Preliminary Note

'Halex' fluorination of 1,2,4,5-tetrachlorobenzene in a pressure reactor

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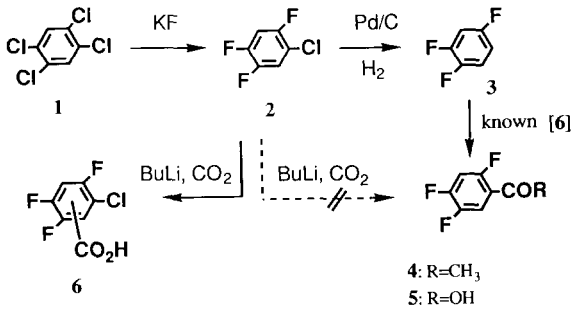
Abstract

Halogen exchange of 1,2,4,5-tetrachlorobenzene with spray-dried potassium fluoride has been found to proceed smoothly using 1,3-dimethyl-2-imidazolidinone as a solvent at 300 °C in a pressure reactor to give 2,4,5-trifluorochlorobenzene without any rearrangement.

The 'Halex' fluorination of trichlorobenzenes at an elevated temperature in a pressure reactor has been announced recently [1]. This leads us to publish the results of our investigations on the 'Halex' fluorination of 1,2,4,5-tetrachlorobenzene (**1**) with spray-dried potassium fluoride (KF). Our main focus was a preparation of 2,4,5-trifluorochlorobenzene (**2**), a useful intermediate for quinolone antibacterial drugs [2, 3].

Early work by Yakobson *et al.* reported the reaction of **1** with KF at 450–460 °C without a solvent. They reported a low yield of a complex mixture of chlorofluorobenzenes including rearranged products via a benzyne intermediate [4].



We have recently disclosed data on the use of 1,3-dimethyl-2-imidazolidinone (DMI) as a solvent for the 'Halex' reaction of chlorobenzonitrile derivatives with KF at an elevated temperature (300 °C) in a pressure reactor

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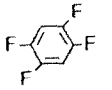
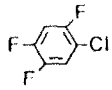
TABLE 1

'Halex' fluorination of 1,2,4,5-tetrachlorobenzene[a]

Run No.	Metal fluoride (equiv.)	Solvent	Additive (0.1 equiv.)	Temp. (°C)	Time (h)	Material recovered (%)[b]				
										
1	KF (3.9)	DMI	–	300	8	0.6	31.0	2.2	30.3	–
2	KF (3.9)	DMI	–	300	24	11.9	48.3	1.0	22.7	–
3	KF (3.9)	DMI	$FeCl_3$	300	8	3.3	42.4	2.5	30.4	–
4	KF (3.5) CsF (0.4)	DMI	–	280	8	3.8	34.5	1.5	23.4	–
5	KF (3.9)	NMP	–	300	8	–	3.3	13.8	6.2	9.9

[a]A 300 ml Hastelloy 'C' pressure reactor equipped with a magnetic drive stirrer was charged with **1** (32.1 g, 0.15 mol), spray-dried KF (34.0 g, 0.585 mol) and 1,2,4-trimethylbenzene (1.7 g, internal standard for GLC) in DMI (150 ml). The reaction mixture was stirred at 300 °C for 8 h. The mixture was cooled to room temperature and filtered to remove inorganic materials. The residue was analyzed by GLC methods.

[b]Yields were determined by GLC using an internal standard technique.

[5]. Based on these results, we have tried the 'Halex' reaction of **1** in DMI. The results are summarized in Table 1. As expected, **2** was produced in a significant yield, and no rearranged products were found in the reaction mixture.

To clarify the structure of the isolated product, **2** was submitted to hydrogenolysis (5% Pd/C, 1 atm H_2) in refluxing ethanol. Product **3** was confirmed by comparison with authentic 1,2,4-trifluorobenzene and 1,3,5-trifluorobenzene. A similar reaction in 1-methyl-2-pyrrolidinone (NMP) afforded a small amount of the desired product **2**, accompanied by a large number of dehalogenated products and tarry materials (Table 1, run 5).

The reaction of **3** with acetyl chloride in the presence of aluminium chloride to give 2,4,5-trifluoroacetophenone (**4**) has been reported, the latter being readily converted to 2,4,5-trifluorobenzoic acid (**5**) [6]*. However, the availability of **3** is a problem for these known routes. 'Halex' fluorination of 1,2,4-trichlorobenzene suffered from less than acceptable yields of **3** (2.5 ~ 8.3%) [9].

Although a formal synthesis of **5** was completed via **3**, we have attempted a direct transformation of **3** into **5**. Treatment of **2** in ether with butyl-lithium (hexane) at −78 °C, followed by solid CO_2 gave a white solid (76% yield) having a melting point of 115–116 °C. GC–MS analysis of the product indicated a mixture of trifluorochlorobenzoic acids **6** (*c.* 7:3) [*m/z* 282 (M^+) after silylation] but no **5**. Unfortunately, the direct conversion of **2** into **5** was unsuccessful, but the present approach via **3** may offer a new route to **5**.

References

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*The preparation of **5** via cyanation [7] or lithiation [8] of 2,4,5-trifluorobromobenzene has been reported.