4.

The system KF (4 eq.) + 18-crown-6 (0.1 eq.) led to a quantitative yield of **6** within 1 h at 200 °C. This result constitutes a noticeable improvement over previous published ones. Similar yields were obtained under either MW or conventional heating inside a thermostated oil bath, revealing no specific MW effects under these conditions.

2.3. *Fluorination of* **3**

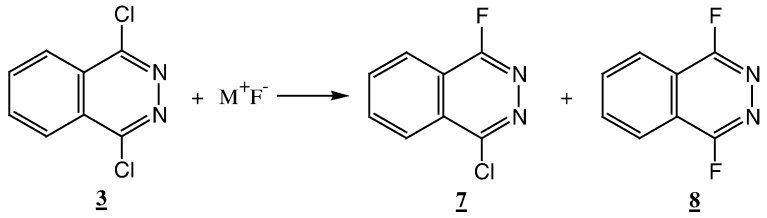
The fluorination of **3** is shown in Scheme 4.

2.3.1. *Conditions for selective monofluorination*

In the literature [13], this monofluorination was realized using PS + NEt_3·3HF in acetonitrile at 85 °C for 96 h with a yield of 37% (conversion in **3** = 86%) and a high selectivity **7**/**8** = 96/4.

Table 4
Difluorination of **2** (5 mmol) under solvent-free PTC conditions and MW activation

Entry	PTA (10%)	KF (eq.)	Temperature (°C)	Time (min)	Conversion	Yield (%) in **5** + **6**	**5**/**6**
17	**18-crown-6**	**5**	**200**	**60**	**100**	**100**	**0/100**
18	TDA-1	5	200	60	90	90	40/60
19	18-crown-6	5	200	30	99	79	2/98
20	18-crown-6	5	150	60	99	94	2/98
21	**18-crown-6**	**4**	**200**	**60**	**100**	**100**	**0/100**
22	18-crown-6	3	200	60	100	97	7/93
23	18-crown-6	2	200	60	93	84	32/68



3 7 8

Scheme 4.

Table 5
Monofluorination of **3** (5 mmol) under solvent-free PTC conditions (KF 1 eq. + 18-crown-6, 10%) and MW activation

Entry	Temperature (°C)	Time (min)	Conversion[a]	Yield[b] (%) in 7 + 8	7/8
24	220	10	67	44	88/12
25	190	30	70	44	88/12
26[c]	**190**	**10**	**67**	**67**	**100/0**
27	170	60	70	26	96/4

[a] Based on consumption of **3**.
[b] g.c. yields using an internal standard (diethyl phthalate).
[c] Using 1.2 eq. of KF.

Table 6
Difluorination of **3** (5 mmol) under solvent-free PTC conditions (PTA = 18-crown-6, 10%) and MW activation

Entry	KF (eq.)	Temperature (°C)	Time (min)	Conversion[a]	Yield[b] (%) in 7+8	7/8
28	5	220	5	100	83	1/99
29	5	205	5	100	90	8/92
30	**4**	**220**	**5**	**100**	**98**	**3/97**
31	2.2	220	5	85	63	86/4

[a] Based on consumption of **3**.
[b] g.c. yields using an internal standard (diethyl phthalate).

The solvent-free system KF (1 eq.) + 18-crown-6 (0.1 eq.) was tested under different conditions. The results are given in Table 5.

Under the conditions of entry 26, monofluorination was accomplished with complete selectivity.

2.3.2. Conditions for difluorination

The reaction time was fixed at 5 min and the temperature and the amount of KF were varied. The main results are given in Table 6.

A very good result (yield = 98%, selectivity = 3/97) was obtained using 4 eq. KF for 5 min at 220 °C.

The best experiment was carried out under conventional heating with similar conditions. We got an 83% yield and a ratio of **7/8** = 38/62 which revealed a large MW specific effect on reactivity, and which also affected the relative amounts of di/monofluorinated products.

3. Conclusion

Solid–liquid solvent-free PTC leads to noticeable improvements over published conventional methods. Yields were enhanced within very short reaction times (usually 1 h instead of several days). The method recommended here involves a cheap and easy-to-handle fluorinating agent (KF) in the presence of catalytic amount of 18-crown-6. It does not use any solvent during the reaction as liquid chlorinated diazines play both the role of electrophile and organic phase for the reaction. In two cases, specific MW effects were highlighted.

4. Experimental

4.1. Microwave equipment

Reactions were performed in a monomode reactor Synthewave 402 (S 402) microwave device from Prolabo. The temperature was measured during the reaction by infrared detection, which indicates the surface temperature after previous calibration of emissivity in each case with an optical fiber thermometer (FTI-10 device from Fiso, optical fiber up to 250 °C). The reactions were conducted in a cylindrical Pirex tube with mechanical stirring to establish homogeneity in temperature. The power was monitored during irradiation to maintain constant temperature.

Commercial diazines were used without purification. Solid 18-crown-6 ether was stored under vacuum over P_2O_5. Other PTCs were used without any purification. Potassium fluoride was used without any purification and drying.

4.2. Typical experiment for MW reactions (2,3-difluoroquinoxaline)

Nine hundred and ninety five milligrams of 2,3-dichloroquinoxaline **2** (5 mmol), 1162 mg of potassium fluoride (20 mmol, 4 eq.) and 133 mg of 18-crown (0.5 mmol, 0.1 eq.) were placed in the reactor. The reaction was performed in an open vessel. The mixture was irradiated in the S 402 with mechanical stirring for 1 h and at 200 °C. After the irradiation time, the temperature was controlled with the optical fiber thermometer, and then the reactor was cooled down to room temperature. The materials were filtered on Celite 545 under vacuum with 50 mL of ethyl acetate. A sample (1/10th) of the crude mixture was analyzed by gas chromatography. Conversion and yield were determinated by the internal standard method to give 830.5 mg of 2,3-difluoroquinoxaline **6** (100% GC yield). Experiments

leading to quantitative yields have been reproduced at least twice.

4.3. Comparison between microwave activation and conventional heating

The reaction was performed and the reaction mixture was placed in a preheated thermostated oil bath at the same temperature as under MW irradiation. The reaction was achieved for the same reaction time. The temperature was controlled with the same optical fiber thermometer as for the calibration of MW's emissivity. The curve of temperature during the reaction time was identical to the one obtained under microwave. The treatment and analysis remained identical.

4.4. Characterization of products

Products **4**, **5** and **6** were characterized by their melting points, **4**: 123–124 °C; **5**: 88–89 °C; **6**: 92–93 °C. Their ^{1}H, ^{13}C and ^{19}F NMR spectra were compared to literature values [13]. Products **7** and **8** were characterized by their ^{1}H and ^{19}F NMR spectra [13]. All the products were also characterized by GC–MS.

GC device: Carlo Erba GC 6000 Vega Series 2, column 12QC2/BP1, 12 m, film thickness 0.1 μm. Carrier gas He 50 kPa, integrator Spectra-Physics SP 4290. Retention times are given below.

Product number	Product name	Retention time/min
4	3-Fluoro-6-phenylpyridazine	7.47
5	2-Fluoro-3-chloroquinoxaline	4.37
6	2,3-Difluoroquinoxaline	2.45
7	1-Fluoro-4-chlorophthalazine	4.80
8	1,4-Difluorophthalazine	7.25
Internal standard	Diethyl phthalate	7.88
Internal standard	Dibutyl phthalate	12.05

References

[1] W.J. Coates, Pyridazines and their benzo derivatives, in: A.R. Katritzky, C.W. Rees, E.F. v. Scriven (Eds.), Comprehensive Heterocyclic Chemistry II, vol.6, Pergamon, 1966, pp. 1–91.
[2] K. Undheim, T. Benneche, Pyrimidines and their benzo derivatives, in: A.R. Katritzky, C.W. Rees, E.F. v. Scriven (Eds.), Comprehensive Heterocyclic Chemistry II, vol.6, Pergamon, 1966, pp. 93–231.
[3] N. Sato, Pyrazines and their benzo derivatives, in: A.R. Katritzky, C.W. Rees, E.F. v. Scriven (Eds.), Comprehensive Heterocyclic Chemistry II, vol.6, Pergamon, 1966, pp. 233–277.
[4] S.P. Stanforth, Tetrahedron 54 (1998) 263–303.
[5] F. Mongin, L. Mojovic, B. Guillamet, F. Trécourt, G. Quéguiner, J. Org. Chem. 67 (2002) 8991–8994.
[6] A. Turck, N. Plé, F. Mongin, G. Quéguiner, Tetrahedron 57 (2001) 4489–4505.
[7] G.C. Finger, L.D. Starr, J. Am. Chem. Soc. 81 (1959) 2674–2675.
[8] R.D. Chambers, J. Hutchinson, W.K.R. Musgrave, J. Chem. Soc. (C) (1964) 3573–3576.
[9] R.D. Chambers, J.A.H. Mc Bride, W.K.R. Musgrave, J. Chem. Soc. (B) (1968) 2116–2119.
[10] R.D. Chambers, J.A.H. Mc Bride, W.K.R. Musgrave, I.S. Reilly, Tetrahedron Lett. 11 (1970) 57–60.
[11] K. Makino, H. Yoshioka, Heterocycles 26 (1987) 1215–1220.
[12] Y. Uchibori, M. Umeno, H. Yoshioka, Heterocycles 34 (1992) 1507–1510.
[13] M. Darabantu, T. Lequeux, J.C. Pommelet, N. Plé, A. Turck, Tetrahedron 57 (2001) 739–750.
[14] A. Loupy, N. Philippon, P. Pigeon, H. Galons, Heterocycles 32 (1991) 1947–1953.
[15] S. Deshayes, M. Liagre, A. Loupy, J.L. Luche, A. Petit, Tetrahedron 55 (1999) 10851–10870.
[16] L. Dolci, F. Dollé, H. Valette, F. Vaufrey, C. Fuseau, M. Bottlander, C. Crouzel, Bioorg. Med. Chem. 7 (1999) 467–479.
[17] M. Karramkam, F. Hinnen, Y. Bramoullé, S. Jubeau, F. Dollé, J. Label. Compd. Radiopharm. 45 (2002) 1103–1105.
[18] A. Loupy, A. Petit, J. Hamelin, F. Texier-Boullet, P. Jacquault, D. Mathé, Synthesis (1998) 1213–1234.
[19] E.V. Dehmlow, S.S. Dehmlow, Phase Transfer Catalysis, 2nd ed. Verlag Chemie, Weinheim, 1983, pp. 62.
[20] G. Soula, J. Org. Chem. 50 (1985) 3717–3721.
[21] L. Perreux, A. Loupy, Tetrahedron 57 (2001) 9199–9223.
[22] L. Perreux, A. Loupy, M. Delmotte, Tetrahedron 59 (2003) 2185–2189.