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



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ARTICLE INFO	A B S T R A C T
Keywords:	Photo-Fries rearrangement of phenyl benzoate is studied using continuous flow for modulating the reactivity of
Photo-fries rearrangement	singlet radical pair by changing the viscosity of the solvent. The effect of flow and proximity of the reactants with
Flow photo chemistry	the light source on the reactivity of radical pair, formed from singlet excited state was investigated in details. In
o-/p-Isomer	non-viscous solvent, the results from flow synthesis were comparable to batch reactor. In viscous solvents, se-
Batch	lectivity of ortho- and para-isomers (o-/p- isomer) of the product could be controlled by changing viscosity as
Residence time	well as the flow rate. Using flow synthesis, <i>ortho-</i> and <i>para-</i> 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 though 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 setup 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 <sup>1</sup>H NMR spectrum in CDCl<sub>3</sub> as a solvent. Ortho- and para-hydroxybenzophenones were obtained by photo-fries rearrangement reaction, then purified it by column chromatography and characterized by <sup>1</sup>H NMR in CDCl<sub>3</sub> as a solvent. For photolysis, phenyl benzoate solution was prepared by dissolving it in methanol and ethylene glycol ( $2 \text{ mg mL}^{-1}$ ). 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 µL sample having concentration of  $1 \text{ mg mL}^{-1}$ ) 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 °C beyond which it was increased progressively at a rate of 10 °C/min up to 250 °C and then it was retained at 250 °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<sup>-1</sup> and analyzed by gas chromatography by injecting 2 µL 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 °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<sub>2</sub>SO<sub>4</sub>. 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. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.11–7.25 (m, 3 H), 7.31–7.39 (m, 2 H), 7.39–7.50 (m, 2 H), 7.52–7.62 (m, 1 H), 8.10–8.19 (m, 2 H).

# 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  $(3.2 \text{ mL min}^{-1}, 6.4 \text{ mL min}^{-1}$  and  $17.5 \text{ mL min}^{-1}$  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)

<sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ: 6.89 (ddd, J = 8.08, 7.14, 1.20 Hz, 1 H), 7.09 (dd, J = 8.08, 0.82 Hz, 1 H), 7.37–7.75 (m, 7 H), 12.06 (s, 1 H).

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

<sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) 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).



Scheme 1. Photo-Fries rearrangement of phenyl benzoate.

#### 3. Results and discussion

In general, the photo-Fries rearrangement is proposed to follow radical pair formation from excited singlet state and subsequent rearrangement [28,29]. The first mechanism indicates a homolytic cleavage of the excited molecule occurring at the ArO-COR bond (Scheme 1). The resulting pair of radicals would be restrained by a solvent cage until they are combined to form the rearranged products else the radical pair would drift apart and the phenoxyl radical would eventually abstract a hydrogen atom to form the respective phenol. Formation of phenol and perhaps para-rearranged product could occur as a result of a homolytic cleavage and hydrogen abstraction. According to this mechanism processes leading to the formation of phenol or rearranged products would represent competitive de-excitation pathways. In the photo-fries rearrangement of phenyl benzoate, the product distribution observed in homogeneous solution in solvents such as benzene and methanol can be altered by using cyclodextrin, micelles and zeolites which helps to enhance the selectivity of ortho-isomer to more than 90% [30-34].

The product distribution can provide the information about the radical-pair combination that occurs in isotropic solutions. The products obtained from Photo-Fries rearrangement infer the mobility and diffusivity of radical pair thus formed. Ortho-(1a) and para-(1b) isomers of rearranged ketones are formed by the mobility of radical pairs whereas phenol formed by diffusion of phenoxyl radical from the solvent cage. In general, for parallel reactions the product isomer ratio depends on the rate constants of competitive reactions and the reaction conditions (viz. temperature, polarity, pH, solvent) [35,36]. In photochemical reactions viscosity of solvent plays a prominent role in deciding the isomer ratio by affecting the translational or rotational rearrangement [37]. Also, the polar solvent favours rearrangement and non-polar solvent favours phenol formation. For example, for tert-butanol, iso-propanol, ethanol and methanol as solvents the viscosity decreases from 3.35 m Pa s to 0.56 m Pa s, and with decreasing viscosity the isomer ratio also decreases from 1.66 to 0.85 [38,39]. Thus, using solvents with higher viscosity will always tend to support the formation of ortho-isomer. In order to explore the effect of radiation time, intensity and solvent, a few controlled experiments were carried out in batch mode. Reaction in methanol and ethylene glycol results in the ortho- to para-isomers ratio (o-/p-, 1a/1b) between 1.29 to 2.2 and 6.3, respectively, which correlates well with the viscosity of the solvents, the observations are shown in Table 1 (Fig. S3-S7) and Table 3.

At a fixed concentration of the substrate  $(2 \text{ mg mL}^{-1})$  the effect of

Table 1

Effect of distance from the light source and radiation time on conversion a	ind
selectivity of isomers in batch mode (Solvent used: Methanol).	

Experimental details			Observations			
Conc. of Phenyl benzoate (mg/ mL)	Distance from lamp (mm)	Time (h)	Temp. in the quartz test tube (°C)	% Conversion (-)	o-/p-	
2	200	1	29	40	1.6	
2	200	2	30	60	1.4	
2	200	3	30	77	1.3	
2	20	1	43	92	2.2	

distance from the light source was found to be significant. For example, at a distance of 20 mm and 200 mm from the light source, the % conversion decreased from 92% to 40% in 1 h, while the corresponding isomer ratio (o-/p-) decreased from 2.2 to 1.6, respectively (Fig. 2). The cage escape product, phenol was not observed under the present experimental conditions. This reduction in the isomer ratio as well as conversion even after longer exposure to UV light was an effect of the local temperature. This indicates the lower conversion can be attributed to the lower intensity of light; the variation in the isomer ratio was due to the orientation of substitution which depends on the local temperature for these parallel reactions. In general, an increase in temperature increases the rate of a chemical reaction. In the set of these two parallel reactions, the overall rate constant  $[k = k_0 e^{-(E/RT)}]$  for the reaction favouring o-substitution is higher than that of p-substitution. This observation is evident from the isomer ratio. Thus, even if the activation energy for these two parallel reactions might be similar, increase in temperature will always favor the faster reaction, which is osubstitution. It is observed from these experiments that, after an exposure for 1 h the isomer ratio decreased with increasing distance from the light source, which supports the effect of temperature [40]. Since the variation in the isomer ratio at complete conversion of the substrate was not significantly different, the total volume of substrate can have effect on the time needed for complete conversion and the corresponding isomer ratio. Such semi-batch mode experiments were performed and are reported in the Supporting Information (SI-3). Such experiments indicated that the % conversion is independent of the substrate volume however the temperature inside the vial varies in time due to continuous addition of one of the reactant and thus can show different reaction completion times.

At a fixed distance from the light source (200 mm), it was observed



Fig. 2. The time history of the effect of distance from the light source on the variation in the conversion and the product isomer ratio at an initial substrate concentration of  $2 \text{ mg mL}^{-1}$  (a) 200 mm and (b) 20 mm from the light source.

that while conversion continues to increase with time, the isomer ratio o-/p- decreased from 1.57 to 1.29. The temperature inside the vial was observed to vary slightly in time. However, the product has higher UV absorbance than the substrate, it is possible that due to reduction in the photon density available at a given wavelength required for the desired reaction to take place, the reaction favouring o-isomer would slow down. In this situation, the isomer ratio o-/p- would continue to decrease with time. In view of this, further experiments were carried out in continuous flow manner using a helical quartz tube (having circular cross-section) kept around a UV light source. The continuous flow mode would help achieve consistency in reaction performance due to differential exposure to the light [41]. Moreover the secondary flow (Dean flow) generated in the helical coil does not allow the velocity profile to remain axisymmetric and lowers the extent of dispersion [42], which is a desirable situation.

Several experiments were carried out by changing the flow rates so that the effect of residence time on reaction progress can be studied. The product distribution upon photolysis of the substrates in two different solvent are shown in Fig. 3. The result indicates that the rates of photo-Fries rearrangement reaction of phenyl benzoate in batch and continuous flow mode are markedly and can be seen from the reaction time or residence time in these two modes [43]. The conversion was higher in flow mode as compared to the batch reaction. As a bench mark study, initially batch mode experiment was repeated with ethylene glycol as the solvent. In a quartz test-tube placed at 20 mm from the UV lamp (having same as radius of the quartz coil used for continuous flow experiments), with methanol as the solvent, complete conversion was obtained in 40 min while in the flow reactor (quartz coil), it was achieved in 5 min (Fig. 3a). Also, the isomer ratio for the

continuous mode remained almost constant (1.68–1.73) for all the residence times investigated. Since the isomer ratio is also an effect of the rate at which the movement of functional groups (or radial pairs) happens in this case, the rate of this movement can be modified by using solvents of different viscosities.

It was observed that with methanol as solvent, the o-/p- ratio obtained from batch and flow reactor (17.6 mL min<sup>-1</sup>) did not change noticeably implying that the molecular level changes did not vary much depending upon the mode of operation. In ethylene glycol as solvent, the selectivity for o-isomer was more as compared to methanol (Fig. S7-S10). The physical properties of both the solvents are given in Table 2. The complete conversion of the substrate was found to occur 12 times faster in quartz coil with ethylene glycol as solvent as compared to a batch. Solvents with higher viscosity were found to restrict 1,5-shift of radical pair, which reduces the selectivity of p-isomer. However higher viscosity also reduces the intensity of photo penetration in the reaction mass and thus needs longer reaction time to achieve 100% conversion.

In order to study the effect of flow rate to the *o-/p*- ratio of the products, experiments were carried out with  $3.2 \text{ mL min}^{-1}$  (0.0075 m/s),  $6.4 \text{ mL min}^{-1}$  (0.0151 m/s) and  $17.6 \text{ mL min}^{-1}$  (0.0415 m/s) flow rates in methanol and ethylene glycol, independently as solvents (Table 3). At lower flow rates, the reaction was seen to be faster due to relatively longer exposure of light. In case of methanol as solvent, there was no change in *o-/p*- product ratio with increase in residence time; however the reaction rate was higher. With ethylene glycol, *o-/p*-isomer ratio was relatively higher which decreased with increasing flow rate (less residence time). There was significant improvement in the *o-/p*- ratio (by 8 folds) with ethylene glycol as the solvent when compared to methanol. The changes in the *o-/p*- product ratio with respect to



Fig. 3. Relative differences in the conversion and isomer ratio from batch and continuous flow (flow rate of  $17.6 \text{ mL min}^{-1}$ ) photochemical reaction in specific solvents: (a) Methanol (MeOH) (b) Ethylene glycol (EG).

#### Table 2

Comparison between solvent system and product distribution.

Solvent	Viscosity (Pa s)	Method	Time (min)	Conversion (%)	o-/p-
Methanol	$5.9  imes 10^{-4}$	Batch Continuous	40 5	92 100	2.2 1.68
Ethylene glycol	$1.6  imes 10^{-2}$	Batch Continuous	180 10	100 100	6.28 2.72

## Table 3

Effect of velocity in the helical coil on the isomer yield and isomer ratio in presence of ethylene glycol and methanol as solvents. In all the runs the conversion at the outlet was 100%.

Superficial velocity	Methanol		Ethylene glycol	
(m/s)	Residence time (min)	o-/p-	Residence time (min)	o-/p-
0.0075	11.13	1.51	42.6	12.4
0.0415	5	1.68	10	2.72

Table 4

Reaction in ethylene glycol and glycerol mixture.

Method	Solvent Ethylene glycol : glycerol	Viscosity (Pa.s)	Residence time (min)	Conversion (%)	o-/p-
Batch	4:1	0.236	180	88.9	4.4
Continuous	4:1	0.236	5.2	100	8.45
Continuous	1.5:1	0.481	6.6	100	8.14

residence time indicated that the geminate radical pair thus formed was in tight solvent cage. At longer residence time radical pairs showed lower mobility resulting in the formation of more *o*-isomer and hence higher *o*-*/p*- isomer ratio [Table 3, Fig. S11-S12, S8 (For MeOH), and S13-S14, S10 (For ethylene glycol)]. It is recommended to have higher flow rates as it helps achieve thinner boundary layer near the tube wall thereby helping better photon penetration, however higher conversion needs longer residence time. These two effects can be brought into effect either by having longer tube or by recirculating the reaction mass through the tube, making it almost like a vigorously stirred batch reactor having very high shear rate.

The effect of viscosity was further investigated by using mixture of ethylene glycol and glycerol mixtures as solvents (Table 4, Fig. S15-S17). The addition of 20% and 40% of glycerol to ethylene glycol increased the viscosity of reaction media by 2 times, which enhanced the reaction rate by 22% with less than 3.6% variation in the isomer ratio. The reaction under consideration is a fast geminate reaction in the solvent cage that provides the o-isomer. In general the high o-/p- ratio of rearranged products can be obtained by (i) confinement of geminate radical pair thus formed by laminar or turbulent flow which is not the case as the width of the flow reactor (in mm) is really huge compared to that of the dimensions of present the molecular system in a solvent cage (few nm) or (ii) by changing the change viscosity, as viscous medium restricts the motion of radical pair to form more o- isomer, which can be realized by the possibility of presence of gradient of viscous regions in the flow reactor in the given solvent system which is responsible for the observation of such high o-/p- ratio of products. We feel that the variation in the shear rate of the reaction media in the vicinity of the tube wall make a difference by causing difference in the motion of radical pair. A lot more data over a wide range of viscosity would help to get better insights on such systems and it will be studied separately.

#### 4. Conclusion

We have studied the reactivity of the singlet radical pair in Photo-Fries rearrangement of phenyl benzoate in continuous flow synthesis by using solvents of different viscosities and shear rates. The observations from batch mode experiments indicated that the local rise in temperature in the reaction media due to longer exposure to radiation changes the reaction rates over the time and also the viscosity of media, together affects the isomer ratio. In the semi-batch mode of experiments, the % conversion is independent of the substrate volume and the % conversion can be controlled by prolonged addition of the substrate by controlling the temperature. In continuous flow, there is a significant reduction in reaction time. The  $o_{-}/p_{-}$  isomer ratio can be increased by using a solvent of higher viscosity as well as confined domain. Ethylene glycol as solvent yields high ortho-regioselectivity as compared to methanol. We have observed significant changes in the *o*-/*p*- product ratio with respect to residence time. The work is being extended for variety of other systems involving radical pairs.

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## Appendix A. Supplementary data

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