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E–*Z* isomerization of 3-benzylidene-indolin-2-ones using a microfluidic photo-reactor†

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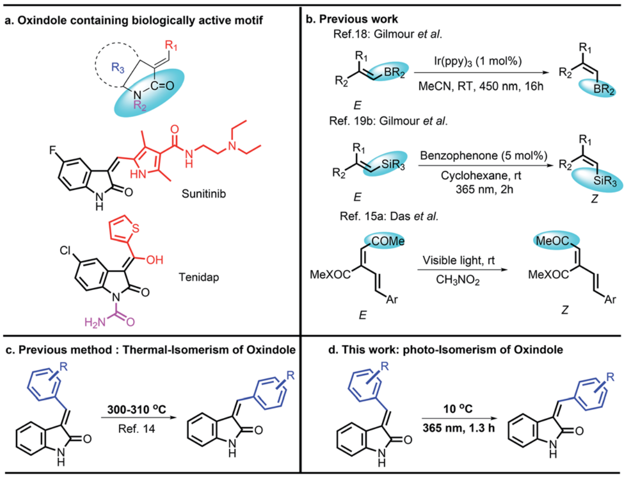
Here, we report controlled *E*–*Z* isomeric motion of the functionalized 3-benzylidene-indolin-2-ones under various solvents, temperature, light sources, and most importantly effective enhancement of light irradiance in microfluidic photoreactor conditions. Stabilization of the *E*–*Z* isomeric motion is failed in batch process, which might be due to the exponential decay of light intensity, variable irradiation, low mixing, low heat exchange, low photon flux *etc.* This photo-μ-flow light driven motion is further extended to the establishment of a photostationary state under solar light irradiation.

Functionalized 3-benzylidene-indolin-2-ones are an important structural motif in organic chemistry and are embedded in many naturally occurring compounds.[1] They found wide applications in molecular-motors,[2] energy harvesting dyes,[3] pharmaceutical chemistry (sunitinib, tenidap),[4] protein kinase inhibitors,[5] pesticides,[6] flavors,[7] and the fragrance industry.[8] In the last few decades, numerous protocols have been developed for the synthesis of novel indolin-2-ones. For instance, palladium (Pd)-catalysed intramolecular hydroarylation of *N*-aryl-propiolamides,[9] Knoevenagel condensation of oxindole and aldehyde,[10] two-step protocols such as Ni-catalyzed CO_2 insertion followed by coupling reaction,[11] Pd-catalysed C–H functionalization/intramolecular alkenylation,[12] Pd(0)/monophosphine-promoted ring–forming reaction of 2-(alkynyl)aryl isocyanates with organoboron compound, and others.[13]

Knoevenagel condensation is one of the best methods for the preparation of 3-benzylidene-indolin-2-ones, but often it gives mixture of *E*/*Z* isomeric products. Otherwise, noble metal-catalysed protocols received enormous interest. However, the limited availability, high price, and toxicity of these metals diminished their usage in industrial applications. Therefore, several research groups have been engaged in search of an alternative greener and cleaner approach under metal-free conditions. To address the diastereoisomeric issue, Tacconi *et al.* reported a thermal (300–310 °C) isomerization reaction of 3-arylidene-1,3-dihydroindol-2-ones,[14] which suffers from poor reaction efficiency and *E*/*Z* selectivity. Therefore, transformations controlling *E*/*Z* ratio of 3-benzylidene-indolin-2-ones remains a challenging task and highly desirable (Scheme 1).

On the other hand, selective *E*/*Z* stereo-isomerization of alkenes has been well established using various methods in the presence of light stimuli,[15a] cations,[15b] halogens or elemental selenium,[16] palladium-hydride catalyst,[10] cobalt-catalyst,[17] Ir-catalyst,[18] organo-catalysts.[19] Among these, light-induced photostationary *E*/*Z* stereoisomerization is very attractive, due to its close proximity towards the natural process. In recent years, several light-driven molecular motors (controlled motion at the molecular level), molecular propellers,[20] switches,[21] brakes,[22] turnstiles,[23] shuttles,[24] scissors,[25] elevators,[26] rotating modules,[27] muscles,[28] rotors,[29] ratchets,[30] and catalytic self-propelled objects have been developed.[31] Further, equipment's relying on molecular mechanics were rapidly developed, particularly in the area of health care.



Scheme 1 Functionalized 3-benzylidene-indolin-2-ones and alkenes in bioactive compounds and the accessible methods.

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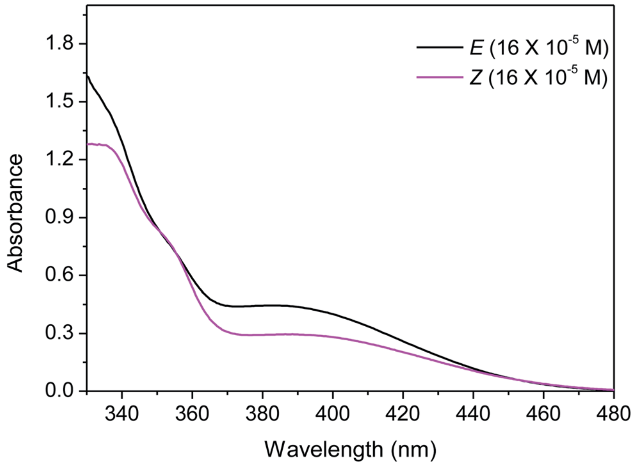


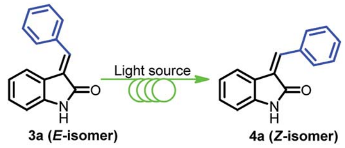
Fig. 1 UV-Vis spectroscopy of the (*E*)-3-benzylideneindolin-2-one (**3a**) and (*Z*)-3-benzylideneindolin-2-one (**4a**) in DMF solvent.

Till date, controlled photo-isomerization of functionalized 3-benzylidene-indolin-2-ones is one of the puzzling problems to the scientific community. Photochemical reactions in batch process have serious drawbacks with limited hot-spot zone due to inefficient light penetration with increasing light path distance through the absorbing media, and the situation becomes poorer when the reactor size increases.[32,33] In contrast, the capillary microreactor platform has emerged as an efficient the artificial tool with impressive advantages, such as excellent photon flux, uniform irradiation, compatibility with multi-step syntheses, excellent mass and heat transfer, which lead to significant decrease the reaction time with improved yield or selectivity over batch reactors.[33a,34] To address the aforementioned challenges, it is essential to develop a highly efficient photo-microchemical flow approach for the controlled isomerization of functionalized 3-benzylidene-indolin-2-ones in catalyst-free and an environment friendly manner.

Results and discussion

The required substrate, (*E*)-3-benzylideneindolin-2-one (**3a**), was synthesised following the literature Knoevenagel condensation procedure (details in ESI†).[14] As most of the *E* to *Z* isomerization of alkenes are contra-thermodynamic in nature, to appropriateness for the photostationary state, electromagnetic radiation, irradiance time, temperature, solvent, and aptness of reactor needs to be optimized. Accordingly, we were interested to find the suitable electromagnetic radiation which can interact with the starting materials. In this regard, the UV-Visible absorption spectrum of the **3a** in DMF is tested, which showed absorption peak close to output spectrum of the medium pressure Hg lamp (Fig. 1). It suggests that the medium pressure Hg lamp is suitable for the photo-chemical reaction. Next, the residence time in photo-flow condition is optimized, using a solution of **3a** (0.25 M) in DMF solvent and infuse into a homemade photo-flow reactor through the leak-proof syringes to the synthesis of (*Z*)-3-benzylideneindolin-2-one **4a** (Table 1, entry 1). The solution **3a**, passing through a commercially available high purity perfluoroalkoxy (PFA) tubing (inner

Table 1 Preliminary study for a photo-flow isomerization of oxyindole under a standard light condition[a]



Entry	Flow rate (μL min^{-1})	Residence time (min)	Temp. (°C)	Yield[e] (%) 4a (*Z*-isomer)	Yield[e] (%) 3a (*E*-isomer)
1	100	15.7	30	12	88
2	200	7.8	30	7	93
3	50	31.4	30	18	82
4	20	78.5	30	44	56
5	10	157	30	44	56
6	20	78.5	20	56	44
7	**20**	**78.5**	**10**	**76 (71)**[f]	**24 (19)**[f]
8	10	157	10	76	24
9[b]	20	78.5	10	18	82
10[c]	NA	960	10	NA	100
11[d]	100	78.5	10	76	24

[a] Reaction conditions: **3a**: 0.25 M in dimethylformamide (DMF) solvent, reactor volume 1.57 mL (PFA tubing id 1000 μm and 2 meter length), light source medium pressure 250 W Hg lamp. [b] Reaction conditions: Light source blue LED (4 W, light out-put 465 nm; 10 lux per cm^2, brand name Lizone). [c] Reaction conditions: Batch process. [d] Reaction conditions: Reactor volume 7.85 mL. [e] Reaction conditions: Yields are based on the LC-MS. [f] Isolated yield in parenthesis.

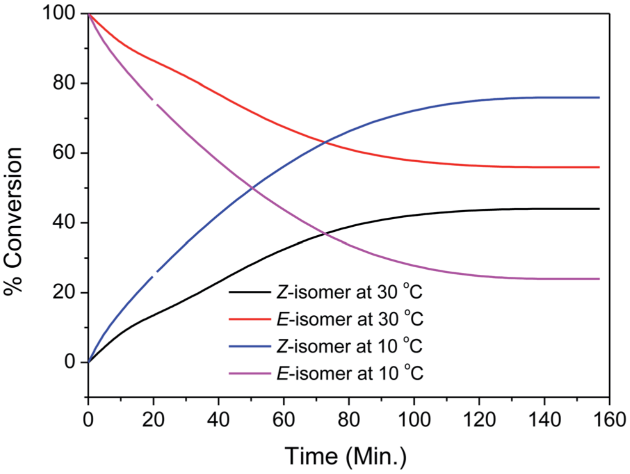


Fig. 2 Time profile. Reaction condition: **3a**: 0.25 M in DMF, reactor volume 1.57 mL (PFA tubing) light source medium pressure 250 W Hg lamp; conversions are based on LC-MS analysis.

diameter (id) = 1000 μm, length = 2 meter, volume = 1.57 mL) held at 30 °C was irradiated with 250 W medium pressure UV lamp at a 100 μL min^{-1} flow rate (irradiation time = 15.7 min) which typically leads to the formation of the brownish colour solution having 12% (yield) of the **4a** product (Table 1, entry 1). Next, the reactions at various temperatures and residence times were carried out to find the optimal condition, with an improved yield of **4a** (Table 1, entries 2 to 6). To our delight, **4a** was obtained in 76% yield at 10 °C with 20 μL min^{-1} flow rate in DMF solvent along with **3a** (24%), separable by column chromatography (Table 1, entry 7, Fig. S2†). Moreover, the increment of the residence time 78.5 to 157 min failed to increase the yield of **4a** (Table 1, entry 8, Fig. 2) by providing the energy-efficient photo-flow system. Further, when the medium pressure 250 W Hg lamp was replaced with blue LED 4 W, the desired product **4a** formed only in 18% yield (Table 1, entry 9). The reaction in batch process under the flow-optimized stock solution condition failed to produce any desired product **4a** (Table 1, entry 10), which may be due to the exponential decay of light intensity in bulk solution, low light irradiation, low mixing, low heat exchange and low photon flux.[35]

In order to improve the photo-flow reaction efficiency, we next investigated the effect of solvents (Table S1†) and found that both. DMF and DMA as good solvents to provide a decent yield in the isomerization at 10 °C in 1.3 h, while hexane failed to stabilize the photo stationary state. Having the optimized controlled-photostationary state in hand on milligram scale, we next moved toward the process intensification reactor in gram scale. The scale-up synthesis of **4a** was examined using 7.85 mL volume reactor by the extension ((inner diameter (id) = 1000 μm, length = 10 meter) of PFA tubing (Table 1, entry 11). The long tubing reactors were irradiated with a medium pressure lamp to maintain the adequate light intensity, and the solution of **3a** was passed to the reactor with a flow rate of 100 μL min^{-1}, although maintaining 10 °C to produce **4a** in 76% yield, resulting in *ca.* 6.0 g d^{-1} productivity (see ESI Video S1†).

Having the preliminary optimized photo-flow process system for the isomerization reaction of 3-benzylideneindolin-2-one (**3a**), we turned our attention towards integrating one-flow process to reduce the laborious extraction and the work-up to get **4a** from the DMF solution, as depicted in Fig. 3.[33a,36] Due to high boiling point of the solvent, DMF (153 °C), it is difficult to evaporate to obtain the product using rotary evaporator. Thus, we switched to extract the product with low boiling solvent, (dichloromethane (DCM)/diethyl ether (DEE)/and industrial favourable *t*-butyl methyl ether (MTBE)), to favourably isolate the product as a separable mixture of **4a** and **3a.** It is well-known phenomenon that DMF (hydrophilic solvent) prefers to move into aqueous-phase and is partially miscible with DCM (relatively hydrophobic solvent). As a result, water (flow rate = 1.25 mL min^{-1}) and extracting solvent DCM (flow rate = 1.25 mL min^{-1}) were infused into an X-junction to the DMF mixture that flowed from the exit of the photo-reactor to form the aqueous-organic droplet in the PTFE capillary to accomplish the extraction of isomer **4a** into the DCM droplet within 0.2 min residence time (see ESI Video S1†). Next, to separate the aqueous organic droplet, we were adapted our previously designed and commercialized continuous flow liquid–liquid micro-separator.[37] Notably, the completion of the DCM–water separation obtained in 0.1 min of the residence time. Notably, additional sodium sulphate or magnesium sulphate is not needed to dry the product.

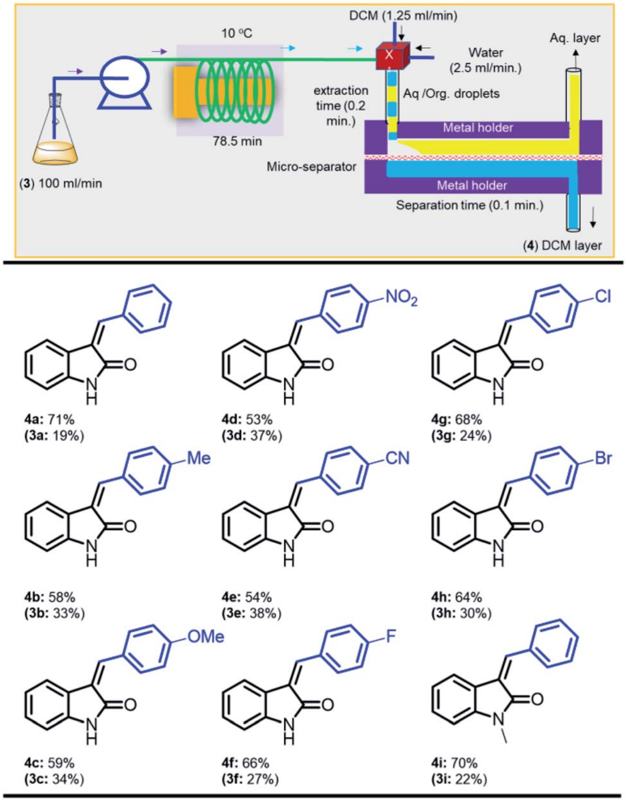


Fig. 3 Reaction condition: **3a**: 0.25 M in DMF, reactor volume 7.8 mL (PFA tubing id 1000 μm and 10 meter length) light source medium pressure 250 W Hg lamp; yields are based on isolated *Z*-isomer and parenthesis yield based on isolated *E*-isomer.

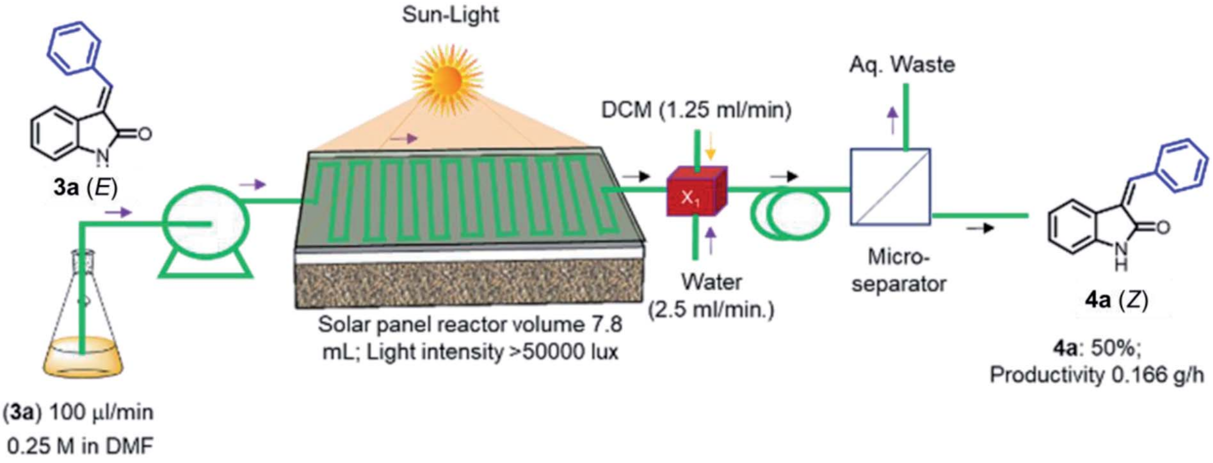


Fig. 4 Isomerization under the solar irradiation. Reactor volume 7.8 mL (PFA tubing id 1000 µm and 10 meter length) light source sunlight; yield is based on isolated yields.

After the successful development of an integrated system for the photostationary state for the conversion of 3-benzylideneindolin-2-one (**3a**) to **4a**, we next examined the scope and limitations of the continuous flow system as well as the effect of the directing group. Toward this, a few electron-releasing and electron-withdrawing 3-benzylideneindolin-2-one derivatives were prepared using substituted aldehydes. Notably, the methyl (**3b**), methoxy (**3c**), nitro (**3d**), cyano (**3e**), fluoro (**3f**), chloro (**3g**), bromo (**3h**) substituted 3-benzylideneindolin-2-ones underwent photostationary state to afford the corresponding *Z*-isomer derivatives **4b** to **4h**, in good yield (53–71%).

Having explored the photostationary state for *E*–*Z* isomerization under fixed wavelength, as an artificial light source, temperature, and solvent conditions, we became interested to develop the photostationary state under the sunlight irradiation (to save the power and present domain application).[33a] The homemade cylindrical shape capillary reactor is suitable only for the laboratory-controlled condition. Hence, a novel arrangement of capillary microreactor needed for highly efficient solar light harvesting, which is unprecedented. The newly designed solar panel microreactor (details fabrication is provided in ESI, Fig. S3†) was placed on roof-top to expose to daylight (the average amount of solar emission 5.25 kW h per m^2per day in Hyderabad, India, manually controlled light intensity > 50 000 lux) to verify the photostationary state of **3a**.[38] As shown in Fig. 4, the solution of **3a** in DMF (0.25 M) infused into the solar panel PFA capillary microreactor with a syringe pump. It was observed that the optimal conversion to **4a** was 50% (isolated yield) in the presence of sunlight. Though the isomerization is low, the overall strategy minimized the laborious extraction and separation process with 0.166 g h^{-1} productivity.

In summary, the photostationary state for *E* to *Z* isomerization of functionalised 3-benzylideneindolin-2-one has been accomplished under controlling of solvent, temperature, and enhanced irradiation in microfluidic condition. This is a first integrated photostationary state system operated under controlled condition as well mixture of light (solar irradiance) condition to form the desired functionalised (*Z*)-3-benzylideneindolin-2-ones. This integrated platform can be useful to those syntheses where the photostationary state for *E*–*Z* isomerization involves in drug discovery, natural products, biology, energy, and environmental chemistry. Genuine-time reaction control for photostationary state for *E*–*Z* isomerization under unstable irradiance (cloudy or rainy days) work is under progress in our laboratory.

Conflicts of interest

The authors declare no competing financial interest.

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