



Modulation of reactivity of singlet radical pair in continuous flow: Photo-Fries rearrangement



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ABSTRACT

Photo-Fries rearrangement of phenyl benzoate is studied using continuous flow for modulating the reactivity of singlet radical pair by changing the viscosity of the solvent. The effect of flow and proximity of the reactants with the light source on the reactivity of radical pair, formed from singlet excited state was investigated in details. In non-viscous solvent, the results from flow synthesis were comparable to batch reactor. In viscous solvents, selectivity of *ortho*- and *para*-isomers (*o*-/*p*- isomer) of the product could be controlled by changing viscosity as well as the flow rate. Using flow synthesis, *ortho*- and *para*-isomer ratio was obtained as high as 8.45 which are twice as compared to batch experiment with in fraction of residence time.

1. Introduction

The photochemical reaction for the selective synthesis of a desired product involves an intermediate having short life time that mostly requires activation free reaction pathways and hence it is a challenging task. There are various approaches that have been adopted to increase the selectivity by using wavelength specific chemical transformations while the extent of reactions can be enhanced significantly by using small confined domains for reaction to ensure that ample photo-generated species are available for the synthesis [1,2]. Molecules enclosed in confined spaces in viscous solvents are expected to experience restrictions on their motion when compared to the open systems. A restriction of translational or rotational freedom of molecules as well as the intermediates often gets reflected in the product distribution [3–5]. In the photo-fries rearrangement of phenyl esters the reaction proceeds through an initial cleavage of phenyl ester to produce a phenoxy and an acyl radical in a solvent cage which may recombine in different ways and gives *ortho*- and *para*-isomers of hydroxybenzophenones [6,7]. The formation of *ortho*- isomer requires less translational motion of one of the radicals than what is needed for the formation of *para*-isomer. In most of the cases formation of *ortho*- and *para*-isomer may dictate the mobility of the radical species involved in the reaction, and this hypothesis has been proved by utilization of highly viscous liquid in which only *ortho*-isomer has been observed [8]. Flow photo chemistry in small, optically transparent channels offers excellent mixing, uniform

irradiation, narrow residence time distribution and an ability to extend the laboratory scale synthesis to large scale production [9–11]. The Small flow dimensions offer large optically active area per unit volume of the substrates, which helps to enhance the reaction rates significantly [12]. The pumping action that generates convective flows with specific flow profiles helps to have relatively narrow residence time distribution compared to conventional mixed flow reactors [13]. In most of the literature, the continuous photochemical reactor is usually a helical coil or a micro-fabricated silica chip [14–16] having one side bound to glass/quartz to facilitate the irradiation. In the helical coils, radius of curvature decides the extent of secondary flow which reduces the axial dispersion in the flow path. A review by Oelgemöller [9,11], Knowels [17], Su and co-workers [18] gives a detailed account of several successful examples of flow photochemistry. Among many, few of the excellent examples include [19–25]: (i) photocyanation of pyrene across an oil/water interface in a polymer microchannel chip, (ii) continuous flow photolysis of aryl azides, (iii) continuous flow synthesis of activated vitamin D3 and its analogues, (iv) flow assisted intramolecular photocycloaddition of 1-cyanonaphthalene derivative, (v) photo rearrangement reactions [26] (vi) singlet oxygen involved photochemical reactions [27] and (vii) continuous flow photopolymerization.

Here we have studied continuous flow Photo-Fries rearrangement of phenyl benzoate for getting complete conversion in short residence time (Fig. 1) The advantage of flow chemistry to achieve improved conversion due to superior light penetration, and control over residence

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Fig. 1. Photo flow reactor set up.

time and consistency in outlet composition for a set of conditions when compared with conventional batch photochemical synthesis. The effect of viscosity of solvent in the product distribution is explored to arrest the radical pair movement to modify the isomer ratio. After this brief Introduction, in the next Section we give details of the experimental set-up and the experimental procedure. Subsequently, we discuss the results on conversion and selectivity of the isomers for variety of conditions in detail. Finally we summarize our observations.

2. Experimental section

2.1. General information

Phenyl benzoate was synthesized and characterized by ^1H NMR spectrum in CDCl_3 as a solvent. *Ortho*- and *para*-hydroxybenzophenones were obtained by photo-fries rearrangement reaction, then purified it by column chromatography and characterized by ^1H NMR in CDCl_3 as a solvent. For photolysis, phenyl benzoate solution was prepared by dissolving it in methanol and ethylene glycol (2 mg mL^{-1}). The solution of phenyl benzoate was irradiated in a quartz tube using a UV source (450 W medium pressure mercury lamp). The percentage conversion and product distribution were obtained by analyzing the samples ($2\text{ }\mu\text{L}$ sample having concentration of 1 mg mL^{-1}) with gas chromatography (Thermo) equipped with flame ionization detector and HP-5 column packed with nitrogen as a carrier gas. GC method was set such that for the first 1 min temperature was set at $100\text{ }^\circ\text{C}$ beyond which it was increased progressively at a rate of $10\text{ }^\circ\text{C}/\text{min}$ up to $250\text{ }^\circ\text{C}$ and then it was retained at $250\text{ }^\circ\text{C}$ for next 3 min. The data based on calibration (given in the SI) was used for the estimation of conversion of phenyl benzoate and selectivity of product isomers.

2.2. Calibration

Solutions of phenyl benzoate, phenol, *ortho*- and *para*-hydroxybenzophenone in methanol were made by keeping the concentration of 0.125, 0.25, 0.5 and 1 mg mL^{-1} and analyzed by gas chromatography by injecting $2\text{ }\mu\text{L}$ of each sample. The obtained peak area was

plotted vs. concentration to get calibration trends for each compound. Since all the data followed linear trends (given in SI) the slope of these lines was further used for calculating the percentage conversion and product distribution.

2.3. Synthesis of phenyl benzoate (1)

In a round bottom flask, first we dissolved benzoyl chloride (0.83 mL, 7.1 mmol) in 15 mL of dichloromethane and then stirred it well at $0\text{ }^\circ\text{C}$. To this solution, triethyl amine (1.98 mL, 14.2 mmol) was added dropwise followed by mixture of phenol (0.69 mL, 7.81 mmol) and dichloromethane (5 mL), and stirred it overnight at room temperature. After overnight stirring this mixture was poured into ice cold water followed by its extraction with dichloromethane. The organic layer was washed with water and dried over Na_2SO_4 . Then solvent was evaporated and then the reaction mixture was purified by column chromatography to afford phenyl benzoate (1.23 g, 88%) as a white solid powder. ^1H NMR (200 MHz, CDCl_3) δ : 7.11–7.25 (m, 3H), 7.31–7.39 (m, 2H), 7.39–7.50 (m, 2H), 7.52–7.62 (m, 1H), 8.10–8.19 (m, 2H).

2.4. General procedure for photo-fries rearrangement reaction in batch reactor

Desired concentration of phenyl benzoate solution was made in methanol/ ethylene glycol as solvent and the solution was degassed with nitrogen gas for 15 min. This solution was irradiated in quartz test tube by keeping at different distances. The reaction mixture was collected at different time intervals for GC analysis and the product distribution was analyzed by gas chromatography.

2.5. Photo flow reactor

The photo flow reactor design was fabricated by quartz coil tubing (Length: 2.5 m, ID: 3 mm) around UV- lamp (450 W medium pressure mercury lamp). This quartz coil tube was equipped with a peristaltic pump and a polymeric tubing for fluid transfer (Tubing ID: 3.18 mm, total reactor volume: 50 mL). This quartz coil reactor was covered with aluminum foil.

2.6. General procedure for flow photo-fries rearrangement reaction

Phenyl benzoate solution was made in methanol/ ethylene glycol as solvent with 10 mM concentration, this solution was pumped through the coil tube at three different flow rates (3.2 mL min^{-1} , 6.4 mL min^{-1} and 17.5 mL min^{-1} respectively). After irradiation, reaction mixture was collected at different time intervals during photolysis at outlet. In order to increase the residence time without changing the velocity in the photochemical tubular reactor, the outlet was connected with the inlet and the reaction mass was pumped using peristaltic pump continuously for very long time until it reaches 100% conversion. This approach helped retain constant superficial velocity in the reactor independent of monitoring time. The product distribution was analyzed by gas chromatography.

2.6.1. 2-Hydroxybenzophenone (*o*-isomer, 1a)

^1H NMR (200 MHz, CDCl_3) δ : 6.89 (ddd, $J = 8.08, 7.14, 1.20\text{ Hz}$, 1 H), 7.09 (dd, $J = 8.08, 0.82\text{ Hz}$, 1 H), 7.37–7.75 (m, 7 H), 12.06 (s, 1 H).

2.6.2. 4-Hydroxybenzophenone (*p*-isomer, 1b)

^1H NMR (200 MHz, CDCl_3) δ : 6.63 (s, 1 H), 6.87–6.99 (m, 2 H), 7.39–7.64 (m, 3 H), 7.69–7.86 (m, 4 H).

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