COMMUNICATION

A C G publications

Org. Commun. XX:X (20XX) X-XX

organic communications

Efficient one-pot cascade synthesis of pyrazolopyridazine in PEG-400

Ranjit A. Gayake,[1] Vasant B. Jagrut[2] and Vivek T. Humne[3*]

[1]Department of Chemistry, Late Nitin Arts and Science College, Pathri, India
[2]Department of Chemistry, Swami Vivekanand Senior College, Mantha, India
[3]Department of Chemistry, Shri R. R. Lahoti Science College, Morshi, India

(Received April 03; Revised September 01, 2022; Accepted September 05, 2022)

Abstract: A one-pot cascade synthesis of pyrazolopyridazine from 4-(bromo(aryl)methyl)-3-chloropyridazines in PEG-400, in an ecofriendly solvent system has been developed. A series of pyrazolopyridazines (**2a-i**) were synthesized by using bidentate electron-donor ligand in good yield (60-85%). The present cascade protocol included nucleophilic substitution, ring closer and oxidative aromatization in single precedential step.

Keywords: Pyrazolopyridazine; heterocyclic compound; cascade; PEG-400.

1. Introduction

The integration of discrete reactions in a one-pot is well illustrated by the cascade method, which allows a direct synthesis of complex molecules from the simple substrate in a highly efficient manner. The cascade reaction has been proven to be more efficient than linear synthesis because it provides superior atom economy with resulting reduce of waste.[1-3] Nowadays, many research group synthesized natural and non-natural products using cascade protocol because it possess many disadvantages such as straightforward one-vessel portfolio, consumption of steps, saving of reagents and high yield.[4-7] The various complex molecules are constructed using different transition metals such as palladium, cobalt, gold, rhodium, iron and aluminium.[8-13] However, enzyme-promoted cascade transformations have been extensively used to perform oxidation of compounds such as catechols, hydroquinones, and various aromatic amines.[14] These methods have several disadvantages such as harsh conditions, toxicity, use of stoichiometric proportion, loading of catalyst and isolation of appropriate enzyme. Therefore, development of efficient, ecofriendly and straightforward protocol for the cascade synthesis is exceedingly desirable.

2. Background

In order to continue our search for better synthetic methodologies for biologically important heterocycles, we chose pyrazolo[3,4-*c*]pyridazine as target. The pyrazolopyridazine is a class of well-

---

[*] Corresponding author: E-Mail: vivekhumne2013@gmail.com

The article was published by ACG Publications
http://www.acgpubs.org/journal/organic-communications © Month-Month 2022 EISSN:1307-6175
DOI: http://doi.org/10.25135/acg.oc.135.2204.2408

known fused ring of the heterocycles possess wide-range biological activities such as analgesic, antimicrobial, anti-inflammatory and antifungal activity.[15-16] Especially, pyrazolo[3,4-*c*]pyridazine is identified as an active inhibition of glycogen synthase kinase (GSK-3) and CDK2/cyclin A.[17] To the best of our knowledge, only one synthetic approach is reported for pyrazolo[3,4-c]pyridazine.[18] In this process, they have synthesized pyrazolo[3,4-*c*]pyridazine as a ERK inhibitor FR180204 in gram scale level in four steps.

Since, polyethylene glycol (PEG) is well known ecofriendly solvent medium in chemical synthesis. Several recent reviews covers the PEG chemistry and their applications in biotechnology and medicine.[19-21] In a last few decades, PEG has been used common in organic synthesis as a solvent due to its high soluble capability of substrate and thermal stability. As a part of our continuing research to develop the new methods for heterocyclic compounds,[22-25] herein we expose the first report of substituted new pyrazolopyridazine in PEG-400 by cascade approach. In the present study, nucleophilic substitution, ring closure and aromatization carried out in a single procedural step in good yield.

3. Experimental

3.1. Chemical Material and Apparatus

All the chemicals and solvents were purchased from Sigma Aldrich and Spectrochem. Analytical thin-layer chromatography (TLC) was performed using Merck Kieselgel 60 F254 precoated plates (0.25 mm) with visualized under UV light (254 and 365 nm) or using iodine staining. Column chromatography was performed on silica gel 60 (100-200 mesh). The NMR experiments were performed with 300 MHz spectrometer, and chemical shifts are expressed in ppm (δ) with TMS as an internal reference. *J* values are given in Hz. The ^{1}H and ^{13}C NMR spectrum are referenced to the residual solvent signals (7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C in $CDCl_3$, 2.50 ppm for ^{1}H and 39.9 ppm for ^{13}C in DMSO-d_6). IR spectra were recorded by using KBr pellets or neat. The product was visualized by UV light (254 nm), PMA and DNP strain in TLC. Commercially available reagents and solvents were obtained and used without further purification. The melting points were calculated with open capillary tubes and are uncorrected.

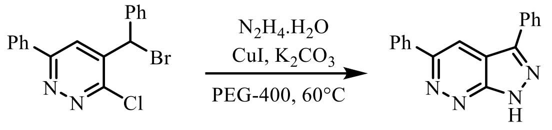
*3.2. General Procedure for the Synthesis of Pyrazolopyridazine (**2**)*

A mixture of substrate **1** (0.55 mmol), potassium carbonate (0.825 mmol) and copper iodide (0.05 mmol) in PEG-400 was stirred at room temperature for 30 min. The reaction mixture was placed in preheated oil bath at 60ºC. Hydrazine hydrate (1.1 mmol) was added as a portion to the reaction mixture. The progress of the reaction was monitored by TLC. The reaction mixture was poured in ice cold water followed by a few drops of acetic acid. The mixture was extracted by ethyl acetate (3 x 20 mL) then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography using n-hexane/EtOAc as the eluent. The PEG-aqueous solution was concentrated under reduced pressure until all of the water was removed, and the recovered PEG was collected and employed in a cascade reaction as a recycled solvent for a new reaction.

4. Present Study

First, we designed from 4-(bromo(aryl)methyl)-3-chloropyridazines as substrates to study for the cascade protocol. We started our strategy from substrates **1a** which was conveniently prepared by the stirring of substituted pyridazinones with phosphorus oxychloride followed by bromination at benzyl-position. The model reaction was studied with substrate **1a**. On this context, first, the treatment of hydrazine hydrate with **1a** at 120 °C in dimethyl formamide (DMF), did not give a significant change. Surprisingly, adding of sodium carbonate (Na_2CO_3) and copper iodide (CuI) to the reaction mixture gave the desired product **2a** in moderate yield. In order to check efficacy of cascade reaction, various bases and salts were studied. However, Na_2CO_3, K_2CO_3, Cs_2CO_3 afforded a good yield while disappointing result was observed for KOH (table 1). Methanol, 1,4-dioxane, tetrahydrofuran, dimethyl sulphoxide and ethylene glycol were investigated for the optimal reaction medium as different solvents. Amongst these solvents, moderate yield (48%) was observed in ethylene glycol for 12 h. Encouraged by our previous report for the development of new method of selective o-deallylation by using a catalytic amount of iodine in PEG-400,[26-28] we thought PEG-400 could be effective for cascade reaction. On replacing of ethylene glycol by PEG-400, surprisingly, the reaction time and temperature was assayed to be shorter with better yields. Based on these results, we establish PEG-400 is a prefect solvent for cascade synthesis of pyrazolopyridazine (Table1).

Table 1. Optimization conditions of the applied method



1a **2a**

Entry	Base/Salt	Time (h)	Yield 2 (%)[a]
a	Na_2CO_3/ CuI	9.0	68
c	$CsCO_3$/ CuI	8.5	69
d	KOH/ CuI	10.0	NR[b]
e	K_2CO_3/KI	5.0	64
f	K_2CO_3/NaI	5.5	70
g	K_2CO_3/CuI	5.0	82

[a]Isolated yield
[b]No Reaction

To understand the role of PEG-400, we performed cascade synthesis of **2a** in various glycols such as triethylene glycol, PEG-600, PEG-4000, PEG-6000 and PEG-8000. The low yield (28%) was obtained with triethylene glycol. However, the viscosity of PEG increases as molecular weight increases. Therefore, temperature of the solvent may be increased to 100 °C for liquefaction of PEG. Whilemean, other PEGs have found nearly identical findings.

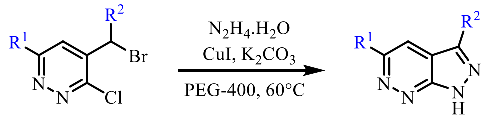
Table 2. Recycling of PEG-400 on cascade synthesis of 3,5-diaryl-1H- pyrazolo[3,4-*c*] pyridazine **1a** with hydrazine hydrate in presence of potassium carbonate at 60°C

Run	**1**	**2**	**3**	**4**	**5**
Yield[a]	89	89	85	83	81

[a]All reactions were carried out with 1 mmol of substrate **1a**

To check the generality of new method and versatility of cascade approach in PEG-400, we sought to extend this methodology to various motifs of substituted pyridazines (Table 3). Gratifying, all the products were obtained in good yield. Remarkably, electron-donating group required longer reaction time and electron-withdrawing aryl functionality at benzyl-position required shorter time for completion of reaction (Table 3, entry f). Aryl functionality containing chloro and methoxy group at benzyl-position albeit good yield while reaction time did not alter (Table 3). However, electron-donating groups required longer reaction time and desired product was isolated in good yield (Table 3 entry g). Under the optimal condition, combination of copper iodide and potassium carbonates were found to be befitting reagents for cascade synthesis of pyrazolopyridazine. To assess the reusability of the solvent, the reaction of compound **1a** was subjected to hydrazine hydrate, copper iodide and potassium carbonate in the presence PEG-400 (10mL) was heated at 60 °C for 6h. After the reaction was completed, it was cooled to room temperature before adding the ice-cold water gently to the reaction mixture. The precipitate was separated and the crude product was purified using column chromatography to get pure target product **2b**. Water was distilled off after the product was isolated, and PEG-400 was washed with diethyl ether (2 mL). The recovered PEG-400 was successfully utilized in five consecutive runs without considerable loss of efficiency of PEG-400 Table 2).

Table 3. Cascade synthesis of pyrazolo[3,4-c]pyridazine in PEG-400[a]

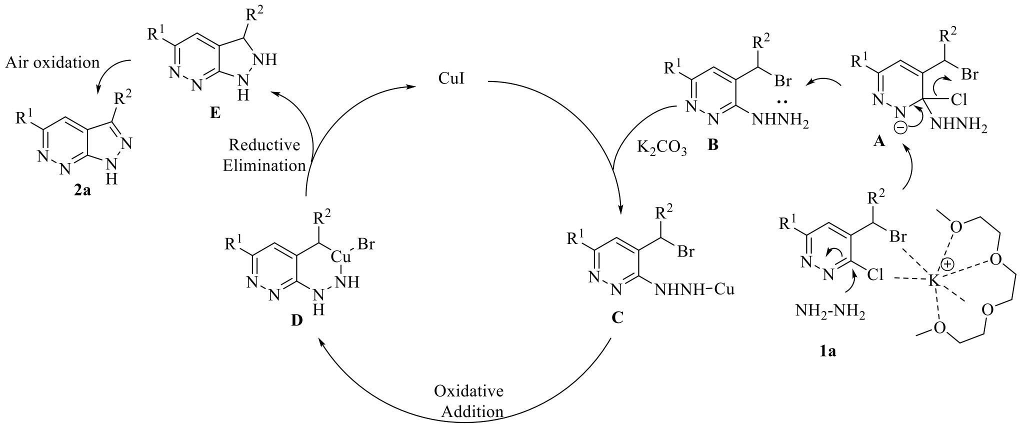


1(a-i) 2(a-i)

Entry	R^1	R^2	Time (h)	Yield[b] %
a	C_6H_5	C_6H_5	5	82
b	C_6H_5	4-ClC_6H_4	4.5	84
c	4-$MeOC_6H_4$	C_6H_5	5	81
d	4-$MeOC_6H_4$	4-ClC_6H_4	5	85
e	4-$MeOC_6H_4$	2-ClC_6H_4	4	76
f	4-$MeOC_6H_4$	4-$NO_2C_6H_4$	3.5	69
g	4-$MeOC_6H_4$	4-$MeOC_6H_4$	10	78
h	3,4-diMeOC_6H_3	C_6H_5	5.5	77
i	3,4-diMeOC_6H_3	4-ClC_6H_4	5	80

[a]Reaction condition: 1 (0.55 mmol), $N_2H_4.H_2O$ (1.1 mmol),CuI (0.05 mmol) K_2CO_3 (0.825 mmol) in PEG-400 (5 mL) at 60 °C; [b]Isolated yield.

The mechanism is represented in scheme 1. In general, the purpose of the use of PEG facilitates the formation of a complex with the cation, similar to crown ether, and thus increases nucleophilities of the anions or bases .[29] It can also serve as an effective phase transfer solvent by forming a compatible chemical bridge between the hydrophobic organic component and the hydrophilic base. Furthermore, the addition of nucleophiles governs the formation of intermediate **B** followed by **A** through nucleophilic substitution. The base is susceptible to form copper-complex C which undergo oxidative addition and produce complex D. Eventually, the reductive elimination and air oxidation lead to desired product **2a**.[30-31]



Scheme 1. Plausible mechanism for the formation of pyrazolo[3,4-*c*]pyridazine

*3,5-Diphenyl-1H-pyrazolo[3,4-c]pyridazine (**2a**)*: Yield: 82%; m.p. 221-225 °C; IR (ν cm^{-1}): 3345, 3044, 2994, 1600, 1567, 1415; ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.32 (s, 1H), 8.39 (s, 1H), 8.10 (d, J = 7.2 Hz, 2H), 8.00 (d, J = 6.9 Hz, 2H), 7.39-7.91 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d$_6$): 161.2, 156.1, 145.3, 133.1, 129.1, 129.3, 129.2, 128.5, 128.3, 127.5, 127.1, 125.3, 113.7; Anal. Calcd. for $C_{17}H_{12}N_4$: C, 74.98; H, 4.44; N, 20.58; found: C, 74.93; H, 4.41; N, 20.52%.

*3-(4-Chlorophenyl)-5-phenyl-1H-pyrazolo[3,4-c]pyridazine (**2b**)*: Yield: 84%; m.p. 185-189 °C; IR (ν cm^{-1}): 3386, 3040, 2986, 1600, 1585, 1410; ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.34 (s, 1H), 8.37 (s, 1H), 8.09 (d, J = 8.0, 2H), 7.94 (d, J = 8.1 Hz, 2H), 7.69-7.47 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d6): 161.2, 156.1, 145.3, 134.3, 133.1, 131.2, 129.4, 129.3, 128.9, 128.8, 127.5, 125.3, 113.7; Anal. Calcd. for $C_{17}H_{11}N_4Cl$: C, 66.56; H, 3.61; N, 18.26; found: C, 66.51; H, 3.68; N, 18.21 %.

*5-(4-Methoxyphenyl)-3-phenyl-1H-pyrazolo[3,4-c]pyridazine (**2c**)*: Yield: 81%; m.p. 208-210 °C; IR (ν cm^{-1}): 2980, 1600, 1563, 1420; ^{1}H NMR (300 MHz, CDCl$_3$): δ 12.34 (s, 1H), 8.38 (s, 1H), 8.01 (dd, J_1 = 8.7 Hz, J_2 = 7.2 Hz, 4H), 7.59-7.48 (m, 3H), 7.08 (d, J = 8.4 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): 161.2, 160.7, 156.1, 145.3, 133.1, 129.3, 128.8, 128.5, 127.5, 125.4, 125.3, 114.8, 113.7, 55.9; Anal. Calcd. for $C_{18}H_{14}N_4O$: C, 71.51; H, 4.67; N, 18.53; found: C, 71.57; H, 4.69; N, 18.55 %.

*3-(4-Chlorophenyl)-5-(4-methoxyphenyl)-1H-pyrazolo[3,4-c]pyridazine (**2d**)*: Yield: 85%; m.p. 198-200 °C; IR (ν cm^{-1}): 2945, 1600, 1540, 1443; ^{1}H NMR (300 MHz, CDCl$_3$): δ 12.35 (s, 1H), 8.31 (s, 1H), 8.06 (d, J = 8.4 Hz, 2H), 7.95 (d, J = 6.9 Hz, 2H), 7.53 (d, J = 8.1 Hz, 2H), 7.07 (d, J = 7.5 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): 159.7, 155.4, 151.3, 141.9, 133.6, 130.4, 129.3, 128.5, 127.8, 127.5, 126.4, 114.3, 113.7, 28.9; Anal. Calcd. for $C_{18}H_{13}N_4Ocl$: C, 64.20; H, 3.89; N, 16.64; found: C, 64.26; H, 3.89; N, 16.68 %.

*3-(2-Chlorophenyl)-5-(4-methoxyphenyl)-1H-pyrazolo[3,4-c]pyridazine (**2e**)*: Yield: 76%; m.p. 188-190 °C; IR (ν cm^{-1}): 3332, 2984, 1600, 1572, 1410; ^{1}H NMR (300 MHz, CDCl$_3$): δ 12.33 (s, 1H), 8.31 (s, 1H), 7.72 (dd, J_1 = 1.8 Hz, J_2 = 8.2 Hz, 1H) 7.56-7.16 (m, 5H), 7.07 (d, J = 7.5 Hz, 2H), 3.90 (s, 3H); NMR (100 MHz, CDCl$_3$): 161.2, 160.7, 156.1, 145.3, 132.3, 130.2, 129.4, 128.6, 128.5, 128.3, 127.4, 125.4, 125.3, 114.8, 113.7, 55.9; Anal. Calcd. for $C_{18}H_{13}N_4OCl$: C, 64.20; H, 3.89; N, 16.64; found: C, 64.25; H, 3.90; N, 16.66 %.

*5-(4-Methoxyphenyl)-3-(4-nitrophenyl)-1H-pyrazolo[3,4-c]pyridazine (**2f**)*: Yield: 69%; m.p. 225-230 °C; IR (ν cm^{-1}): 3445, 1600, 1550, 1485, 1411; ^{1}H NMR (300 MHz, DMSO-d_6): d 12.32 (s, 1H), 8.31 (s, 1H), 8.08 (d, J = 8.0 Hz, 2H), 7.55 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.01 (d, J = 8.5 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): 161.2, 160.7, 156.1, 148.4, 145.3, 139.2, 128.5, 125.4, 125.3, 121.6, 114.8, 113.7, 55.9; Anal. Calcd. for $C_{18}H_{13}N_5O_3$: C, 62.24; H, 3.77; N, 20.16; found: C, 62.20; H, 3.75; N, 20.13%.

*3,5-Bis(4-methoxyphenyl)-1H-pyrazolo[3,4-c]pyridazine (**2g**)*:Yield: 78%; m.p. 180-185 °C; IR (ν cm^{-1}): 3389, 3030, 2985, 1600, 1567, 1408; ^{1}H NMR (300 MHz, CDCl$_3$): δ 12.31 (s, 1H), 8.31 (s, 1H), 7.48 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 7.03 (dd, J_1 = 8.1 Hz, J_2 = 8.2 Hz, 4H), 3.85 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): 161.2, 160.7, 156.1, 145.3, 128.5, 125.3, 114.8, 113.7, 55.9; Anal. Calcd. for $C_{19}H_{16}N_4O_2$: C, 68.66; H, 4.85; N, 16.86; found: C, 68.66; H, 4.85; N, 16.86%.

*5-(3,4-Dimethoxyphenyl)-3-phenyl-1H-pyrazolo[3,4-c]pyridazine (**2h**):* Yield: 77%; m.p. 180-181 °C; IR (ν cm^{-1}): 3400, 2983, 1610, 1550, 1490; ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.35 (s, 1H), 8.35 (s, 1H), 7.45-7.29 (m, 7H), 7.01 (d, J = 8.3 Hz, 1H), 3.95 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): 161.2, 156.1, 150.3, 149.8, 145.3, 133.3, 133.1, 129.3, 128.8, 127.5, 126.5, 126.4, 125.3, 120.8, 115.8, 113.7, 112.3, 56.2; Anal. Calcd. for $C_{19}H_{16}N_4O_2$: C, 68.66; H, 4.85; N, 16.86; found: C, 68.60; H, 4.80; N, 16.81%.

3-(2-Chlorophenyl)-5-(3,4-dimethoxyphenyl)-1H-pyrazolo[3,4-c]pyridazine (**2i**): Yield: 80%; mp 191-196 °C; IR (ν cm^{-1}): 3410, 2890, 1600, 1510, 1448, 1418; ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.36 (s, 1H), 8.31 (s, 1H), 8.06-7.93 (m, 3H), 7.54-7.42 (m, 3H), 7.07 (d, *J* = 8.1 Hz, 1H), 3.90 (s, 6H); *13*C NMR (100 MHz, DMSO-d_6): 161.2, 156.1, 150.3, 149.8, 145.3, 132.3, 130.1, 130.0, 129.4, 128.9, 127.4, 126.4, 125.3, 120.8, 115.8, 113.7, 112.3, 56.2; Anal. Calcd. for $C_{19}H_{15}N_4O_2Cl$: C, 62.22; H, 4.12; N, 15.27; found: C, 62.26; H, 4.17; N, 15.28 %.

In conclusion, we have developed a simple and cost-effective method for the synthesis of pyrazolopyridazine by cascade process in PEG-400. With the development of highly regioselective conditions for the synthesis of pyrazolopyridazine derivatives, we were able to prepare a wide variety of analogues. The cascade protocol was worked smooth with electron-donating groups. Further studies toward broadening the scope to include related heterocycles and applications are underway.

Acknowledgements

VTH is thankful to Department of Chemistry, Savitribai Phule Pune University for providing characterization data and Shri. R. R. Lahoti Science College, Morshi to provide necessary facilities.

Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/organic-communications

ORCID

Ranjit A. Gayake: 0000-0003-2760-9601
Vasant B. Jagrut: 0000-0002-3328-1991
Vivek T. Humne: 0000-0002-3412-5149

References

[1] Foster, R. A. A.; Willis, M. C. Tandem inverse-electron-demand hetero-/retro-Diels–Alder reactions for aromatic nitrogen heterocycle synthesis. *Chem. Soc. Rev.* **2013**, *42*, 63-76.

[2] Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. Cascade Reactions in Total Synthesis. *Angew. Chem. Int. Ed* **2006**, *45*, 7134-7186.

[3] Ihara, M. Cascade reactions for syntheses of heterocycles. *Arkivoc* **2006**, *7*, 416.

[4] Nicolaou, K. C.; Chen, J. S. The art of total synthesis through cascade reactions. *Chem. Soc. Rev.* **2009**, *38*, 2993-3009.

[5] Kuttruff, C. A.; Zipse, H.; Trauner, D. Concise total syntheses of variecolortides A and B through an unusual hetero-Diels-Alder reaction. *Angew. Chem. Int. Ed.* **2011**, *50*, 1402-1405.

[6] Granger, B. A.; Jewett, I. T.; Butler, J. D.; Hua, B.; Knezevic, C. E.; Parkinson, E. I.; Hergenrother,P. J.; Martin, S. F. Synthesis of (±)-actinophyllic acid and analogs: Applications of cascade reactions and diverted total synthesis. *J. Am. Chem. Soc.* **2013**, *135*, 12984-12986.

[7] Uchiro, H.; Shionozaki, N.; Tanaka, R.; Kitano, H.; Iwamura, N.; Makino, K. First total synthesis of oteromycin utilizing one-pot four-step cascade reaction strategy. *Tetrahedron Lett.* **2013**, *54*, 506-511.

[8] Williams, F. J.; Jarvo, E. R. Palladium-catalyzed cascade reaction for the synthesis of substituted isoindolines. *Angew. Chem. Int. Ed.* **2011**, *50*, 4459-4462.

[9] Lyons, T. W.; Brookhart, M. Cobalt-catalyzed hydrosilation/hydrogen-transfer cascade reaction: A new route to silyl enol ethers. *Chem. Eur. J.* **2013**, *19*, 10124-10127.

[10] Patil, N. T.; Mutyala, A. K.; Lakshmi, P. G. V. V.; Gajula, B.; Sridhar, B.; Pottireddygari, G. R.; Rao, T. P. Au(I)-catalyzed cascade reaction involving formal double hydroamination of alkynes bearing tethered carboxylic groups: An easy access to fused dihydrobenzimidazoles and tetrahydroquinazolines. *J. Org. Chem.* **2010**, *75*, 5963-5975.

[11] Hodgson, D. M.; Labande, A. H.; Pierard, F.; Expósito Castro, M. A. The scope of catalytic enantioselective tandem carbonyl ylide formation−intramolecular [3+2] cycloadditions. *J. Org. Chem.* **2003**, *68*, 6153-6159.

[12] He, X.; Yan, Z.; Hu, X.; Zuo, Y.; Jiang, C.; Jin, L.; Shang, Y. FeCl3-catalyzed cascade reaction: an efficient approach to functionalized coumarin derivatives. *Synth. Commun.* **2014**, *44*, 1507-1514.

[13] Wipf, P.; Waller, D. L.; Reeves, J. T. Transition-metal-mediated cascade reactions: The water-accelerated carboalumination−claisen rearrangement−carbonyl addition reaction. *J. Org. Chem.* **2005**, *70*, 8096-8102.

[14] Cannatelli, M. D.; Ragauskas, A. J. Laccase-catalyzed synthesis of 2,3-ethylenedithio-1,4-quinones. *Org. Chem. Curr. Res.* **2013**, *2*, 1-2.

[15] Biagini, P.; Biancalani, C.; Graziano, A.; Cesari, N.; Giovannoni, M. P.; Cilibrizzi, A.; Piaz, V. D.; Vergelli, C.; Crocetti, L.; Delcanale, M.; Armani, E.; Rizzi, A.; Puccini, P.; Gallo, P. M.; Spinabelli, D.; Caruso, P. Functionalized pyrazoles and pyrazolo[3,4-*d*]pyridazinones: Synthesis and evaluation of their phosphodiesterase 4 inhibitory activity. *Bioorg. Med. Chem.* **2010**, *18*, 3506-3517.

[16] Stevens, K. L.; Reno, M. J.; Alberti, J. B.; Price, D. J.; Kane-Carson, L. S.; Knick, V. B.; Shewchuk, L. M.; Hassell, A. M.; Veal, J. M.; Davis, S. Y.; Griffin, R. J.; Peel, M. R. Synthesis and evaluation of pyrazolo[1,5-*b*]pyridazines as selective cyclin dependent kinase inhibitors. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5758.

[17] Bran, M. F.; Cacho, M.; Garcia, M. L.; Mayoral, E. P.; Lopez, B.; Pascual-Teresa, B.; Ramos, A.; Acero, N.; Llinares, F.; Mingarro, D. M.; Lozach, O.; Meijer, L. Pyrazolo[3,4-c]pyridazines as novel and selective Inhibitors of cyclin-dependent kinases. *J. Med. Chem.* **2005**, *48*, 6843-6854.

[18] Patnaik, S.; Dietz, H. C.; Zheng, W.; Austin, C.; Marugan, J. J. Multi-Gram Scale Synthesis of FR180204. *J. Org. Chem.* **2009**, *74*, 8870.

[19] Chen, J.; Spear, S. K.; Huddleston, J. G.; Rogers, R. D. Polyethylene glycol and solutions of polyethylene glycol as green reaction media. *Green Chem.* **2005**, *7*, 64-82.

[20] Das, B.; Krishnaiah, M.; Balasubramanyam, P.; Veeranjaneyulu, B.; Nandankumar, D. A remarkably simple N-formylation of anilines using polyethylene glycol. *Tetrahedron Lett.* **2008**, *49*, 2225-2227.

[21] Ghom, M. H.; Naykode, M. S.; Humne, V. T.; Lokhande, P. D. A one-pot direct regioselective iodination of Fischer-Borsche product using periodic acid in PEG-400. *Tetrahedron Lett.* **2019**, *60*, 1029-1031.

[22] Humne, V. T.; Ulhe. A. G. Copper-mediated rapid and facile oxidative dehydrogenation of dihydrobenzocarbazoles. *Synth. Comm.* **2020**, *50*, 1064-1074.

[23] Mahajan, P. S.; Humne, V. T.; Tanpure, S. D.; Mhaske, S. B. Radical Beckmann rearrangement and Its application in the formal total synthesis of antimalarial natural product isocryptolepine via C–H activation. *Org. Lett.* **2016**, *18*, 3450-3453.

[24] Humne, V. T.; Naykode, M. S.; Ghom, M. H.; Lokhande, P. D. Total synthesis of diverse oxygenated carbazoles by modified aromatization using molecular iodine. *Tetrahedron Lett.* **2016**, *57*, 688-691.

[25] Naykode, M. S.; Humne, V. T.; Lokhande, P. D. A one-pot direct iodination of the fischer–borsche ring using molecular iodine and its utility in the synthesis of 6-oxygenated carbazole alkaloids. *J. Org. Chem.* **2015**, *80*, 2392-2396.

[26] Konda, S. G.; Humne, V. T.; Lokhande, P. D. Rapid and selective deallylation of allyl ethers and esters using iodine in polyethylene glycol-400. *Green Chem.* **2011**, *13*, 2354-2358.

[27] Humne, V. T.; Hasanzadeh, K.; Lokhande, P. D. Selective O-deallylation of dihydropyrazoles by molecular iodine in the presence of active N-allyl and formyl groups. *Res. Chem. Intermed.* **2013**, *39*, 585-595.

[28] Humne, V. T.; Lokhande, P. D. Efficient deallylation of allyl phenyl ethers by molecular iodine in peg-400 and their utility for flavone synthesis. *Synth. Comm.* **2014**, *44*, 929-935.

[29] Das, B.; Reddy, V. S.; Krishnaiah, M. An efficient catalyst-free synthesis of thiiranes from oxiranes using polyethylene glycol as the reaction medium. *Tetrahedron Lett.* **2006**, *47*, 8471-8473.

[30] Burley, G. A.; Davies, D. L.; Griffith, G. A.; Lee, M.; Singh, K. Cu-catalyzed N-Alkynylation of Imidazoles, Benzimidazoles, Indazoles, and Pyrazoles using peg as solvent medium. *J. Org. Chem.* **2010**, *75*, 980-983.

[31] Chen, J.; Yuan, T.; Hao, W.; Cai, M. Simple and efficient CuI/PEG-400 system for amination of aryl halides with aqueous ammonia. *Tetrahedron Lett.* **2011**, *52*, 3710-3713.