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Direct fluorination
of 1,3-dicarbonyl compound in a continuous flow reactor at industrial scale

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KEYWORDS

Direct fluorination, flow chemistry, MEPI, silicon carbide.

ABSTRACT

Direct fluorination of an Axyntis® 1,3-dicarbonyl compound is investigated at industrial scale in a commercial continuous flow reactor under gas-liquid conditions. The considered flow reactor manufactured by Boostec®, is made of silicon carbide that offers relevant heat transfer performances with regards to reaction exothermicity, as well as corrosion resistance. A screening of the operating conditions and more precisely on solvent and on catalyst was performed to demonstrate the feasibility of the reaction in a continuous mode. To work in a safe and non-hazardous environment regarding the reaction characteristics, experiments have been carried out at the MEPI facility (Maison Européenne des Procédés Innovants). The results show that in slug flow regime full conversion could be achieved with few seconds residence time while reaching a productivity level about 200 g per hour.

INTRODUCTION

In the recent years, there has been an increasing interest in process intensification (1-4) and in the use of continuous intensified reactors, which allow complex chemical reactions to be performed with enhanced heat and mass transfer (5, 6). Such features allow complex chemical reactions to be carried out under unconventional operating conditions and then present significant benefits from process intensification viewpoint: an improved productivity related to the increase of reactants concentration, an improved selectivity related to the plug flow behaviour and the accurate thermal control and a reduced impact on the environment related to the reduction of solvent consumption. With regards to process safety, the concept of heat exchanger reactor also offers many perspectives (7, 8). The accurate thermal control and mixing performances will prevent from side-reactions and thermal runaway and the small reactive volume will limit the risks and consequences of failures in strategic systems. Many technologies are today available at different scales according to the considered objectives: lab scale (micro-reactor) for the screening of new reaction routes and feasibility studies, pilot scale (milli-reactor) for demonstrations and small productions and production scale (meso-reactor) for large productions.

From a process viewpoint, the direct fluorination reactions appear as a good example for flow reactors consideration (9-12). In fact, such reaction class is of great interest for fine, agrochemical and pharmaceutical chemistries (13, 14) and presents fast kinetics associated with strong heat generated in the course of the reaction and consequently, a hazardous nature of the processing (15). Direct fluorination is also known for poor selectivity and small overall yield, involved by mass transfer limitations related to the multiphase nature of systems: gas-liquid or more complex ones. In the recent years, such statement has led research groups to consider flow reactors and their potential for enhancing mass and heat transfer for direct fluorination (16-19). Many studies have been performed at lab scale on micro-reactors and demonstrate the feasibility to carry out direct fluorination in a continuous mode and under safe conditions.

These works emphasize the impact of the size reduction and of the micro-structured features to obtain a significantly improved control of the reaction that allows high concentrated fluorine (up to 50 percent) to be considered and increased selectivity and conversion levels to be reached. These studies are based on different equipments as falling film, bubble column or thin-film multi-channel reactors, at micro-scale offering limited productivity: largest liquid flow-rates are about 20 $mL \cdot h^{-1}$. These micro-reactors are producing typically from 0.1 to 10 g per hour and are then well suited for screening or to produce few grams (20-22). The question is how to benefit from enhanced mass and heat transfer for industrial production up to several tons per year which requires production rates at least 100 times higher. Despite the promising perspectives of such processing, scale-out has been quite exclusively envisaged by numbering up of these micro-reactors and very few transpositions to pilot (23) or production scale are reported in literature.

The purpose of the present work is to carry out direct fluorination from a commercial production scale equipment. In this way, direct fluorination of a 1,3-dicarbonyl compound commercialized by Axyntis® was investigated in a Boostec® silicon carbide flow reactor.

The challenge of this study lies in the feasibility in continuous and at high scale without any data available on the chemistry (kinetics, reaction heat), on the processing (no information on existing batch process) and on analytics (no existing method and no standard of the product available). To achieve this goal, the considered reactor presents micro-structured channels designed for multiphase reactions and allows a production rate from 1 to 100 tons per year. The study has been performed by MEPI (Maison Européenne des Procédés Innovants), a piloting and demonstration platform for Process Intensification technologies, operating since end of 2007, in Toulouse, France.

Based on the facility concept described by the Action Plan Process Intensification (24), MEPI offers complete package of services (Figure 1). Its installation on a Seveso site offers large guaranties in terms operability under clean and safe conditions that was particularly important in the context of the present study.

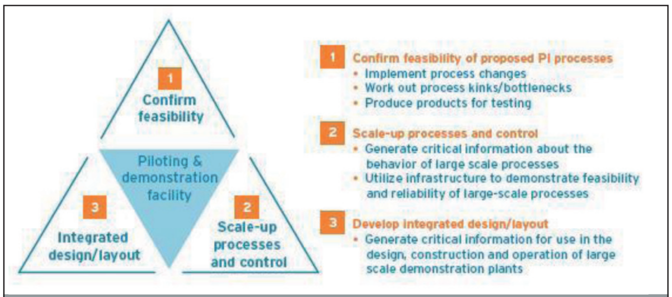

Figure 1. Objectives of piloting & demonstration facility, courtesy: creative energy.

RESULTS AND DISCUSSION

Reaction presentation: direct fluorination of 1,3-dicarbonyl compound

Fluorination reactions are of interest as they give access to organic compounds widely used in pharmaceutical and speciality chemistry. Industrial interest over mono or multi-fluorinated molecules has been enhanced last years because of their properties in the formation of biologically active molecules (13). A wide range of fluorinating agents has been well studied and are available to obtain such organo-fluorinated compounds. Those reagents are quite efficient but involve a strong complexity in terms of chemistry (multi-step synthesis) and of processing. As a consequence, a lot of studies were done last years on the direct fluorination of organic compounds with native fluorine and at a low temperature (from -20°C to 0°C) to avoid thermal runaways. Direct fluorination is generally carried out in solvents favouring the polarization of F_2 and which are also good acceptor for the counter ion (11, 25).

The classical solution lies generally in a mixture of solvents that presents both characteristics: non protic solvents, with high electro-negativity as acetonitrile (ACN) and very protonic acids to accept the counter-ion as formic acid, acetic acid or concentrated sulphuric acid. On the peculiar case of carbonyl compounds literature also reports a lot of works (25-27). Ester or ketones derivatives are preferably fluorinated at secondary sites that are further removed from the electron withdrawing group. Nevertheless fluorination is also possible on sites adjacent to the carbonyl group (a position) and in this case, fluorination occurs on the enol form of the molecule. Figure 2 describes this direct fluorination mechanism for di-carbonylated compounds.

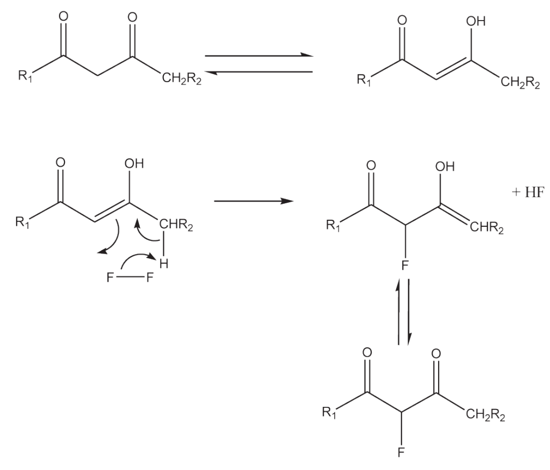

Figure 2. Mechanism of direct fluorination for 1,3-dicarbonyl compound.

As a consequence, enolisation kinetics plays an important role in this type of fluorination. To reach high conversion, fluorine gas introduction has to be carefully regulated, with a flow-rate adapted to enol formation rate and which limits gas hold-up. Obtaining such an addition behaviour in continuous flow reactors is really challenging, as it involves multiples and well-positioned additions. To by-pass such an issue, a strategy commonly adopted lies in use of catalysts to speed-up enolisation rate. In this way, a wide range of molecules, both organic and inorganic, have been tested (26, 27). The activity of these catalysts is given by their ability to accelerate enolisation rate and the kinetics of fluorinated compound liberation to form a new complex. With regards to carbonylated compounds, most efficient catalyst seems to be bases such as sodium acetate or metallic salts, nitrates in particular. This catalytic approach has then been adopted for the purpose of the present work.

Piloting of fluorination

Direct fluorination of a 1,3-dicarbonyl compound has been carried out in a commercial Boostec® silicon carbide reactor, at pilot scale. Catalytic activation has been applied to obtain significant conversion levels in a short residence time. As the main objective of this study is to demonstrate the feasibility of such a fluorination, various parameters have been studied. All experiment have been performed at pilot scale, with flow-rates respectively set at 720 $g{\cdot}h^{-1}$ for di-carbonyl solution and 2040 $g{\cdot}h^{-1}$ for fluorine gas solution. The concentration of di-carbonyl solution was fixed at 25 percent weight (about 2 mol/L depending on solvent). For supply and safety considerations, fluorine 5 percent mol. diluted in nitrogen has been used, that corresponds to a fluorine flow-rate of 136 $g{\cdot}h^{-1}$ and a molar ratio of 3.1 equivalents. Such flow-rates lead to a gas-liquid system with a strong gas hold-up. Hence and like in micro-reactors studies (23), slug flow behaviour is observed that limits interfacial area.

Even if recirculations inside the liquid flow between bubbles are reported to enhance significantly the mixing (23), this scenario is not optimal for mass transfer performances. The related impact on fluorination conversion has to be determined. Regarding heat transfer, as the silicon carbide reactor shows strong performances (28), such a behaviour does not affect the isothermal profile obtained for all experiments.

Assuming that the slug flow regime involves gas and liquid phases to have the same residence time, a global residence time is estimated. Its value is computed taking into account the global volume flow-rate (sum of gas and liquid) and the reactor volume. Variation of volume flow-rates and particularly of the gas phase, due to temperature, composition, and pressure variations all along the reactor, are not taking into account. Depending on operating conditions and the solvent used, residence time is about few seconds inside the reactor.

Effect of the solvent nature

A screening of solvents has been realised, to optimize the fluorination of 1,3-dicarbonyl compound. As the considered 1,3-dicarbonyl compound does not involve specific solubility issues, the screening has only been performed with a conversion criterion. Three solvent systems reported in literature (11, 25) have been tested: acetonitrile, acetic acid and a mixture of acetonitrile and acetic acid, 50/50 weight. To perform an accurate comparison, the same catalyst has been used during all tests, $Ni(NO_3)_2$. Because of the solvent properties, keeping the same temperature has not been possible. In fact, the freezing point of acetic acid is around 16°C that involves increasing the reaction temperature to prevent the reactor from clogging.

As a consequence, reactions with pure acetic acid as solvent are carried out at 20°C and reaction with acetonitrile/acetic acid mixture at 5°C. As commonly applied in literature, molar excess of fluorine has been set to 3.1. Results are presented in table 1.

Solvent nature	Catalyst nature	Molar ratios / Di-carbonyl Catalyst	 Fluorine	Temperature (°C)	GC results (based on peak area)
ACN	$Ni(NO_3)_2$	0.2	3.1	0	97 %
50/50 solution	$Ni(NO_3)_2$	0.2	3.1	5	100 %
Acetic acid	$Ni(NO_3)_2$	0.2	3.1	20	98 %

Table 1. effect of solvent nature on conversion.

Results should be analysed with a special care regarding the uncertainties on analytics and as temperature varies depending of the solvent. Nevertheless, some tendency appears. The 50/50 mixture of acetonitrile/acetic acid then constitutes the optimal solvent. As expected, in that case the combination of the acetonitrile high polarity to the protonic characteristic of acetic acid, leads to full conversion of 1,3-dicarbonyl compound.

Effect of the catalyst nature

A screening of catalysts has been performed aiming at optimizing the fluorination of 1,3-dicarbonyl compound. According to literature (26, 27), three catalysts have been considered: nickel nitrate, copper nitrate and sodium acetate. For the comparison, the same operating conditions have been applied, in terms of flow-rates, of solvent nature, of temperature and of catalyst and fluorine molar ratios, respectively set to 0.2 and 3.1. All results are gathered in table 2.

Solvent nature	Catalyst nature	Molar ratios / Di-carbonyl Catalyst	 Fluorine	Temperature (°C)	GC results (based on peak area)
acetonitrile / acetic acid mixture (50/50 w.)	$Ni(NO_3)_2$	0.20	3.1	5	100 %
	$Cu(NO_3)_2$		3.1		96 %
	CH_3COONa		3.2		48 %

Table 2. effect of catalyst nature on conversion.

The catalyst screening reveals that sodium acetate is the less efficient catalyst with a poor conversion achieved in the reactor. Metallic based catalysts and particularly nickel nitrate, seem more efficient to reach high conversion level in the considered residence time. From an industrialisation viewpoint, the catalyst choice appears more complex: metallic salts show a higher efficiency but involve higher post-treatment costs compared to sodium acetate which is cheaper and easier to handle.

EXPERIMENTAL SECTION

Continuous flow reactor equipment

The reactor equipment was a silicon carbide based flow reactor (29, 30), engineered jointly by LGC (Laboratoire de Génie Chimique) and Boostec. Based on the principle of the heat exchanger (Figure 3), it consists of an assembly of 11 plate modules in a single compact frame: 5 silicon carbide modules dedicated to the reactive medium (grey plates) and 6 modules for utility fluid (blue plates) to ensure thermal control. The advantage of a compact frame is to avoid the transition zones between reactive plates without any thermal control. To respect the material continuity, silicon carbide inserts have been integrated inside utility plate for the reactive medium circulation from plate to plate. Moreover, to comply with corrosion constraints all connecting (inlet, outlet, side-injection) are made of silicon carbide or titanium.

The design of reaction plates has been defined to fit with the reaction requirements in terms of residence time, injections and mixing efficiency. The reactor internal volume is about 50 mL which contrasts at equal-productivity with the normal batch equipment which suffers from significant accumulation of chemicals. In the context of this study, only a single side-injection system has been set, close to the reactor inlet (Figure 3). All reactive modules integrate plate fins to improve the heat exchange surface. The resultant thermal performances are impressive for pilot scale equipment: the heat exchange capacity is about 20,000 $kW{\cdot}m^{-3}{\cdot}K^{-1}$ (26). The thermal behaviour inside the reactor is measured by 16 thermocouples located all along the reactive medium circulation that means approximately one thermocouple per second of residence time. It allows the isothermal behaviour to be accurately validated in spite of the strong exothermicity of direct fluorinations.

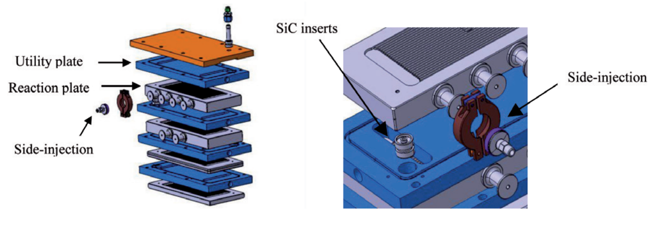

Figure 3. Boostec® silicon carbide flow reactor.

Auxiliaries

The process was divided in two parts: reaction and post-treatment. Reaction part is constituted of the fluidic module and the flow reactor. The fluidic module allows raw materials to be introduced inside the flow reactor with constant and regulated flow-rates and also all operating conditions to be recorded. In this way, it is composed by controlled gear pumps for liquid injections, mass flow-meters (Coriolis Effect), temperature and pressure sensors and safety equipments such as safety valves, check valves, etc. Introduction of gas is performed by specific valves which regulate pressure to ensure constant flow-rate according to pressure drops.

Post-treatment step is composed of a reaction quench occurring in a 16L stirred and jacketed batch reactor made of Hastelloy. This reactor is cooled down to 5°C and previously half filled with a sodium hydroxide 10 percent weight solution to neutralize the hydrofluoric acid formed during fluorination. As pure hydrofluoric acid is in its gaseous form under the quench conditions, the fluorination solution is injected directly inside the basic solution by a bubbling system to favour solubilisation and destruction. For safety reasons, a Nitrogen blanketing is carried out inside the vessel and the resultant gas flow is collected and treated inside a gas-liquid column to destroy the hydrofluoric acid remaining (see Figures 4 and 5).

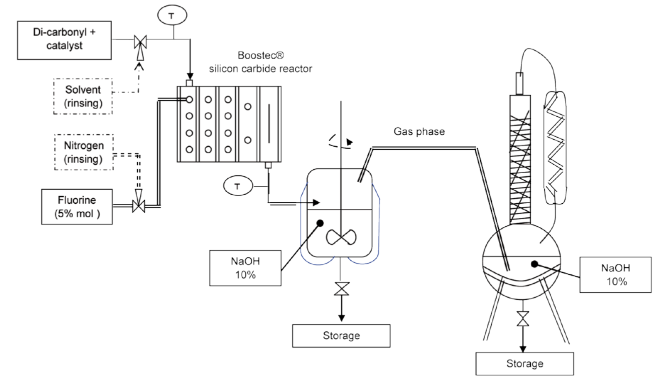

Figure 4. Picture of the continuous flow process used for fluorination at the MEPI facility.

Figure 5. Picture of the continuous flow process used for fluorination at the MEPI facility.

To assure non-hazardous operating, MEPI has proceeded to a full safety review using the Seveso site support and University expertise. It allows the design of the process including the equipments and the material choice, and the operating procedures (start-up, sample withdrawing, shut-down) to be precisely defined. The sampling is done at the flow reactor outlet by dropping the reactive solution in a given volume of sodium hydroxide solution to neutralize the potential hydrofluoric acid released. The organic phase is then analysed after dichloromethane extraction assuming that 1,3-dicarbonyl compounds (raw-material and product) do no transfer into the water phase.

A small amount of acetic acid is added to buffer the sample at an acidic pH forcing the 1,3-dicarbonyl compound to stay into the organic layer. This procedure also favours the decantation and extraction steps.

Analytics

The samples collected during run-tests are analysed using gas chromatography equipment (GC) from ThermoFisher Scientific. A method was established to estimate the conversion of the fluorination reaction. In this way, the absence of standard for the fluorinated product and by-products makes the set-up of this method more difficult to realise. In a preliminary step, standard solutions of 1,3-dicarbonyl compound in dichloromethane were analysed to identify the retention time of the raw material and to evaluate the sensitivity of the method according to concentration. The identification of the fluorinated compounds was then performed by a GC-MS analysis to confirm the retention times of the two compounds of interest. The mass spectra validated the attribution of the signal to the 1,3-dicarbonyl compound and the product and then make rough estimation of conversion possible.

Nevertheless, the GC method presents limitations and uncertainties. Taking into account these uncertainties and those related to the post-treatment of samples, the GC method cannot been used for mass quantification and only a rough estimation of conversion based on a peaks area comparison has been performed.

CONCLUSION

Direct fluorination of a 1,3-dicarbonyl compound was investigated in a pilot/production scale process based on a commercial flow reactor. The MEPI facility demonstrates the feasibility of this production where no informations on chemistry, on processing or on analytics were available. The methodologies applied allow the fluorination process to be successfully operated for more than 70 hours without any hazardous issue.

More than 20 experiments with different operating conditions have been carried out and allow an optimal process to be defined in terms of chemistry: solvent and catalyst choice. The associated results highlighted the heat and mass transfer performances of the flow reactor. In fact, despite the strong heat released by fluorination and the strong gas hold-up leading to a slug flow gas-liquid regime, full conversion without any local hot spot has been reached.

At the flow-rate conditions applied during this feasibility study and assuming a 100 percent reaction yield, the reactor could produce 200 g per hour of fluorinated product. However the available heat transfer and mixing capacities open the door to potential improvements of this productivity. Optimisation of raw material concentrations (1,3-dicarbonyl compound and fluorine) and of fluorine excess appears then possible under non-hazardous conditions. These considerations show the high potential of Boostec® silicon carbide reactor for direct fluorination at industrially scale.

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