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Microwave-assisted synthesis of 1,4-bis(difluoromethyl)benzene

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Abstract A fast, mild, and practical microwave-assisted protocol for synthesis of 1,4-bis(difluoromethyl)benzene from 1,4-bis(dichloromethyl)benzene and KF was developed. The new protocol increased the yield and reduced the reaction time significantly in contrast to the conventional heating procedure. Also, the synergistic effect of a composite phase transfer catalyst was studied.

Keywords Microwave-assisted synthesis · 1,4-bis(difluoromethyl)benzene · Phase transfer catalyst fluorination

Introduction

[2.2]Paracyclophanes are excellent precursors of thin film polymers and known as "parylenes" in the industry (Gorham 1966). Parylene N (Scheme 1, **1a**), which is extensively applied in electronics and semiconductor industries, is highly stable up to 130 °C (Dolbier and Beach 2003). It is well known that the substitution of C–H bond by C–F bond could enhance the thermal stability and reduce the dielectric constant and moisture absorption of the resulting polymers (Amii et al. 2013). Thus, parylene HT (Scheme 1, **1b**) is more promising than parylene N to be used as conformal coating in many fields with exacting requirements (Dolbier et al. 1997).

1,1,2,2,9,9,10,10-Octafluoro[2.2]paracyclophane (**2**, AF4) is the chemical vapor deposition (CVD) precursor of parylene HT polymer (Chow et al. 1970). Many endeavors have been made to synthesize **2** and its derivatives (Roche and Dolbier 2000; Amii et al. 2001; Zhu et al. 2002; Dolbier et al. 2008; Hicks et al. 2014). In particular, the novel synthesis process developed by Dolbier et al. (2000a) is convenient, inexpensive, and highly scalable for both research and commercial use (Scheme 2). The raw material of this process, 1,4-bis(chlorodifluoromethyl)benzene (**3**), could be obtained from Scheme 3 (Dolbier et al. 2000b). The material 1,4-bis(trichloromethyl)benzene is commercial available, but the application of Scheme 3 is still limited by the requirement of an autoclave and the use of toxic anhydrous hydrogen fluoride.

Nevertheless, **3** can be easily prepared from 1,4-bis(difluoromethyl)benzene (**4**) through photochemical chlorination(Scheme 4) (Chow et al. 1970). Equivalently, **4** is also an important intermediate in the preparation of **2**. There are several studies about the synthesis of **4** (Boswell et al. 1974; Li et al., 2015). For instance, Boswell et al. (1974) disclosed the preparation of **4** from the reaction of 1,4-benzenedialdehyde with SF_4 (Scheme 5). However, the requirement of an autoclave and the high cost of SF_4 prohibitively raise the cost of this process. Furthermore, Dolbier et al. (2000b) developed a preparation method of **4** from the reaction of 1,4-bis(dichloromethyl)benzene (**5**) with CsF or KF without any solvent (Scheme 6). However, serious gelation would occur in the reaction, which complicates the mixture stirring and reactor cleaning. Besides, the use of CsF would dramatically raise the cost of **4**, and the application of KF as a fluorinating agent asks for an

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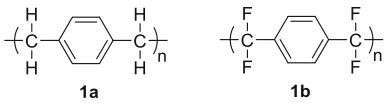
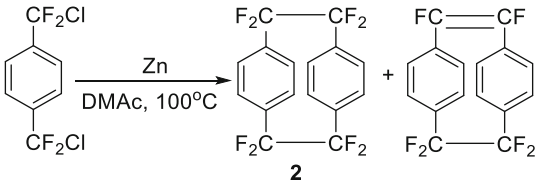
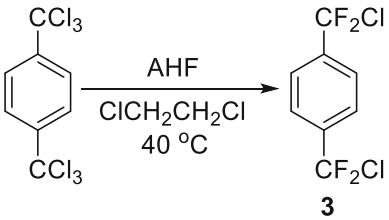


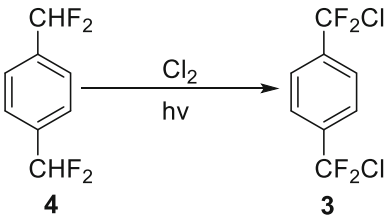
Scheme 1 Chemical structures of parylene N (**1a**) and parylene HT (**1b**)



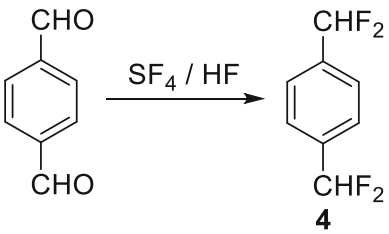
Scheme 2 Synthesis of 1,1,2,2,9,9,10,10-Octafluoro[2.2]paracyclophane (**2**) from 1,4-bis(chlorodifluoromethyl)benzene



Scheme 3 Conversion from 1,4-bis(trichloromethyl)benzene to 1,4-bis(chlorodifluoro-methyl)benzene (**3**)



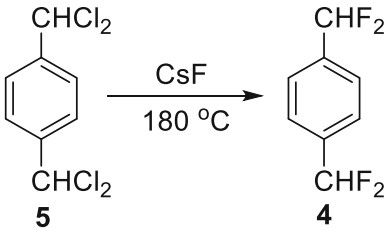
Scheme 4 Conversion from 1,4-bis(difluoromethyl)benzene (**4**) to 1,4-bis(chlorodifluoro-methyl)benzene (**3**)



Scheme 5 Conversion from 1,4-benzenedialdehyde to 1,4-bis(difluoromethyl)benzene (**4**)

excessively high temperature and long reaction time. Therefore, we need a more convenient, low-cost and time-economic scheme for synthesis of **4**.

In recent years, microwave-assisted synthesis has rapidly developed as an efficient scheme due to the improvement in reaction rate, yield, and purity compared to conventional methods (Jha et al. 2014; Polshettiwar and Varma 2008; Roberts and Strauss 2005). Therefore,



Scheme 6 Conversion from 1,4-bis(dichloromethyl)benzene (**5**) to 1,4-bis(difluoromethyl) benzene (**4**)

microwave-assisted synthesis is attractive for application in organic synthesis and methodology development research (Bhowmik et al. 2011; Cao and Duan 2016; Zhang et al. 2016). Herein, we report the microwave-assisted synthesis of **4** from the commercially available **5** and KF in short reaction time and mild conditions for the first time. The effects of catalyst, temperature, and solvent on the product yield were also studied.

Experimental

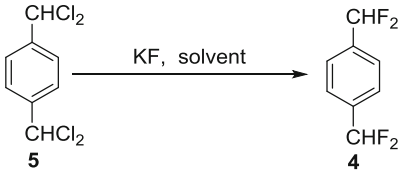
Chemistry

KF (Aladdin, Shanghai, China) was dried under vacuum for 12 h before use. *N*,*N*-dimethylformamide (DMF), xylene, and sulfolane were obtained from Sinopharm Chemical Reagent Co., Ltd (Shanghai, China) and dried using molecular sieve 4A. All other chemicals, unless otherwise noted, were purchased from commercial suppliers and were used without further purification. The microwave-assisted reaction in an open-vessel system (Type A) was carried out in a XH-100B microwave reactor (Beijing XiangHu, China) at constant power (600 W) with stirring and temperature control (PT100 resistance temperature sensor). Reaction in the pressurized microwave system (Type B) was carried out in a WX-8000 instrument (Preekem, Shanghai, China) at constant power (600 W) with a PT100 resistance temperature sensor in a G30 vessel (50 mL capacity). ^{1}H NMR spectrum was recorded on a Bruker Avance AV-600 spectrometer at 600 MHz in $CDCl_3$ with tetramethylsilane as internal reference. ^{13}C and ^{19}F NMR spectra were recorded on a Bruker Avance AV-300 spectrometer. IR spectra were recorded on a Nicolet AVATAR 5700 FT-IR spectrophotometer in the range of 4000–400 cm^{-1} using KBr pellets.

Fluorination of 5 with conventional heating (general procedure)

5 (1 equiv, 5.0 g, 0.02 mol), solvent (15 mL), KF (6 equiv, 7.0 g, 0.12 mol), and phase transfer catalyst

Table 1 Screening experiments on the fluorination of **5** with KF (model reaction)



5 **4**

Entry	Solvent	Catalyst[a]	Time (h)	Temp (°C)	Yield[c] (%)
1	–	–	12	280	22
2	–	–	48	280	28
3	DMF	–	48	130	25
4	Xylene	–	36	135	28
5	Sulfolane	–	36	160	40
6	Sulfolane	–	30	200	45
7	Sulfolane	–	24	220	48
8	Sulfolane	–	24	240	32
9	Sulfolane	Ph_4PCl	18	200	53
10	Sulfolane	18-Crown-6	18	200	45
11	Sulfolane	[b]Ph_4PCl/18-crown-6	10	200	68

[a] The addition amount of catalyst was 5 mol% relative to **5** unless noted otherwise

[b] The component of the composite phase transfer catalyst was 3 mol% Ph_4PCl and 1 mol% 18-crown-6

[c] Isolated yield

(5 mol%) were added in a 50 mL flask equipped with a condenser. This mixture was thoroughly stirred and heated to corresponding temperature for 12–48 h, and the progress of the reaction was monitored by TLC (EtOAc-hexane, 1:5 v/v). The liquid phase was then distilled from the flask at reduced pressure (about 30 mmHg). Gas chromatographic analysis of the distillation was carried out using a 30 m SE-30 capillary column, and the analysis indicated that a high purity (>97%) of target product was obtained.

4: bp 81–83 °C/30 mmHg. ^{1}H NMR (600 MHz, $CDCl_3$), δ 6.68 (2 H, t, $J = 54$ Hz), 7.61 (4 H, s); ^{13}C NMR (75 MHz, DMSO-D6), δ 114.8 (t, $J_{CF} = 236$ Hz), 126.7 (t, $J_{CF} = 5.6$ Hz), 136.92 (t, $J_{CF} = 24.2$ Hz); ^{19}F NMR (282 MHz, $CDCl_3$), δ −111.3; IR (KBr), υ/cm^{-1}: 1600–1430 (Ar–C), 1050 (–CHF_2), 817 (Ar–H).

Fluorination of 5 with microwave heating (open vessel, type A, general procedure)

5 (1 equiv, 5.0 g, 0.02 mol), solvent (15 mL), KF (6 equiv, 7.0 g, 0.12 mol), and phase transfer catalyst (5 mol%) were added in a 50 mL flask equipped with a condenser in the microwave reactor. This mixture was thoroughly stirred and heated to corresponding temperature for 410 h, and the progress of the reaction was monitored by TLC (EtOAc-hexane, 1:5 v/v). Further workup and analysis was carried out as described in conventional heating method.

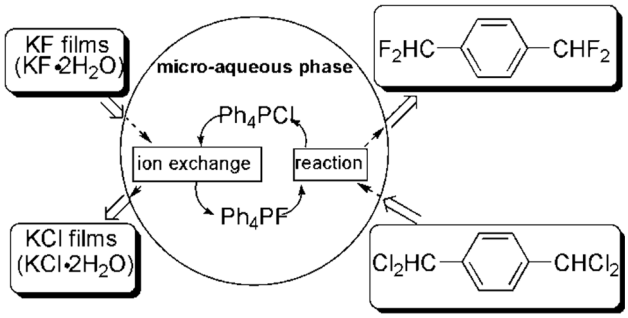
Fluorination of 5 in a closed microwave reactor (type B, general procedure)

5 (1 equiv, 5.0 g, 0.02 mol), solvent (15 mL), KF (6 equiv, 7.0 g, 0.12 mol), and phase transfer catalyst (5 mol%) were added in a 50 mL pressure flask (G30) and irradiated with stirring in the pressurized microwave reactor. This mixture was thoroughly stirred and heated to corresponding temperature for 2–5 h, and the progress of the reaction was monitored by TLC (EtOAc-hexane, 1:5 v/v). Further workup and analysis was carried out as described in conventional heating method.

Results and discussion

We started our investigations on the fluorination of **5** with KF to give **4** without microwave, which we selected as a model reaction for the exploration of optimal conditions, such as the reagent stoichiometry, solvent, temperature, reaction time, and catalytic additives. The results of the optimization experiments are summarized in Table 1.

We initially attempted to synthesize **4** from **5** and KF under standard conditions: solvent-free, 12 h, and 280 °C (Dolbier et al. 2000b). Unfortunately, the yield under these conditions was only 22% (Table 1, Entry 1), and was not much improved by prolonging the reaction time to 48 h. Then we tried a solvent, which is always used as an activation factor in nucleophilic substitution reaction (Koivula



Scheme 7 A plausible phase transfer catalysis mechanism of preparing 1,4-bis(difluoromethyl)benzene (**4**)

et al. 2011). However, the use of DMF as a solvent at 130 °C did not accelerate the fluorination. We then screened other solvents, such as xylene and sulfolane. The fluorination in xylene at 135 °C generated a yield of 28%, which was comparable to the application of DMF, but the use of sulfolane at 160 °C obviously improved the reaction efficiency, with a yield of 40%. Also, we investigated the effect of reaction temperature on the yield with the use of sulfolane. The higher reaction temperature, up to 220 °C, helped to shorten the reaction time and increase the yield (Table 1, entries 5–7). However, the temperature rise over 220 °C caused a dramatic solvent decomposition and reduced the yield of **4** (Table 1, Entry 8).

Given that the fluorination of **5** to **4** is a solid–liquid phase Halex process (halogen-exchange) and can be efficiently activated by the addition of a phase transfer catalyst (PTC) (Miyajima et al. 2000; Macfie et al. 2001; Fan et al. 2012), we investigated the effect of PCT on the reaction. The addition of Ph_4PCl (5 mol%, as a catalyst) into sulfolane at 200 °C distinctly improved the fluorination efficiency, giving a product in 53% yield after 18 h (Table 1, Entry 9). A plausible PTC mechanism is shown in Scheme 7. The first step is related to the dissolution of KF crystals in micro-aqueous phase and the formation of nucleophile [F^-]. Then, [F^-] and Ph_4PCl would exchange ions to form Ph_4PF, which is organophilic and diffuses freely to the bulk organic phase. The second step involves the fluorination reaction of Ph_4PF with **5** in the organic phase to form **4** and Ph_4PCl. Finally, the third step involves the transport of the co-product Ph_4PCl, the leaving group to the interfacial region and the transport of another nucleophile [F^-] to the next PTC cycle. Similarly, the addition of 18-crown-6 (5 mol%) in sulfolane at 200 °C improved the yield to 45% after 18 h (Table 1, Entry 10), which was attributed to the enhanced transport of [F^-] by crown ether (Pliego and Riveros 2012).

To our surprise, when a composite PTC system (3 mol% Ph_4PCl and 1 mol% 18-crown-6) was used, the heating treatment at 200 °C for 10 h was sufficient to raise the yield of **4** to 68% (Table 1, Entry 11). Obviously, the composite PTC system improved the yield in shorter time than the single PTC system, which may be due to the different catalytic mechanisms of the two systems. In the single PTC system, 18-crown-6 is only able to enhance the nucleophilic ability of fluoride anion, while Ph_4PCl could only improve the stability of Meisenheimer complex which is generated in the reaction (Chen et al. 2015; Liang et al. 2013; Behbehani and Ibrahim 2015). However, the simultaneous use of the two catalysts at a specific ratio would generate an amazing synergistic effect on the reaction (Shipilov et al. 2003).

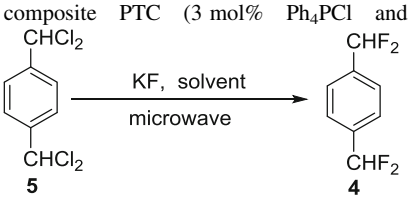
Thus, the optimal conditions for fluorination of **5** are: 6 equivalents of KF and a composite PTC (3 mol% Ph_4PCl and 1 mol% 18-crown-6) at 200 °C for 10 h.

Although this simple protocol allowed the synthesis of desired **4**, it suffered from two drawbacks, namely long reaction time and moderate product yield, which made this protocol uneconomic. Thus, a microwave irradiation method was adopted to solve these problems. Microwave-assisted synthesis is practically able to improve the reaction efficiency and shorten the reaction time (Mundra and Mahesh 2016). A series of fluorination reactions were conducted under microwave irradiation conditions, and the results clearly elucidated the advantages of this protocol.

Therefore, we investigated the fluorination reaction between **5** and KF in two types of microwave reactors. In the case of an open-vessel microwave reactor (Type A, reaction under atmospheric pressure at a constant power of 600 W), we varied systematically the reaction conditions, such as reaction time and solvent (Table 2).

Interestingly, the reaction time was significantly reduced in all microwave-assisted processes. In particular, 4 h of

Table 2 Microwave-assisted synthesis of **4** in the presence of a composite PTC (3 mol% Ph_4PCl and 1 mol% 18-crown-6)



5 **4**

Reactor type	Solvent	Time (h)	Temp (°C)	Yield[a] (%)
A	–	6	240	75
A	DMF	6	130	60
A	Xylene	10	135	63
A	Sulfolane	4	220	91
A	Sulfolane	4	180	89
B	Sulfolane	2	280	71
B	Sulfolane	4	180	85
B	Xylene	5	180	77
B	DMF	3	180	67

[a] Isolated yield

irradiation in sulfolane at 180 °C was enough to raise the yield of **4** to 89% (Table 2, Type A). The yields of **4** were significantly improved compared to the experiments without microwave (Table 1). The reason may be that the C–Cl bond and K–F bond were weakened by microwave irradiation, which promoted the formation of Meisenheimer intermediate (Behbehani and Ibrahim 2015). Besides, the use of high boiling point solvents, such as xylene and sulfolane, improved the yields to 63 and 91%, respectively.

The pressurized microwave reactor (Type B) for the fluorination offered a broader temperature range and facilitated heating above the normal boiling point of the solvent, as well as possible benefits of the pressure effect. For instance, the yield further increased and the reaction time was reduced to 5 h in the reaction at 180 °C in xylene, probably because the solvothermal conditions in the closed reactor contributed to the fluorination. However, this method was useless in the reaction at 280 °C in sulfolane, probably due to the severe decomposition of sulfolane and catalyst at high temperature. Although the yield of **4** was moderate in the case of xylene, this route is limited by the application range and discontinuity.

Conclusions

We developed a practical and fast microwave-assisted protocol for preparation of **4** from commercially available **5** and cheap KF in a composite PTC system (3 mol% Ph_4PCl and 1 mol% 18-crown-6) in sulfolane at 180 °C. The introduction of microwave increased the yield and significantly shortened the reaction time from dozens of hours to a few hours. Further explorations of the reaction mechanism are under progress and will be reported.

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