Research on Chemical Intermediates
https://doi.org/10.1007/s11164-021-04530-7

Concentrated solar radiation-assisted one-pot/multicomponent synthesis of pyranopyrazole derivatives under neat condition

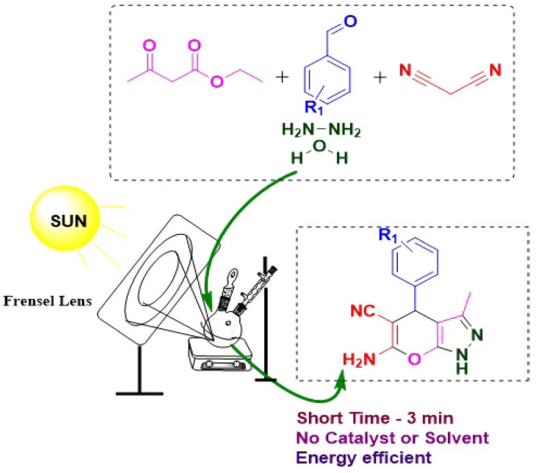
Yatin U. Gadkari[1] · Navnath T. Hatvate[2] · Vikas N. Telvekar[1]

Received: 11 May 2021 / Accepted: 28 June 2021

Abstract

Concentrated solar radiation (CSR)-assisted synthesis of pyranopyrazole derivatives under solvent and catalyst-free condition has been reported in the present protocol. One-pot multicomponent synthesis from aromatic/heteroaldehyde, ethyl acetoacetate, malononitrile, and hydrazine hydrate leads to the final desired compounds in a good yield. This operationally simple methodology has several advantages such as green and clean reaction profile, simple workup and purification procedures, extremely short reaction time, atom efficiency, and being economical. The current energy-efficient method saves almost 98% of energy as compared to the conventional method.

Graphical abstract



Keywords Multicomponent reaction · Solar radiation · Pyranopyrazole · Energy efficient · Eco-scale · E-factor

Extended author information available on the last page of the article

Published online: 10 July 2021

Introduction

Currently, green chemistry has emerged as a vibrant tool in the field of medicinal, combinatorial, and organic chemistry owing to the use of environmentally benign reagent and safe green conditions. Considering the well-known hazards of organic solvents and poor recovery of catalyst impelled scientist to develop a green industrial viable process which not only follows green chemistry principles but also achieves a high yield of product in shorter duration [1–8]. For this, various methodologies have been developed so far that involve the use of microwave irradiation, ultrasonication, mechanochemistry, UV irradiation, etc. [9, 10]. But the need for skilled labors and special costly equipment is a serious concern for scale-up study and sustainability. Thus the development of a clean green viable approach is still in demand.

Nitrogen-containing heterocycles have a wide presence in naturally occurring and biologically active compounds. They act as important precursors for the synthesis of currently used pharmaceutical active molecules [11]. In particular, pyranopyrazole derivatives have gained much attention in recent years due to their medicinal and agrochemical significance. Some biologically active pyranopyrazoles are given in Fig. 1 [12]. They represent privileged scaffold having an interesting pharmacological profile such as analgesic, anti-inflammatory, fungicidal, anti-tumor, bactericidal, vasodilatory, insecticidal, molluscicidal, anticancer agents, and also act as a potent inhibitor of human Chk1 kinase [13–18].

In recent years, multicomponent reactions (MCRs) have become a powerful tool in combinatorial chemistry as they can synthesize complex and diverse compounds rapidly from assembling three or more reactants in one pot with high efficacy and atom economy. MCRs have many advantages such as simplified workup, short reaction times, energy-efficient, minimization of waste, easy purification, wide substrate scope tolerance, versatility, and eco-friendliness [19, 20].

Recent studies revealed a favorable approach for the synthesis of dihydropyrano[2,3-*c*]pyrazoles involving a multicomponent reaction between aldehydes, ethyl acetoacetate, hydrazine hydrate, and malononitrile. This transformation was carried out using different methods such as ultrasonication, microwave irradiation, or use of a different catalyst such as CTACl, piperazine, piperidine, N-methyl morpholine, L-proline, heteropolyacids, alumina, sodium benzoate, amberlyst, per-6-amino cyclodextrin, imidazole, and glycine [21–33].

Although various methodologies are reported in the literature, many of them are having limitations and shortcoming which includes the use of toxic chemicals, higher

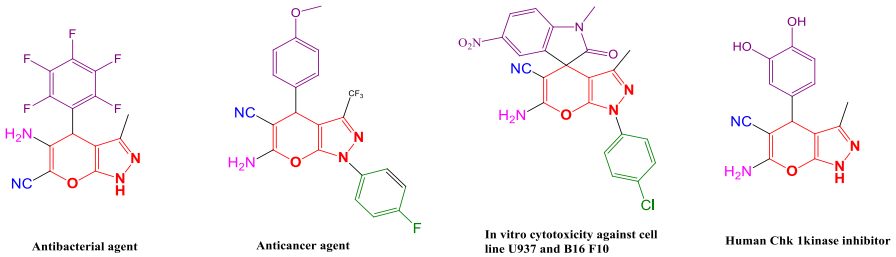


Fig. 1 Examples of biologically important pyranopyrazole derivatives

reaction temperature, longer duration, expensive reagents, less yield, etc., with due consideration, thus designing a new protocol for the synthesis of dihydropyrano[2,3-*c*]pyrazoles derivatives is still in demand.

The use of a renewable source of energy i.e. solar radiations in catalyzing chemical reactions has received much attention from researchers as it is a safe, reliable, green, widely available, and cost-free approach. The presence of a large number of UV and IR radiations in sunlight is responsible for photochemical and thermal reactions [34, 35]. Previously CSR has been used to carry out various organic transformations such as N-acylation and N-formylation reactions in an aqueous medium, synthesis of DES and N-Phenyl phthalimide, Hantzsch synthesis of dihydropyridines, oxidation of alcohol, and benzylic bromination. [36–40]. Earlier, we used concentrated solar radiation in the synthesis of 3, 4-dihydropyrimidin-2(1H)-ones/thiones and isoxazole-5(4H)-one [41]. Due to our current interest in the synthesis of heterocyclic compounds [42–44], in this report, we are extending the use of concentrated solar radiation (CSR) in the synthesis of pyranopyrazole derivatives under solvent and catalyst-free conditions.

Experimental

All the chemicals and solvents used were purchased from commercial sources Sigma-Aldrich, Avra**,** SD Fine chemical, and Spectrochem companies and were used without further purification. The purity determination of the starting materials and reaction monitoring was accomplished by thin-layer chromatography (TLC) on Merck silica gel G F_{254} plates. All target compounds were characterized by their ^{1}H, ^{13}C NMR and Mass spectra. ^{1}H and ^{13}C NMR spectra were obtained on a 400-MR NMR Spectrometer from Agilent Technologies using tetramethylsilane (TMS) as an internal standard and DMSO-d_6 as a solvent. Mass spectra were recorded on a direct insertion probe on Agilent Technologies 5975 series. Melting points of all the compounds were recorded by the AnalabThermoCal melting point apparatus in the open capillary tube. The intensity of solar radiation was measured with the help of a Pyranometer (Dynalab Tech. Ltd., India), i.e., solar radiation flux density (W/m2). The reaction was carried out from 12.30 to 1.00 pm which is a peak solar intensity time. It also measures solar irradiation over a view of 180°.

Concentrated solar radiation (CSR) assembly

Synthesis of dihydropyrano[2,3-*c*]pyrazoles was carried out by CSR, and the setup is shown in Fig. 2 [45]. Assembly had Fresnel lens with a dimension of 30 cm (*X*-axis): 30 cm (*Y*-axis). The lens was fixed on a stand using a clamp in such a way that its focal point should fall on the central portion of RBF and also, its refraction could cover the complete volume of RBF. The reaction flask was fixed to another stand using another clamp and a mechanical stirrer was used for stirring. Sunlight was focused through the Fresnel lens directly on the reaction mixture in a reaction flask. This setup could be rotated in 180° as per the moving

Fig. 2 Actual image of the CSR assembly for synthesis of dihydropyrano[2,3-*c*]pyrazoles

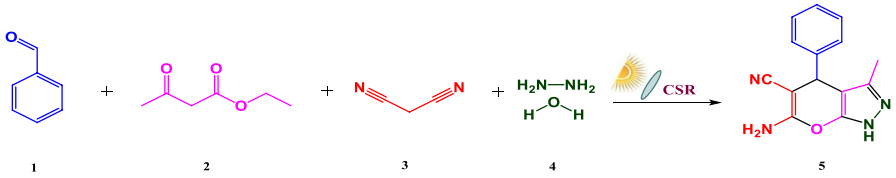
position of the sun to achieve maximum solar efficiency. A thermometer gun was used to measure the temperature of the reaction mixture and it was 90–100 °C. The atmospheric temperature at the same time was found to be 30 °C.

General procedure for the synthesis of pyranopyrazole derivatives

A mixture of aldehyde (10 mmol), ethyl acetoacetate (10 mmol), malononitrile (10 mmol), and hydrazine hydrate (10 mmol) was taken in a round-bottom flask (Scheme 1). RBF was kept under the concentrated solar radiation (CSR) setup with continuous stirring on a magnetic stirrer. After 3–4 min, the precipitate was observed. The progress of the reaction was monitored by TLC. The precipitated product was recrystallized from hot ethanol to afford pure pyranopyrazole derivatives.

Results and discussion

As a preliminary test, hydrazine hydrate, ethyl acetoacetate, benzaldehyde, and malononitrile were taken in the round-bottom flask and stirred in water under CSR for 10 min, the reaction led to 82% of the desired product. The reaction was



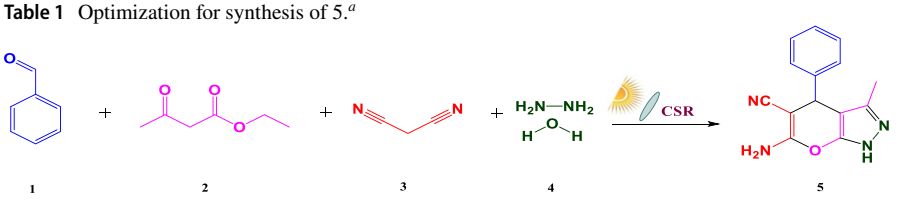
Scheme 1 One-pot multicomponent synthesis of pyranopyrazole using concentrated solar radiation (CSR)

optimized using different solvents as shown in Table 1. Very less yield was obtained in acetonitrile and dimethylformamide, whereas solvents like ethanol, toluene, and the tetrahydrofuran reaction proceed with a product yield of 52, 68, and 40%, respectively. As all reactants are liquid and taking advantage of this, we stirred the mixture of all reactants without any solvent under CSR and remarkably, the desired product was formed immediately and the reaction was completed within 3 min with 98% yield. Further, the recrystallization from ethanol leads to a spectroscopically pure product.

Optimized reaction conditions were applied on a wide variety of substrates, and results are incorporated in Table 2. It is observed that various substituent on the benzaldehyde had no significant effect on the outcome of the reaction (Table 2, entries 5–13). Polar (Table 2, entries 8, 10, 11) and halide (Table 2, entries 6, 12, 13) substitution was tolerated by these reaction conditions. Bulkier aldehyde such as the naphthaldehyde (Table 2, entries 14) has no issue in reactivity. Heterocyclic aldehydes (Table 2, entries 15, 16) gave the final product without compromising on yield.

According to the literature [46, 47], the formation of pyranopyrazole is a three-step process, the first step is believed to be the formation of 5-methyl-2,4-dihydro-pyrazol-3-one **17**, and the second one is the condensation of an aldehyde with malononitrile **18**, while in the third step, both Intermediates **17** and **18** are condensed to form the final product **5**. To know, which step requires solar radiation, we carried several control experiments (Scheme 2), and we found that every step which is in Scheme 2 required CSR because they did not give any significant conversion at room temperature or conventional heating at 90–100 °C. Solar radiation contains UV–Visible radiation and infra-red radiation as well. The photocatalytic property of UV radiations and very rapid vibrational movements of bonds (IR irradiation) leads to rapid collision of reactants which ultimately

Table 1 Optimization for synthesis of 5.[a]

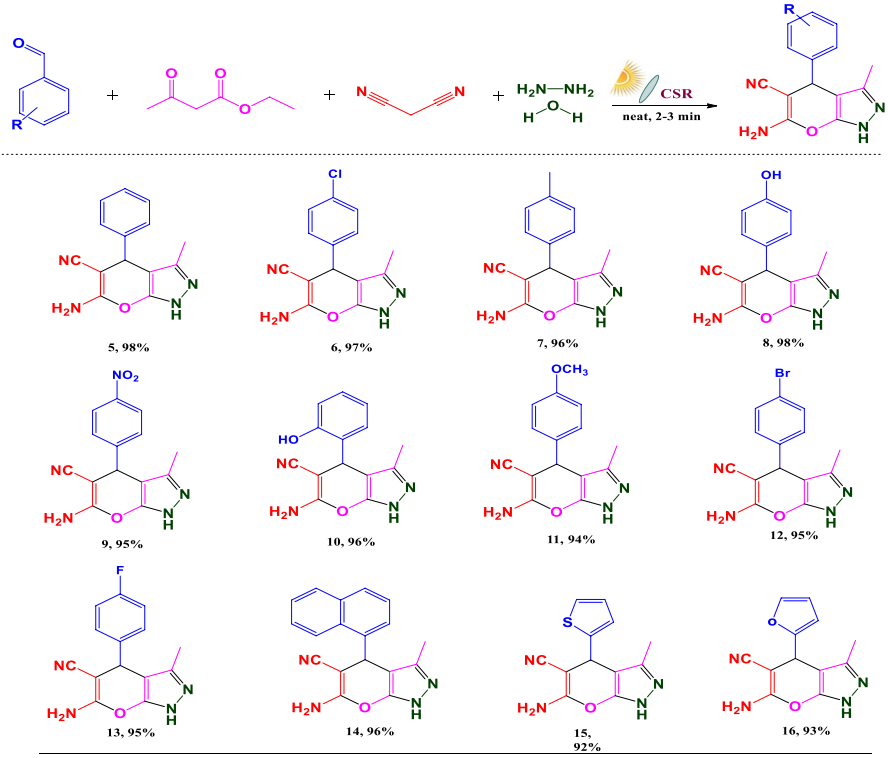


1 2 3 4 5

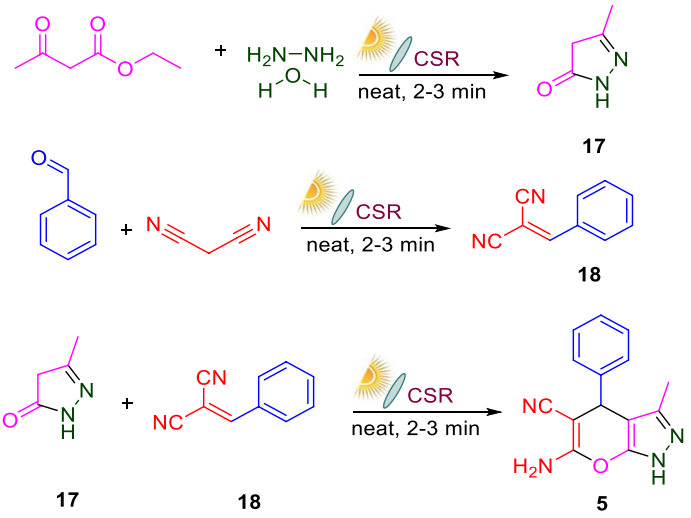
Entry	Solvents	Yield of **5**(%)[b]
1	Water	82
2	Acetonitrile	30
3	DMF	24
4	Ethanol	52
5	Toluene	68
6	THF	40
7	None	98

[a]Reaction conditions: 10 mmol of **1**, 10 mmol of **2**, 10 mmol of **3**, 10 mmol of **4** were stirred under CSR in mentioned solvents. [b]Isolated yield

Table 2 Substrate scope for pyranopyrazole derivatives [a,b]



[a]Reaction conditions: 10 mmol of **1**, 10 mmol of **2**, 10 mmol of **3**, 10 mmol of **4** were stirred using CSR under solvent-free conditions. [b]Isolated yield



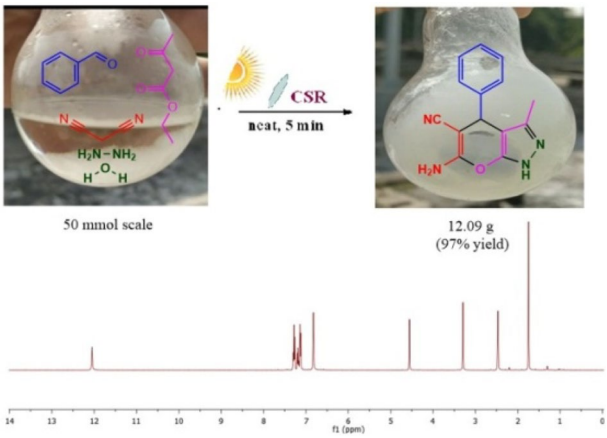
Scheme 2 Control experiments on intermediates

boosts chemical transformation in a very short time. The synergistic effect of UV and IR radiation could be the probable reason for the enhancement of the chemical reaction rate. [42–44]

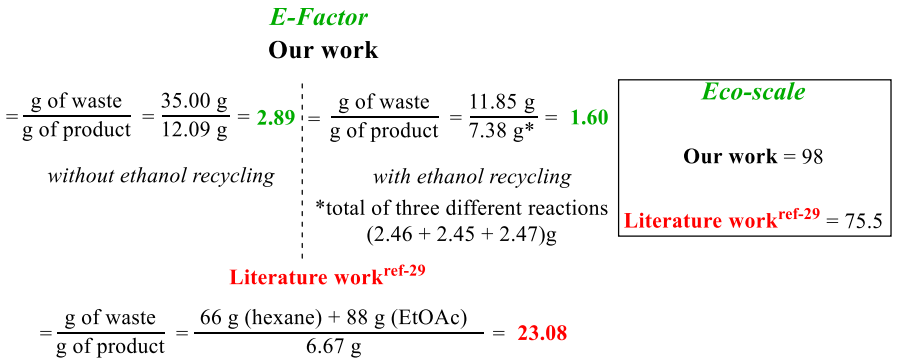
By considering the interest of the pharmaceutical industries, we carried out the scale-up study of the above compound and as expected reaction underwent smoothly without sacrificing the outcome. Thus, the above reactions were scaled up at 50 mmol under CSR and were completed in *ca.* 5 min. Further recrystallization of the crude product with ethanol gave a spectroscopically pure product (Scheme 3).

Eco-scale and E-Factor calculation

To access the environmentally benign nature of this process, we determined E-factor and Eco-scale value and reported herewith. For the calculation of the E-factor, we adopted two methods based on ethanol used for recrystallization and compared it with the literature [48]. For current work, E-factors without ethanol recycling is 2.89, and with ethanol recycling, it found to be 1.60 respectively (Scheme 4). For the synthesis of pharmaceuticals and fine chemicals, we should know that this value is at least an order of magnitude lower than Sheldon E-Factor [49, 50]. However; this waste (ethanol) is biodegradable. Similarly, for the literature work, a high E-factor (23.08) was calculated. An Eco-scale value [51] for current and literature work was found to be 98 and 75.5, respectively. Thus it clearly shows the greener nature of the current method than the literature one. (See ESI).



Scheme 3 On top: scale up of reaction and at the bottom: NMR spectra of filtered product



Scheme 4 Eco-scale and E-Factor calculations

Efficiency of energy consumption

The energy required for the synthesis of pyranopyrazoles is the total energy consumed (kJ) per unit of the pyranopyrazoles obtained (*g*). The time required for the synthesis of pyranopyrazoles was 6 h for the conventional method [52] while 3 min for the CSR technique. As per earlier records [36–40], energy required to synthesize pyranopyrazole per gram is calculated and found to be 35.17 (kJ)/g while using CSR, only 0.68 (kJ)/g was required (Table 3). Thus, the current CSR protocol is highly energy efficient which saves almost 98% of energy than a conventional method and reduces reaction time as well (98%).

To understand the significance of the current approach, the results obtained using the CSR technique is compared with various catalysts already reported in the literature [24, 52–59] for the synthesis of pyranopyrazoles. As can be seen from Table 3, CSR-assisted synthesis of pyranopyrazoles derivatives under solvent and the catalyst-free condition is more efficient than any other catalyst in terms of shorter reaction time, higher yield, better energy efficiency, greener, and environmentally friendlier conditions suitable for industrial applications.

Conclusion

A highly efficient, sustainable and environmentally benign approach for the synthesis of pyranopyrazole derivatives via concentrated solar radiation was successfully developed. Extremely fast conversion using renewable energy source under solvent and catalyst-free condition make this protocol attractive to a green chemist. Multigram scale up to 50 mmol denotes its pharmaceutical significance. Further key features include simple experimental setup, broad substrate tolerance, high yield, economical, easy workup procedures, etc.

Table 3 The comparison of CSR with other reported catalyst in the literature for the synthesis of pyranopyrazole derivatives [a]

Entry	Catalyst	Solvent	Time (min)	Reaction conditions	Yield (%)[b]	References
1	Aluminium oxide	Water	35–90	100° C	80	[24]
2	Triphenyl phosphine	Water	60	reflux	82	[53]
3	Cetyldimethyl benzyl ammonium chloride	Ethanol	45	reflux	73	[54]
4	Morpholine	Ethanol–Water	540	reflux	83	[55]
5	Triethylamine	None	360	reflux	82	[52]
6	Lipase from Aspergillus niger	Ethanol	60	30° C	90	[56]
7	Tetraethylammonium bromide;	Water	15	reflux	90	[57]
8	n-octyltriphenylphosphonium bromide	Water	90	reflux	90	[58]
9	Nano-Al_2O_3/BF_3/ Fe_3O_4	Ethanol–Water	25	reflux	90	[59]
10	None	None	3	CSR	98	This work

[a]Reaction conditions: 10 mmol of benzaldehyde, 10 mmol of ethyl acetoacetate, 10 mmol of malononitrile, 10 mmol of hydrazine hydrate using different catalyst in mentioned solvents. [b]Isolated yield

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11164-021-04530-7.

Acknowledgements YUG acknowledges COEPI, TEQIP–III for financial support.

References

1. I.T. Horvath, P.T. Anastas, Chem. Rev. **107**, 2169 (2007)
2. S. Ganasen, V. Velaichamy, Int. J. Sustain. Dev. **9**, 11 (2016)
3. C.J. Li, P.T. Anastas, Chem. Soc. Rev. **4**, 1413 (2012)
4. M. Thirugnanasambandam, S. Iniyan, R. Goic, Renew. Sust. Energ. Rev. **14**, 312 (2010)
5. J.H. Clark, Green Chem. **1**, 1 (1999)
6. S. Caddick, Tetrahedron **51**, 10403 (1995)
7. G. Cravotto, P. Cintas, Soc. Rev. **35**, 180 (2006)
8. S.L. James, T. Friscic, Chem. Soc. Rev. **42**, 7494 (2013)
9. M.N.F. Abd Malek, N.M. Hussin, N.H. Embong, P. Bhuyar, M.H.A. Rahim, N. Govindan, G.P. Maniam, Biomass Convers. 1–11(2020)
10. Q.Q. Zhou, Y.Q. Zou, L.Q. Lu, W.J. Xiao, Angew. Chem. Int. Ed. **58**, 1586 (2019)
11. M.M. Heravi, V. Zadsirjan, RSC Adv. **10**, 44247 (2020)
12. B.P. Tripathi, A. Mishra, P. Rai, Y.K. Pandey, M. Srivastava, S. Yadav, J. Singh, New J. Chem. **41**, 11148 (2017)
13. M. Koohshari, M. Dabiri, P. Salehi, RSC Adv. **4**, 10669 (2014)
14. F.M. Abdelrazek, P. Metz, N.H. Metwally, S.F. El-Mahrouky, Arch. Pharm. **339**, 456 (2006)
15. M.R. Nadia, Y.K. Nahed, A. Fahmy, A.A.F. El-Sayeda, Der Pharma Chem. **2**, 400 (2010)
16. S.C. Kuo, L.J. Huang, H. Nakamura, J. Med. Chem. **27**, 539 (1984)
17. N. Foloppe, L.M. Fisher, R. Howes, A. Potter, A.G. Robertson, A.E. Surgenor, Bioorg. Med. Chem. **14**, 4792 (2006)
18. V.Y. Sosnovskikh, M. Barabanov, B. Usachev, R. Irgashev, V. Moshkin, Rus. Chem. Bull. **54**, 2846 (2005)
19. E. Ruijter, R. Scheffelaar, R.V. Orru, Angew. Chem. Int. Ed. **50**(28), 6234 (2011)
20. B. Ganem, Acc. Chem. Res. **42**(3), 463 (2009)
21. M.B. Reddy, V.P. Jayashankara, M.A. Pasha, Synth. Commun. **40**, 2930 (2010)
22. D. Shi, J. Mou, Q. Zhuang, L. Niu, N. Wu, X. Wang, Synth. Commun. **34**, 4557 (2004)
23. H. Mecadon, M.R. Rohman, I. Kharbangar, B.M. Laloo, I. Kharkongor, M. Rajbangshi, B. Myrboh, Tetrahedron Lett. **52**, 3228 (2011)
24. H. Mecadon, M.R. Rohman, M. Rajbangshi, B. Myrboh, Tetrahedron Lett. **52**, 2523 (2011)
25. K. Kanagaraj, K. Pitchumani, Tetrahedron Lett. **51**, 3312 (2010)
26. A.M. Zonouz, I. Eskandari, H.R. Khavasi, Tetrahedron Lett. **53**, 5519 (2012)
27. M. Bihani, P.P. Bora, G. Bez, H. Askari, ACS Sustainable Chem. Eng. **1**, 440 (2013)
28. A. Siddekha, A. Nizama, M.A. Pasha, Spectrochimi. Acta. **81**, 431 (2011)
29. R.H. Vekariya, K.D. Patel, H.D. Patel, Res. Chem. Intermed. **42**, 7559 (2016)
30. A. Javid, A. Khojastehnezhad, H. Eshghi, F. Moeinpour, J. Ebrahimi. Org. Prep. Proced. Int. **48**, 377 (2016)
31. A.R. Moosavi-Zare, M.A. Zolfigol, E. Noroozizadeh, M. Tavasoli, V. Khakyzadeh, A. Zare, New J. Chem. **37**, 4089 (2013)
32. S. Ambethkar, V. Padmini, N. Bhuvanesh, J. Adv. Res. **6**, 975 (2015)
33. K.K. Gangu, S. Maddila, S.N. Maddila, S.B. Jonnalagadda, RSC Adv. **7**, 423 (2017)
34. L.H. Kligman, Arch. Dermatol. Res. **272**, 229 (1982)
35. M.Y. Akhalaya, G.V. Maksimov, A.B. Rubin, J. Lademann, M.E. Darvin, Ageing Res. Rev. **16**, 1 (2014)
36. S. Deshpande, B. Gadilohar, Y. Shinde, D. Pinjari, A. Pandit, G. Shankarling, Sol. Energy. **113**, 332 (2015)
37. T. Rüther, A.M. Bond, W.R. Jackson, Green Chem. **5**, 364 (2003)
38. P. Ghorpade, B. Gadilohar, D. Pinjari, Y. Shinde, G. Shankarling, Sol. Energy. **122**, 1354 (2015)
39. J.O. Rathi, G.S. Shankarling, Sol. Energy. **189**, 471 (2019)

40. Y.U. Gadkari, N.T. Hatvate, V.N. Telvekar, Sustain Chem Pharm. **21**, 100444 (2021)
41. Y.U. Gadkari, N.L. Jadhav, N.T. Hatvate, V.N. Telvekar, Chem. Select. **5**, 12320 (2020)
42. N.T. Hatvate, S.M. Ghodse, V.N. Telvekar, Synth. Commun. **49**(24), 3553 (2019)
43. N.T. Hatvate, S.M. Ghodse, V.N. Telvekar, Synth. Commun **48**(3), 285 (2018)
44. Y.U. Gadkari, R.D. Shanbhag, V.N. Telvekar, Lett. Org. Chem. **18**, 1 (2021)
45. Y.U. Gadkari, N.T. Hatvate, B.S. Takale, V.N. Telvekar, New J. Chem. **44**, 8167 (2020)
46. M.A. Zolfigol, M. Tavasoli, A.R. Moosavi-Zare, P. Moosavi, H.G. Kruger, M. Shiri, V. Khakyzadeh, RSC Adv. **3**, 25681 (2013)
47. P. Shrivas, R. Pandey, S. Zodape, A. Wankhade, U. Pratap, Res. Chem. Intermed. **46**, 2805 (2020)
48. A.S. Nagarajan, B.S. Reddy, Synlett **12**, 2002 (2009)
49. R.A. Sheldon, Green Chem. **19**, 18 (2017)
50. Q.W. Gui, X. He, W. Wang, H. Zhou, Y. Dong, N. Wang, J.X. Tang, Z. Cao, W.M. He, Green Chem. **22**, 118 (2020)
51. K. VanAken, L. Strekowski, L. Patiny, Beilstein J. Org. Chem. **2**, 3 (2006)
52. H.M. Al-Matar, K.D. Khalil, A.Y. Adam, M.H. Elnagdi, Molecules **15**, 6619 (2010)
53. I. Amine Khodja, A. Fisli, O. Lebhour, R. Boulcina, B. Boumoud, A. Debache, Lett. Org. Chem. 13(2), 85–91 (2016)
54. K. Ablajan, W. Liju, A. Tuoheti, Y. Kelimu, Lett. Org. Chem. **9**(9), 639 (2012)
55. C.F. Zhou, J.J. Li, W.K. Su, Chin. Chem. Lett. **27**(11), 1686 (2016)
56. P.P. Bora, M. Bihani, G. Bez, J. Mol. Catal. B Enzym. **92**, 24 (2013)
57. G.S. Kumar, C. Kurumurthy, B. Veeraswamy, P.S. Rao, B. Narsaiah, Org. Prep. Proced. Int. **45**(5), 429 (2013)
58. F. Boukezzoula, T. Boumoud, B. Boumoud, A. Debache, Lett. Org. Chem. **12**(10), 734 (2015)
59. E. Babaei, B.B.F. Mirjalili, Inorg. Nano-Met. Chem. **50**(1), 16 (2020)

Authors and Affiliations

Yatin U. Gadkari[1] · Navnath T. Hatvate[2] · Vikas N. Telvekar[1]

✉ Vikas N. Telvekar
vn.telvekar@ictmumbai.edu

[1] Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology, Mumbai 400 019, India

[2] Institute of Chemical Technology, Marathwada Campus, Jalna 431213, India