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

Chada Raji Reddy, a,b Veeramalla Ganeshab and Ajay K. Singh a,*

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 photo-reactor 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-arylpiprolidamines,9 Knoevenagel condensation of oxindole and aldehyde,10 two-step protocols such as Ni-catalyzed CO2 insertion followed by coupling reaction,11 Pd-catalysed C–H functionalization/intramolecular alkenylation,12 Pd(0)/monophosphine-promoted ring–forming reaction of 2-(alkylaryl)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-aryliden-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,17 cobalt-catalyst,18 Ir-catalyst,19 organo-catalysts.20 Among these, light-induced photostationary E/Z stereo-isomerization 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.2 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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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.\textsuperscript{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.\textsuperscript{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, (\textit{E})-3-benzylideneindolin-2-one (3a), was synthesised following the literature Knoevenagel condensation procedure (details in ESI\textsuperscript{†}).\textsuperscript{14} As most of the \textit{E} to \textit{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 (\textit{Z})-3-benzylideneindolin-2-one 4a (Table 1, entry 1). The solution 3a, passing through a commercially available high purity perfluoroalkoxy (PFA) tubing (inner

![Fig. 1 UV-Vis spectroscopy of the (\textit{E})-3-benzylideneindolin-2-one (3a) and (\textit{Z})-3-benzylideneindolin-2-one (4a) in DMF solvent.](image)

Table 1: Preliminary study for a photo-flow isomerization of oxyindole under a standard light condition\textsuperscript{a}

| Entry | Flow rate (\textmu L min\textsuperscript{-1}) | Residence time (min) | Temp. (°C) | 4a (\textit{Z}-isomer) | 3a (\textit{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)\textsuperscript{f} | 24 (19)\textsuperscript{f} |
| 8     | 10                                       | 157                  | 10         | 76                     | 24                     |
| 9a    | 20                                       | 78.5                 | 10         | 18                     | 82                     |
| 10f   | NA                                       | 960                  | 10         | NA                     | 100                    |
| 11g   | 100                                      | 78.5                 | 10         | 76                     | 24                     |

\textsuperscript{a} Reaction conditions: 3a: 0.25 M in dimethylformamide (DMF) solvent, reactor volume 1.57 mL (PFA tubing id 1000 \textmu m and 2 meter length), light source medium pressure 250 W Hg lamp. \textsuperscript{b} Reaction conditions: Light source blue LED (4 W, light out-put 465 nm; 10 lux per cm\textsuperscript{2}, brand name Lizone). \textsuperscript{c} Reaction conditions: Batch process. \textsuperscript{d} Reaction conditions: Reactor volume 7.85 mL. \textsuperscript{e} Reaction conditions: Yields are based on the LC-MS. \textsuperscript{f} Isolated yield in parenthesis.
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.\textsuperscript{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\textsuperscript{-1}) and extracting solvent DCM (flow rate = 1.25 mL min\textsuperscript{-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 previously designed and commercialized continuous flow liquid–liquid micro-separator.\textsuperscript{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.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Fig.3.png}
\caption{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.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Fig.2.png}
\caption{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.}
\end{figure}

\begin{table}
\centering
\begin{tabular}{|c|c|c|}
\hline
Solvent & Reaction condition & Yield \%
\hline
DMF & 10°C, 1.25 mL min\textsuperscript{-1} & 76
\hline
Hexane & 10°C, 1.25 mL min\textsuperscript{-1} & 0
\hline
\end{tabular}
\caption{Yield of 4a under various reaction conditions.}
\end{table}

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\textsuperscript{-1}, although maintaining 10 °C to produce 4a in 76% yield, resulting in ca. 6.0 g d\textsuperscript{-1} productivity (see ESI Video S1†).
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), and 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). 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 rooftop to expose to daylight (the average amount of solar emission 5.25 kW h per m² per day in Hyderabad, India, manually controlled light intensity > 50 000 lux) to verify the photostationary state of 3a. 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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References
1 X. Ma, X. Xie, L. Liu, R. Xia, T. Li and H. Wang, Chem. Commun., 2018, 54, 1595–1598.
2 D. Roke, M. Sen, W. Danowski, S. J. Wezenberg and B. L. Feringa, J. Am. Chem. Soc., 2019, 141, 7622–7627.
3 Y. S. Tingare, M.-T. Shen, C. Su, S.-Y. Ho, S.-H. Tsai, B.-R. Chen and W.-R. Li, Org. Lett., 2013, 15, 4292–4295.
4 A. Millemaggi and R. J. K. Taylor, Eur. J. Org. Chem., 2010, 2010, 4527–4547.
5 F. A. Al-Obeidi and K. S. Lam, Oncogene, 2000, 19, 5690–5701.
6 L.-S. Huang, D.-Y. Han and D.-Z. Xu, Adv. Synth. Catal., 2019, 361, 4016–4021.
7. J. Xu, L.-D. Shao, D. Li, X. Deng, Y.-C. Liu, Q.-S. Zhao and C. Xia, *J. Am. Chem. Soc.*, 2014, 136, 17962–17965.
8. M. Zhu, C. Zheng, X. Zhang and S.-L. You, *J. Am. Chem. Soc.*, 2019, 141, 2636–2644.
9. T.-S. Jiang, R.-Y. Tang, X.-G. Zhang, X.-H. Li and J.-H. Li, *J. Org. Chem.*, 2009, 74, 8834–8837.
10. W. Zhang and M.-L. Go, *Bioorg. Med. Chem.*, 2009, 17, 2077–2090.
11. B. Miao, Y. Zheng, P. Wu, S. Li and S. Ma, *Adv. Synth. Catal.*, 2017, 359, 1691–1707.
12. S. Ueda, T. Okada and H. Nagasawa, *Chem. Commun.*, 2010, 46, 2462–2464.
13. T. Miura, T. Toyoshima, Y. Takahashi and M. Murakami, *Org. Lett.*, 2008, 10, 4887–4889.
14. A. C. Coda, A. G. Invernizzi, P. P. Righetti, G. Tacconi and G. Gatti, *J. Chem. Soc., Perkin Trans. 2*, 1984, 615–619.
15. (a) S. R. Chowdhury, S. Mondal, D. K. Maiti, S. Mishra and I. Das, *Org. Lett.*, 2019, 21, 1578–1582; (b) R. Dorel, C. Miro, Y. Wei, S. J. Wezenberg and B. L. Feringa, *Org. Lett.*, 2018, 20, 3715–3718.
16. S. Ortgies and A. Breder, *ACS Catal.*, 2017, 7, 5828–5840.
17. (a) H. Liu, M. Xu, C. Cai, J. Chen, Y. Gu and Y. Xia, *Org. Lett.*, 2020, 22, 1193–1198; (b) Q.-Y. Meng, T. E. Schirmer, K. Katou and B. König, *Angew. Chem., Int. Ed.*, 2019, 58, 5723–5728.
18. J. J. Molloy, J. B. Metternich, C. G. Daniliuc, A. J. B. Watson and R. Gilmour, *Angew. Chem., Int. Ed.*, 2018, 57, 3168–3172.
19. (a) K. Livingstone, M. Tenberge, F. Pape, C. G. Daniliuc, C. Jamieson and R. Gilmour, *Org. Lett.*, 2019, 21, 9677–9680; (b) S. I. Faßbender, J. J. Molloy, C. Mück-Lichtenfeld and R. Gilmour, *Angew. Chem., Int. Ed.*, 2019, 58, 18619–18626.
20. N. L. Mutter, J. Volarić, W. Szymanski, B. L. Feringa and G. Maglia, *J. Am. Chem. Soc.*, 2019, 141, 14356–14363.
21. M. Suda, Y. Thathong, V. Promarak, H. Kojima, M. Nakamura, T. Shiraogawa, M. Ebara and H. M. Yamamoto, *Nat. Nanotechnol.*, 2019, 10, 2455.
22. R. Portman, *Nat. Nanotechnol.*, 2008, DOI: 10.1038/nnano.2008.177.
23. M. K. J. ter Wiel, R. A. van Delden, A. Meetsma and B. L. Feringa, *J. Am. Chem. Soc.*, 2003, 125, 15076–15086.
24. T. van Leeuwen, A. S. Lubbe, P. Stacko, S. J. Wezenberg and B. L. Feringa, *Nat. Rev. Chem.*, 2017, 1, 0096.
25. M. Zaremba and V. Siksny, *Proc. Natl. Acad. Sci.*, 2010, 107, 1259–1260.
26. S. Silvi, M. Venturi and A. Credi, *Chem. Commun.*, 2011, 47, 2483–2489.
27. M. Guentner, M. Schildhauer, S. Thumser, P. Mayer, D. Stephenson, P. J. Mayer and H. Dube, *Nat. Commun.*, 2015, 6, 8406.
28. (a) Y. Liu, A. H. Flood, P. A. Bonvallet, S. A. Vignon, B. H. Northrop, H.-R. Tseng, J. O. Jeppesen, T. J. Huang, B. Brough, M. Baller, S. Magonov, S. D. Solares, W. A. Goddard, C.-M. Ho and J. F. Stoddart, *J. Am. Chem. Soc.*, 2005, 127, 9745–9759; (b) L. Greb and J.-M. Lehn, *J. Am. Chem. Soc.*, 2014, 136, 13114–13117.
29. N. Kourmura, R. W. J. Zijlstra, R. A. van Delden, N. Harada and B. L. Feringa, *Nature*, 1999, 401, 152–155.
30. B. Lau, O. Kedem, J. Schwabacher, D. Kwasnieski and E. A. Weiss, *Mater. Horiz.*, 2017, 4, 310–318.
31. B. L. Feringa, *Adv. Mater.*, 2020, 32, 1906416.
32. S. Protti and M. Fagnoni, *Photochem. Photobiol. Sci.*, 2009, 8, 1499–1516.
33. (a) S. Kumar, D. Aand, S. Pabbaraja, D.-P. Kim and A. K. Singh, *ACS Sustainable Chem. Eng.*, 2019, 7, 19605–19611; (b) X.-J. Wei, W. Boon, V. Hessel and T. Noël, *ACS Catal.*, 2017, 7, 7136–7140.
34. (a) D. Cambié, C. Bottecchia, N. J. W. Straathof, V. Hessel and T. Noël, *Chem. Rev.*, 2016, 116, 10276–10341; (b) D. Aand, B. Mahajan, S. Pabbaraja and A. K. Singh, *React. Chem. Eng.*, 2019, 4, 812–817; (c) J. Mateos, A. Cherubini-Celli, T. Caroffiglio, M. Bonchio, N. Marino, X. Company and L. Dell’Amico, *Chem. Commun.*, 2018, 54, 6820–6823.
35. M. B. Plutschack, B. Pieber, K. Gilmore and P. H. Seeberger, *Chem. Rev.*, 2017, 117, 11796–11893.
36. D. Aand, S. Karekar, B. Mahajan, A. B. Pawar and A. K. Singh, *Green Chem.*, 2018, 20, 4584–4590.
37. Micro-separator available with Amar Equipment, http://www.amarequip.com/docs/Flow-chemistry-catalog.pdf.
38. *Hyderabad solar irradiation intensity*, http://www.synergenviorn.com/tools/solar-irradiance/india/telangana/Hyderabad, accessed, Nov 27, 2018.