



Facile and Selective Synthesis of 2,3,4,5-Tetrafluorobenzoyl Chloride with Triphosgene

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The method of 2,3,4,5-tetrafluorobenzoyl chloride synthesis with triphosgene was studied. High catalytic activity and the yield of carbonyl chloride on the chlorination of acid were achieved. The yield could be reached 95 mol % when the catalyst (DMF) was 5 mol % of acid, 1,2-dichloroethane used as solvent, $n(\text{triphosgene}):n(\text{acid})$ value 0.37:1.00 and the reaction was carried out at 353 K for 4 h.

Key Words: 2,3,4,5-Tetrafluorobenzoic acid, 2,3,4,5-Tetrafluorobenzoyl chloride, Triphosgene.

INTRODUCTION

Carboxylic acid chlorides are one of the most important organic intermediates in the preparation of pharmaceuticals, cosmetics, surfactants and paper auxiliaries. The common pathway to obtain carboxylic acid chloride is involved the chlorination of carboxylic acid with PCl_3 , POCl_3 , PCl_5 , SOCl_2 , SO_2Cl_2 or COCl_2 . Of industrial importance were the reactions with thionyl chlorides, phosphorus trichloride and phosgene. However, the chlorination with reagents such as PCl_3 , PCl_5 or POCl_3 will give inorganic salts and even present environmental problem. The preparation of carboxylic acid chlorides with phosgene had high purity and yield, but the phosgene was highly toxic gas and easy to diffuse, which made the synthesis potentially hazardous.

In recent years, triphosgene [*bis*(trichloromethyl)carbonate] (BTC)¹, a substitution of phosgene, has received much attention. Compared with phosgene, BTC is not only safer to use and more conveniently handled, for transportation and storage. Being a solid compound and decomposing slightly at the boiling point, it could be exactly weighted. Accordingly, triphosgene could be used in various organic reactions such as chloroformylation, carbonylation, dehydration²⁻⁶. Furthermore, BTC normally performed under mild reaction conditions and afforded excellent yields. The synthesis of carboxylic acid chlorides with BTC was also reported in literature⁷⁻¹¹. Herein, we report an efficient, mild and selective method for the preparation of 2,3,4,5-tetra-fluorobenzoyl chloride using DMF as catalysts with good yields.

EXPERIMENTAL

A 4-necked round bottomed flask equipped with a mechanical stirrer, digital thermometer, nitrogen inlet-outlet and a condenser was charged with BTC (5.5 g, 18.5 mol) and 1,2-dichloroethane (30 mL). The resulting mixture was heated slowly to 353 K and a solution of 2,3,4,5-tetrafluorobenzoic acid (9.7 g, 50 mol) and N,N-dimethylformamide (0.18 g, 5 mol % of acid) in 1,2-dichloroethane (50 mL) was added dropwise over 1 h at 353 K then the mixture was further stirred for 4 h at the same temperature. The reaction mixture was cooled to 273 K and filtered to remove BTC. The products were analyzed with GC. Reactants and products were identified by comparison with authentic samples. Biphenyl was used as an internal standard.

RESULTS AND DISCUSSION

Catalytic chlorination reactions are influenced by many factors, which include the presence of catalytic activators or poisons, temperature, pressure, solvent agitation and other conditions specific to the particular process. One of the most important considerations is the chlorinated reagents. When triphosgene was used on the chlorination of acid, good catalytic properties were obtained over organic amine or organic base as catalyst. As mentioned preciously, the N,N-disubstituted formamides, specially the formamide often serves as catalyst and shows good properties for the preparation of carbonyl chloride with triphosgene. We investigated the effect of different catalyst amount on the chlorination of 2,3,4,5-

tetrafluorobenzoyl acid with BTC. From Table-1, we observed that DMF could catalyze the chlorination of 2,3,4,5-tetrafluorobenzoyl acid with BTC. Good yield of 2,3,4,5-tetrafluorobenzoyl chloride (TFBC) was obtained. DMF (5 mol %) exhibited the best yield of 2,3,4,5-tetrafluorobenzoyl chloride (95.1 mol %).

TABLE-1

ACYLATION OF TBA WITH TRIPHOSGENE OVER DIFFERENT CATALYSTS [REACTION CONDITION: 0.05 mol 2,3,4,5-TETRAFLUORO BENZOIC ACID; REACTION TEMPERATURE WAS 353 K; $n(\text{TRIPHOSGENE}):n(\text{ACID})$ (MOLE RATIO) = 0.37:1, THE SOLVENT WAS 1,2-DICHLOROETHANE AND REACTION TIME WAS 4 h]

Catalyst	Conversion (%)	Yield of products (mol %)	
		TFBC	TFBH
DMF (0.12 g)	87.1	85.1	14.4
DMF (0.18 g)	98.3	95.1	2.6
DMF (0.24 g)	95.3	88.3	10.7
DMF (0.36 g)	91.7	85.5	12.5
Tributylamine	94.4	40.2	58.6
Triethylamide	89.2	47.7	51.3
Pyridine	91.9	52.8	46.2
Imidazole	89.6	68.8	29.8

Some products with high boilingpoint could not be determined by GC analysis; TFBH = 2,3,4,5-tetrafluorobenzoyl anhydride.

Different catalysts have also influence on both catalytic activity and yield of TFBC. Pyridine, imidazole, triethylamine (TEA) and tributylamine (TBA) were also used as catalyst on the chlorination of acid with triphosgene. The different physical and chemical properties make them different effects on the chlorination of TFBA. The results were also listed in Table-1. From Table-1, we observed that good yield of TFBC was obtained in the presence of DMF. The good yield of TFBC may be related to the nature of DMF. The nucleophilicity of DMF was moderate. When DMF was used as catalyst, there was always excess of phosgene with DMF to form Vilsmeier salts (Fig. 1). The Vilsmeier salts which were the actual reactive chlorinating reagent could be reacted with carboxylic acid to give the carbonyl chloride¹². Meanwhile, DMF catalyst didn't combine with the coproduction hydrogen chloride and kept their catalytic activity in the reaction system, so the high yield of carbonyl chloride was obtained. Tributylamine and triethylamine were strong base in the organic field. When they were used as catalyst, they could rapidly catalyze the decomposition of triphosgene combining with hydrogen chloride. They could also react with hydrogen chloride to quaternary ammonium salt and lose their catalytic activity.

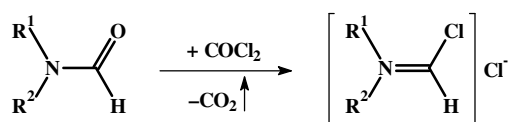
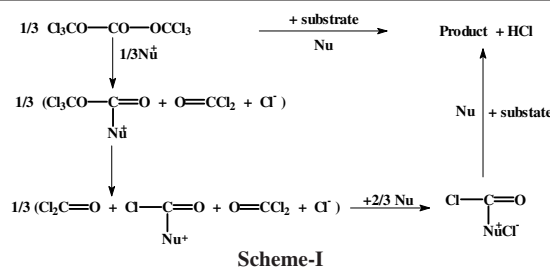


Fig. 1. Vilsmeier salt

Eckert and Forster^{1,8} proposed a cyclic route for nucleophilic reactions of BTC (**Scheme-I**). According to this scheme, 1/3 mol of BTC reacts with 1/3 mol of nucleophile 2 to form 1/3 mol of phosgene. In the next step a second and a third mole of phosgene evolve which are "quenched" by 2/3 mol of nucleophile,



Scheme-I

forming product 3. 1/3 mol of BTC was needed for a mole TFBC. In the experimental conditions, the loss of phosgene was inevitable, therefore we studied the influence of substrate concentration on the chlorination of TFBA with TBC over DMF catalyst. The results were listed in Fig. 2. From Fig. 2, it was found that the conversion of TFBA was over 99 %. The yield of TFBC increased monotonously with increasing the amount of TBC. However, the yield of TFBC decreased when the molar ratio BTC to acid was higher than 0.37. Lower yield was related to strong reductibility of triphosgene. When BTC was used, it was resolved in organic solvent. The solution was added dropwise to control reaction rate. So the molecular utilization was high and the reaction didn't require too much BTC. The appropriate range was 0.35-0.45:1 ($n(\text{BTC}):n(\text{acid})$). It was much lower than the use of phosgene (the mole ratio phosgene to acid was over 2:1).

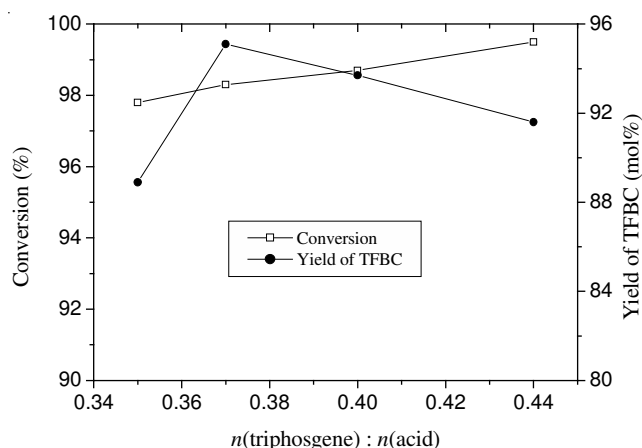


Fig. 2. Effect of mole ratio of raw materials on the chlorination of 2,3,4,5-tetrafluorobenzoyl acid with triphosgene over DMF

Based on above experiment results, we studied the influence of solvent and reaction temperature on the chlorination of acid over DMF catalyst in particular. The results were summarized in Table-2. It was found that the chlorination rate increased with increasing reaction temperature. The highest yield of carbonyl chloride was obtained in chlorobenzene at 373 K. Compared with other solvent, chlorobenzene and 1,2-dichloroethane were the best solvent on the chlorination of 2,3,4,5-tetrafluorobenzoyl acid with DMF. Good solubility and large polarity of solvent were responsible for higher yield on the chlorination of TFBA. However, chlorobenzene was used, the product of TFBC couldn't be separated through a simple distillation because of the proximity boiling point between TFBC and chlorobenzene. Therefore, dichloroethane was used as solvent in chlorination reaction.

TABLE-2
CHLORINATION OF 2,3,4,5-TETRAFLUOROBENZOIC ACID
WITH TRIPHOSGENE IN DIFFERENT SOLUTION AND
REACTION TEMPERATURE*

Solvent	Temperature (K)	Conversion (%)	Yield of products (mol%)	
			TFBC	TFBH
1,2-Dichloroethane	343	92.3	95.0	2.9
1,2-Dichloroethane	353	98.3	95.1	2.6
THF	Reflux	90.3	67.2	26.9
Toluene	373	95.5	80.5	16.6
Chlorobenzene	353	96.9	68.2	29.6
Chlorobenzene	363	97.8	88.5	9.8
Chlorobenzene	373	98.5	96.5	2.2
Chlorobenzene	383	98.0	88.9	9.6

*Reaction conditions were similar to Table-1. The catalyst was DMF and the amount of catalyst was 0.18 g.

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