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ONE-POT MCR REACTION VIA DIFFERENT BASE USED AS CATALYST ANDPEG-400 AS A SOLVENT

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ABSTRACT
Our motto for this work is green and natural resources use for the development of multicomponent reaction (MCRs) significant approach for the fabrication of polyfunctional molecules in an operatively easy and atom-economic manner, and the finding of novel MCRs appeal to various building blocks. Herein, the latest pyran-based phthalazinone pyrazole hybrids were synthesized by a facile one-pot MCR done by triethylamine, di-isopropyl ethyl amine (DIPEA), tripropylamine (TPA) as a catalyst. Check study led to the recognition of tripropylamine (TPA) with PEG-400 as the potential catalyst and green solvent, respectively, and the reusability of PEG-400 up to 5 cycles. This protocol opens a new perception for the introduction of rational design and the building blocks of MCRs.

Keywords: High-Reusability of Solvent, Green Chemistry, Micro-Wave, Eco-Environment Friendly.
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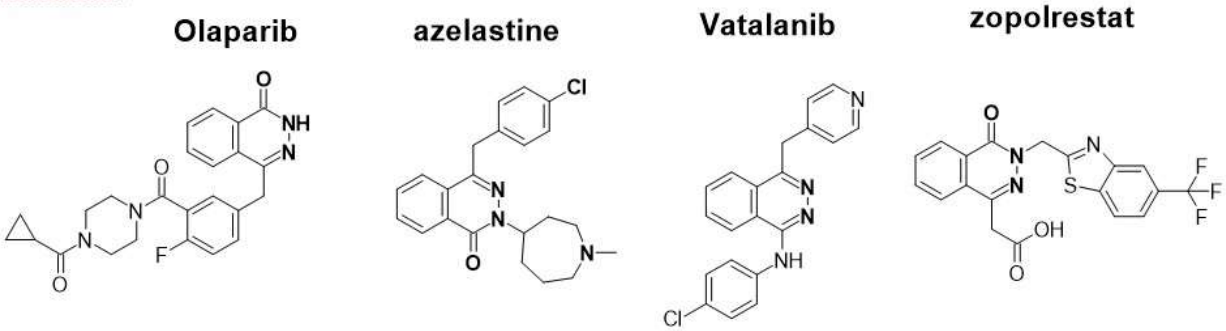
INTRODUCTION

The importance of nitrogen present heterocyclic molecules in med-chemistry is unavoidable and ample for biological with pharmaceutical applications agrochemical, pesticide, polymer, and materials chemistry fields[3,4], optical brighteners, corrosion inhibitors, plastics or dyes[5], and UV-screens for increase SPF Index[6]. Additional activities like antibacterial, anti-HIV activity, anticancer, antifungal, herbicidal antiallergic, and anti-tuberculosis[7].Herein, derivatives werebased on MCR reaction utilizing triethylamine, di-isopropyl ethyl amine (DIPEA), and tripropylamine (TPA) as a catalyst. Check the efficiency of PEG-400 as the superb green solvent, and the reusability of PEG-400 up to 5 cycles. So in the present work, some novel and known heterocycle derivatives from PEG-400 solvent with various catalysts render chemical methodology it could initiate vital pharmacophore in a clean and eco-friendly way. Bhenki *et al.* represent the 5-SULFOSALICYLIC ACID used for 4-methylcoumarins formation via Pechmann condensation reaction.[8]



EXPERIMENTAL

Materials

All raw material used for synthesis is purchased from local chemical suppliers. Melting point and TLC have been done in our house facility, Spectral analysis like IR,^{1}HNMR,^{13}CNMR, and mass spectra are done by an outside facility like NFDD-Rajkot and VIT-Vellore.

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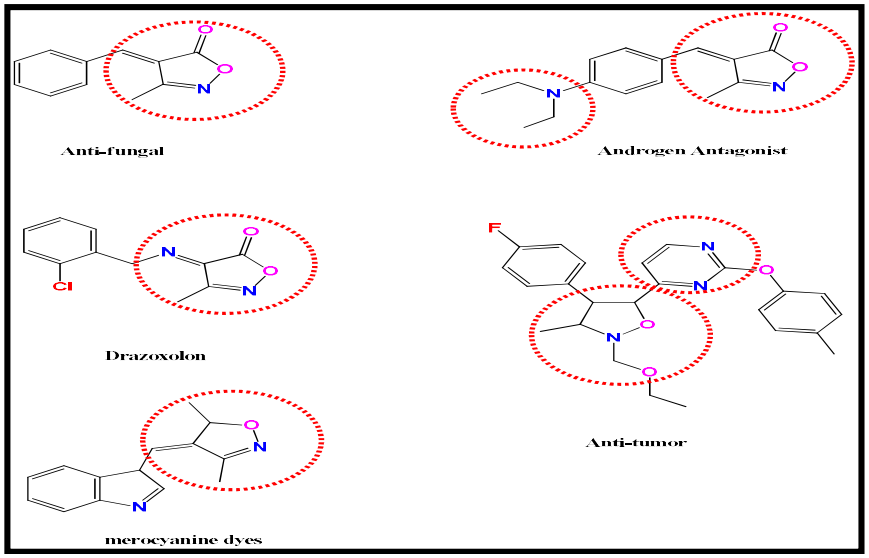

Fig.-1: Some Examples of Pyran-Linked Phthalazinone-Pyrazole, 3-Methyl--4--Aryl-Methylene-Isoxazole-5(4*H*)-Ones Based Approval Molecules Used as Drug.

Method for Pyran-Linked Phthalazinone-Pyrazole(A)

3-(1,4-dioxo-3,4-dihiyiidrophthalazin-2(1H))222-3-1oxopropanenitrile:(1equi),1H-pyrazole-5-carbaldehyde (1equiv), and malononitrile (1equiv) or was charged PEG-400 (5 vol) in the presence of 20 mol% TEA, DIPEA, and TPA one by one (0.23 g) as a catalyst and mix well for 2-3 min and kept in the microwave for 5-10 min at 80°C temp or 300 watt and reaction checked TLC. Filter reaction mass andrecrystallizewith Ethanol. Check melting point, IR, NMR, and mass spectra.

Method for 3-methyl-4arylimethylene isoxazole-5(4-*H*)-ones(B)

A take hydroxylamine hydrochloride, ethyl acetoacetate and aromatic aldehyde in equivalent mole ratio and PEG-400 was an addition in catalytic amount charged in RBF starring for 5 min. than heating at 80°C or irradiated under the microwave (300W) for the appropriate time. After completion of the reaction precipitation formed filter reaction mass and crystalline by hot-Ethanol. Check melting point by melting point apparatus. Product confirmed by IR, NMR, and Mass spectra.

Optimization Studies for Pyran-Linked Phthalazinone-Pyrazole Reaction

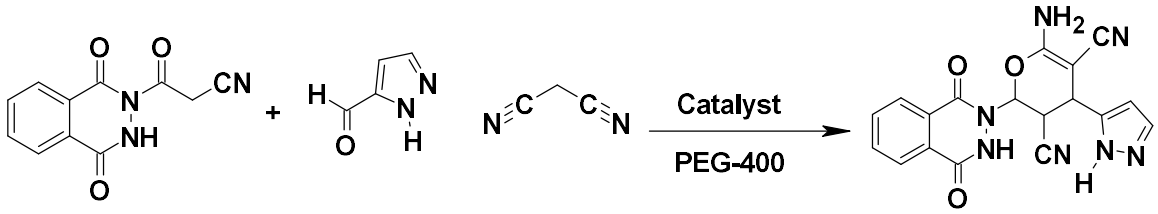

Fig.-2: Reaction scheme of Phthalazinone-Pyrazole Reaction

Table-1: Optimization of Phthalazinone-pyrazole Reaction via Base

Entry	Solvent	10% mole catalyst A	20% mole catalyst B	30% mole catalyst C	Pka Value	Temp (°C)	Time (Min)	Yield (%) A	Yield (%) B	Yield (%) C
1	Ethanol	-----	-----	-----	----	80	12	------	---	----
2	Ethanol	L-Proline	L-Proline	L-Proline	10.96	80	12	82	88(1)	81(1)
3	PEG-400	----	-----	-----	----	80	12	50	60	51
4	PEG-400	TEA	TEA	TEA	10.76	80	12	91	92	89
5	PEG-400	DIPEA	DIPEA	DIPEA	10.98	80	12	88	89	88
6	PEG-400	TPA	TPA	TPA	10.82	80	12	87	86	86

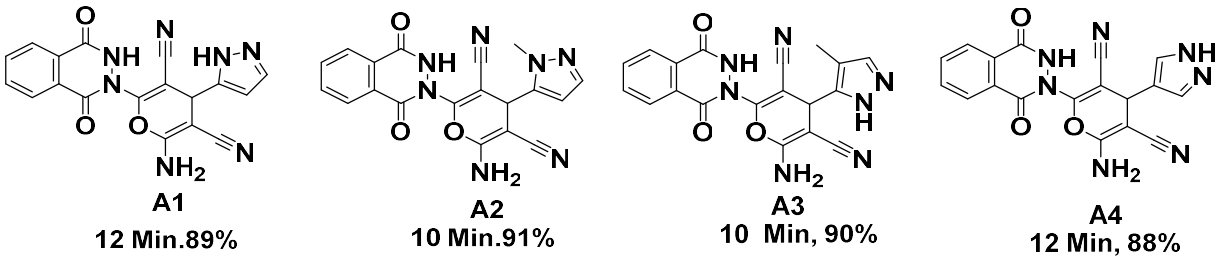

Fig.-3: Formed Derivatives with Yield

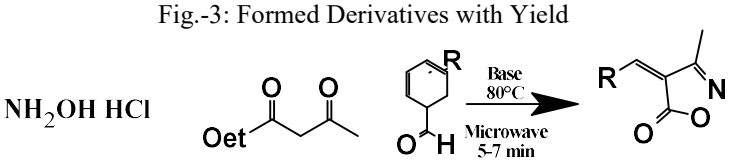

Fig.-4: Optimization Studies for 3(methyl)-4-aryl-methylene isoxazole-5(4*H*)-ones

Table-2: Optimization of Isoxazole derivatives reaction via Base

Entry	Solvent	10% mole catalyst A	20% mole catalyst B	30% mole catalyst C	Pka Value	Temp (°C)	Time (Min.)	Yield (%) A.	Yield (%) B.	Yield (%) C.
1	Ethanol	-----	-----	-----	----	80	7	------	---	----
2	Ethanol	Pyridine	Pyridine	Pyridine	8.77	100	25	78	80	80[12]
3	PEG-400	----	-----	-----	----	80	5	60	62	59
4	PEG-400	TEA	TEA	TEA	10.76	80	5	88	94	91
5	PEG-400	DIPEA	DIPEA	DIPEA	10.98	80	5	89	92	86
6	PEG-400	TPA	TPA	TPA	10.82	80	5	79	83	71

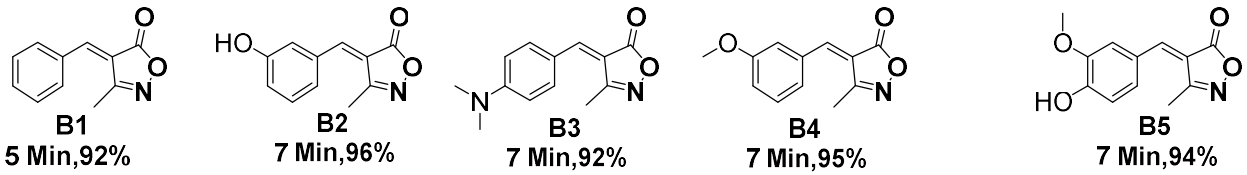

Fig.-5: Formed Derivatives with Yield

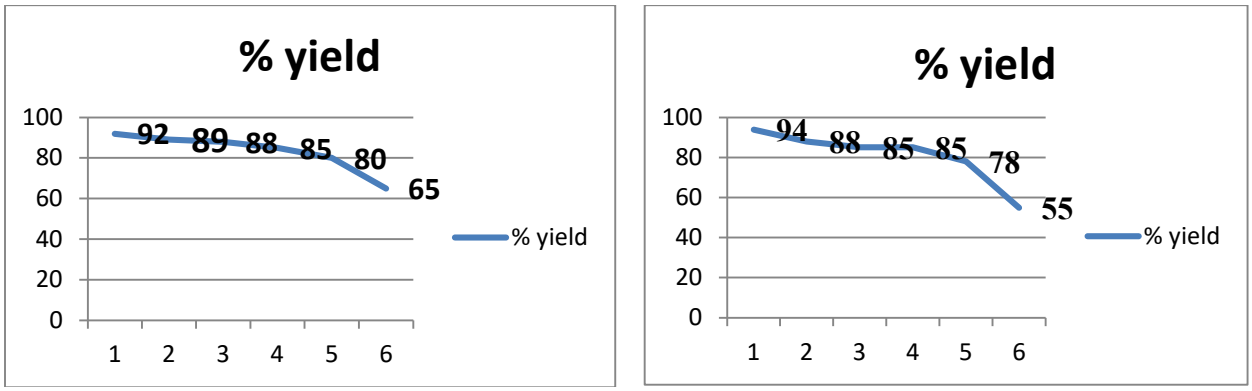

Fig.-6: Reusability of Solvent PEG-400 in Formation of phthalazinone-pyrazole and3-methyl-4arylmethylene isoxazole-5(4H)-ones

RESULTS AND DISCUSSION

In the first part of pyran-linked phthalazinone-pyrazole derivatives formation via various organic base catalysts, Triethylamine is quite good than DIPEA and TPA as a catalyst. The reaction is optimized at 80°C temps and 300 watts for 12 min is a fine condition for yield with good purity[A1 to A4].Any functional group of aldehydes does not have any major impact on the formation of the product yield.The second part of the paper is based on the role of the base catalyst on synthesized 2,3-methyl-aryl-methylene isoxazole-5-(4*H*)-onesderivatives via TEA, DIPEA, and TPA as catalysts. Previously reported

yield pyridine as a catalyst and ethanol as solvent. It gives an 80% yield and our work got a higher yield with PEG-400 as a solvent, it's a green and easy to reusable solvent for the next cycle. In PEG-400 use as a solvent the reusable for up to 5 cycles and gave the same yield after cycle 5 in both reactions it reduces its acting as a solvent.

Physical and Spectral Data of Synthesized Compounds

2-Amino-6-(1,4-dioxo-3,4-dihydrophthalazin-2(1H)-yl)-4-(1Hpyrazol-5-yl)-4H-pyran-3,5-dicarbonitrile (A1)

Mp°C:249–251°C; IR by FTIR (cm $^{-1}$):3180–3540 (-NH-), 2190 (-CN-), 1740 (-CO-); ^{1}HNMR: 6.49 (1H)7.42-8.1 (5H), 8.25 (1H), 9.82 (2H), 11.45 (1H), 12.15. ^{13}CNMR:49.1,78.1,86.2,114.0,115.7,124.2,125.7, 128.1, 129.5, 132.1, 133.9, 136.7, 156.1, 158, 163.3, 164.0 [M+2]: 375.

2-Amino-6-(dioxo-3,4-dihydro-phthalazin-2(H)yl)-4-(1:methyl-1H-pyra:zol-5-yl)-4H-pyran,3,5-dicarbo-nitrile (A2)

Mp°C :241–243°C,IR by FTIR (cm $^{-1}$):3100–3520 (-NH-),2260 (-CN-), 1740 (-CO-); ^{1}HNMR:3.0 (3H), 6.53 (1H), 7.40 (1H), 7.89–8.10 (4H), 8.15 (1H), 9.54 (2H), 12.05 (1H); ^{13}C NMR: 29.1, 48.5, 75.4, 86.7, 115.1, 115.70, 124.5, 126.9, 128.2, 129.6, 130.1, 134.7, 136.1, 155.9, 156.2, 163.0, 163.6 [M+1]: 388.

2-Amino-6(1,4-dioxo-3,4-di-hydrophthalazin-2(1H)-yl)-4-(4-methyl-1H-pyrazol-5yl)-4H-pyran-3,5-di-carbonitrils(A3)

Mp°C: 239–241°C;141 IR by FTIR (cm $^{-1}$): 3137–3580 (-NH-),2253 (-CN-), 1745 (-CO-); 1HNMR: 3.49(3H), 6.41 (1H), 7.85–8.10 (4H,), 8.20 (1H), 9.82 (2H), 11.30 (1H),12.10 (1H); ^{13}C NMR: δ 34.2, 49.4, 74.2, 85.2, 115.2, 116.7,123.4,126.7,128.5,129.4,132.1, 134.0, 136.5, 154.9, 156.8, 162.1, 163.5 [M + 2]: 389.

2-Amino-6(1,4-dioxo-3,4-di-hydrophthalazin-2(1H)-yl)-4-(1H-pyrazol-4yl)-4H-pyran-3,5-dicarbonitrile(A4)

Mp°C:255–257°C,IR by FTIR (cm $^{-1}$):3038–3580(-NH-),2256(-CN-),1740(-CO-), ^{1}H-NMR:6.51(1H), 7.40–8.25 (6H), 9.87 (2H), 11.30 (1H), 12.20(1H,);^{13}CNMR:45.2,75.1, 86.7, 114.7, 116.0, 126.1, 127.7, 129.3,129.9,131.6,135.1,138.1, 155.1, 158.1, 164.1, 164.1 [M + 1]: 375.

4-Benzylidene-3-methyl-isoxazol-5-(4H)-one(B1)

Mp°C:139–141IR by FTIR (cm $^{-1}$):3232, 2363, 1734,1560,1355,1295,1180;^{1}HNMR:2.35(3H),7.51(1H),7.52-7.65 (3H), 8.42(2H), ^{13}CNMR:11.5,114.7,118.1, 126.9, 137.2, 152.6, 162.9, 168.62; [M+1] 188.19

4-(4-Hydroxy-benzylidene)-3-methyl-isoxazol-5-(4H)-one(B2)

IR by FTIR (cm $^{-1}$):3570,1740,1545, 1537,1427,1190,1110,^{1}HNMR:2.25(3H),6.82(2H), 7.72 (1H), 8.47 (2H),11.47(1H);^{13}CNMR:11.2, 116.8, 120.1, 124.1, 136.2,151.2,155.3,165.4,168.5; [M+1]204.2.

4-(3-Di-methylamino)benzylidene)-3-methyl-isoxazol-5-(4H)one(B3)

IR by FTIR (cm^{-1}): 1730,1590, 1545,1432,1178,1099,^{1}HNMR:2.21(3H,),3.15(6H),6.90(2H),7.60(1H),8.51,^{13}CNMR:11.2,45.3,109.1,119.1, 122., 137.7, 151.4, 152.1, 161.9,168.8. [M+2]:232.2.

CONCLUSION

Synthesized compounds from the various base and PEG-400 as a solvent have efficiency higher than previously reported solvent for such type of reactions and base catalyst has an impassive effect on reaction rate. It's almost half than the previously reported time duration of these type reactions. It's accomplishment for the green and efficient path for drug development by PEG-400 and base catalyst system.

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