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Rapid And Efficient Synthesis Of 2,3-Dihydro-1H-1,5-Benzodiazepines Using Eco-Friendly Green Solvent Mixture (Glycerol: DMC)

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ABSTRACT
A novel eco-friendly methodology synthesizes 1 ,5-Benzodiazepines using a glycerol-dimethyl carbonate (DMC) solvent composite and ultrasound irradiation, addressing environmental limitations of conventional methods. The glycerol- DMC system serves as a biodegradable medium, utilizing glycerol's polarity and DMC's solvating properties. Sonochemical activation generates localized temperatures above 5000 K and pressures of ~1000 bar, accelerating reactions while ensuring uniform mixing. The method achieves high yields (93–96%) within 2-5 minutes, as glycerol stabilizes intermediates and DMC activates carbonyl groups. Ultrasound irradiation reduces energy consumption by 40–60% and enhances reaction efficiency, allowing Green solvent to be reused for three cycles. This protocol eliminates traditional solvents and enables solvent recovery via vacuum distillation. Spectroscopic analyses confirm product purity, Gram-scale syntheses maintain >90% yield under optimized conditions (40 kHz ultrasound, 7:3 glycerol:DMC ratio, 60°C). This approach establishes sustainable heterocyclic synthesis for pharmaceutical and agrochemical industries while supporting UN Sustainable Development Goals.
Keywords: *Green condition, Sono chemistry, Biocompatible and eco-friendly solvent, Ultrasound irrigation*

INTRODUCTION
The development and adoption of green solvents, such as glycerol and dimethyl carbonate, are pivotal for advancing sustainable chemistry and mitigating the environmental impact of chemical processes. As research in this domain progresses, several promising future directions and innovations have emerged. Key focus areas and potential future findings include: 1. Design of Novel Green Solvents 2. Improved Recycling and Reusability 3. Solvent-Free Reactions 4. Smart and Switchable Solvents 5. Computational Design of Green Solvents 6. Integration with Green Chemistry Principles 7. Expansion into New Applications 8. Regulatory and Industrial Adoption 9. Hybrid Solvent Systems 10. Global Collaboration and Innovation. The future of green solvents, such as glycerol, appears promising, with ongoing research dedicated to developing more sustainable, efficient, and versatile alternatives to traditional solvents. Innovations in bio-based solvents, recycling technologies, solvent-free reactions, and computational designs are paving the way for greener and more sustainable chemical industries. By embracing these advancements, the environmental impacts of chemical processes can be reduced, thereby achieving the goals of green chemistry. 1,5-Benzodiazepines are N-present heterocyclic rings, recognized as biologically active scaffolds in drug discovery, with applications as anxiolytic, sedative, hypnotic, muscle relaxant, anti-inflammatory, antiviral, and analgesic agents [4]. Currently, numerous marketed drugs are synthesized from benzodiazepines, including clobazam, lofendazam, arfendazam, triflubazam, nevirapine, and telenzepine [5]. Although various synthetic methods have been reported, the most commonly employed approach for producing 1,5-benzodiazepines involves the condensation reaction between diamines and carbonyl compounds, a glycerol-like natural solvent was employed in the ultrasonic reaction mode as both the solvent and catalyst for the reaction. This method yields a high output in a short time with no solvent waste in the vapor phase post-reaction.

RESULTS AND DISCUSSION
The solvent and catalytic efficiency of various green solvents, such as Glycerol, Dimethyl carbonate, diethyl carbonate, and ethanol, were studied. The Glycerol and Dimethyl carbonate (7:3) ratio gave the best result for the easy, less time a n d high- yielding synthesis of 1,5-benzodiazepines derivatives (Table 2).

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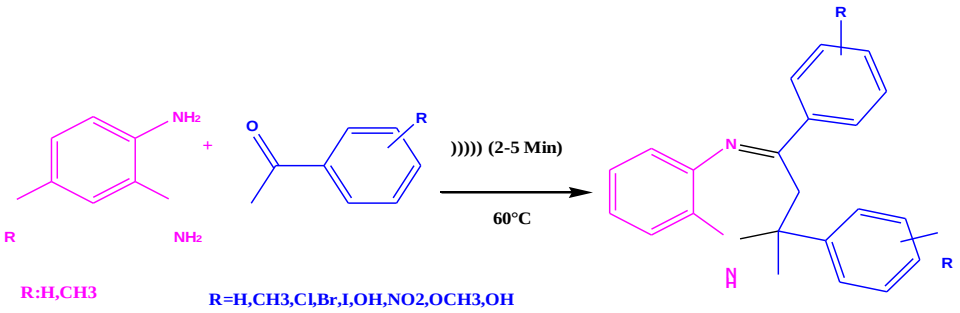


Table 1: Previously reported work for Synthesis of 2,3-Dihydro-1H-1,5-Benzodiazepine:

Sr.Num	Catalyst	Method/Solvent	Time(Min)/Yield(%)	Reference Number-Year
1	H-MCM-22 zeolite	RT, ACN solvent	60/87	9-2012
2	Oxalic acid (10 mol%)	80°C, solvent-free conditions	180/88	10-2013
3	HY zeolite	50°C, solvent-free conditions	240/93	11-2014
4	La2O3 and La(OH)3	Water ,60° C	300/79	12-2016
5	Graphite oxide (GO)	80°C, solvent-free	30/92	13-2017
6	MIL-101(Al) MOF	Solvent-free or water as solvent	90/94	15-2019
7	Silica sulfuric acid	Solvent-free, 120°c	60/90	14-2021
8	Ferrocene anchored activated carbon	Chloroform solvent,90°C	480/90	16-2022
9	ACT@IRMOF core-shell	Refluxe,Ethanol solvent	60/95	17-2025

Table 2. Solvent selection of the synthesis of 1,5-benzodiazepin derivatives.

Entry	Solvent combination (6 volumes)	Time, Min	Yield, %	Recovery (%)
1	Glycerol	10	94	87
2	Ethanol	10	84	60
3	Dimethyl carbonate	10	75	69
4	Diethyl carbonate	10	79	65
5	Water	10	65	90
6	Methanol	10	74	60
7	Glycerol:Water (5:5)	10	71	95
8	Glycerol:DMC (5:5)	10	91	75
9	Glycerol:DMC (7:3)	05	97	81

Table 2 its use for check the efficiency of various solvent individually and composite form during this evaluation is useful for the solvent selection, entry 01 Glycerol as such used as a solvent recovery of

Glycerol is high but the its difficult to separate, that another green solvents like ethanol, Methanol

recovery not more than 70% its gave high loss in vapor form, so make the composition in water in entry7 and Dimethyl carbonate entry 8,it have good solubility and recovery in entry 8,so;we processed in table-03 for the further optimization of time and Solvent ratio parameters.

Table 03: optimization of time and Solvent ratio parameters.

Table 3 its optimization and solvent selection for the good yield in less time with good recovery, during optimization we are observed in entry 01 at certain temp the heat does not impact on the improvement on yield, than entry-3got good yield with clean reaction and easy to separate solvent from reaction mass ,but the entry 4,5,6 got good recovery of solvent after reaction but the some product loss in the solvent

Entry	DMC (ml)	GLYCEROL (ml)	Ratio	Temp (°C)	Time(min)	Yield (%)	Recovery of solvent (%)
1	5	5	(1:1)	50(Ultrasonic)	5	91	75
2	4	6	(4:6)	60(Ultrasonic)	5	95	75
3	**3**	**7**	**(3:7)**	**60 (Ultrasonic)**	**5**	**97**	**81**
4	2	8	(2:8)	60(Ultrasonic)	5	85	89
5	1	9	(1:9)	60 (Ultrasonic)	5	79	92
6	0.5	9.5	(0.5:9.5)	60 (Ultrasonic)	5	87	95

and viscosity of solvent is very high due to this reason product difficult to separate from solvent, trace amount of product lynching with solvents so it's useless for next cycle reaction. The composite solvent was recovered and recycled under optimized reaction conditions using acetophenone and o-Phenylenediamine (OPDA) as reference substrates summarized in Table-3. Comparative yields were obtained using the recycled composite solvent for up to three cycles (Entries-1-3, Table-3).

Spectral data of selected compounds:

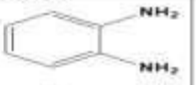
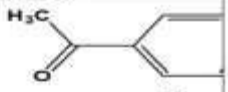
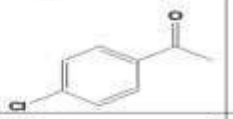
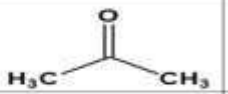
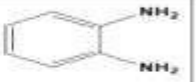
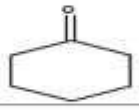
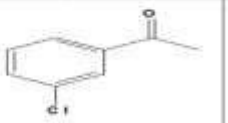
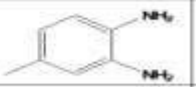
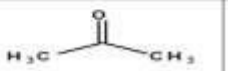
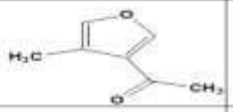
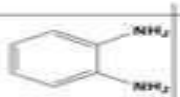
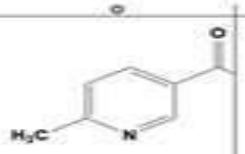
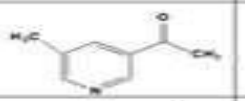
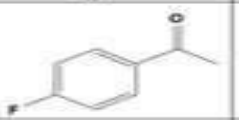
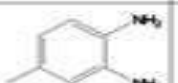
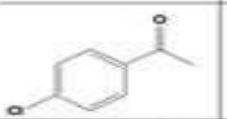
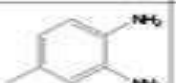
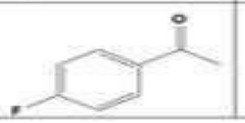
1) 2-methyl-2,4-diphenyl-2,3-dihydro-1*H*-1,5-benzodiazepine:(1)^{1}HNMR:δ:1.49(3H),2.8(2H), 4.89(1H) ,6.99-7.48 (12H), 8.16 (2H). ^{13}C NMR: δ 25.7(1C), 41.9(1C), 125.1-129.6(14C), 132.3-139.4 (4C), 150.4 (1C), 157.8 (1C). Mass Spectra:313.08

2) 2,4-bis(4-chlorophenyl)-2-methyl-2,3-dihydro-1H-1,5-benzodiazepine::^{1}HNMR:δ:1.13(3H),2.2-2.6(2H), 4.5(1H) ,6.19-7.40 (11H), 7.79-7.81(1H). ^{13}C NMR: δ 25.7(1C), 41.95(1C), 122.0 (1C), 125.0 (1C), 127.8 (1C), 128.1-128.7 (8C),129.60(1C), 130.3-130.5 (2C), 133.4 (1C), 137.7 (1C), 138.2 (1C), 139.9 (1C), 157.4 (1C), 157.8 (1C),Mass Spectra:383.10

3) 2,4-bis(4-Methoxyphenyl)-2-methyl-2,3-dihydro-1H-1,5-benzodiazepine ^{1}HNMR:δ:1.35(3H),2.41-2.43(2H), 3.73-3.80(6H),4.01-4.03(1H) ,4.10(1H),4.78-4.81(1H),5.32-5.43(2H), 6.59-7.26 (8H),^{13}C NMR: δ 25.7(1C),32.4(1C),55.3(2C), 114.5(4C), 122.6 (1C),124.4(1C), 125.0 (1C), 127.8 (1C), 128.1-128.7 (5C), 138.2 (2C),150.5(1C). 157.4 (2C),159.7(2C)Mass Spectra:374.14

(6) 2,4-Bis(3-chlorophenyl) 2-methyl-2,3-dihydro-1H-1,5-benzodiazepine:.:*^{1}H NMR (600 MHz, CDCl$_3$).* d 7.70 (1H), 7.41–7.46 (2H),7.40 (1H), 7.42–7.25 (3H), 7.10–7.04 (5H),6.80 (1H), 4.80 (1H),2.89 (1H), 1.75 (3H). ^{13}C NMR: δ 25.8 (1C), 42.0 (1C), 116.0-116.0 (2C), 122.0 (1C), 125.0 (1C), 127.0-127.0 (2C), 127.8 (1C), 128.5-128.7 (2C),129.3-129.5 (3C),133.0-133.2 (2C), 133.4 (1C), 138.1-138.3 (2C), 139.9 (1C), 157.4 (1C), 157.8 (1C).Mass Spectra:: *m/z* 380.91 $(M + H)^{+}$.

(12) 2,4-bis(4-fluorophenyl)2-methyl-2,3-dihydro-1H-1,5-benzodiazepine:^{1}H NMR: ^{1}H NMR: δ 1.37-1.47 (3H), 2.84 (2H),4.83(1H), 6.93-7.39 (12H), ^{13}C NMR: δ 25.8 (1C), 42.0 (1C), 114.8-114.8 (4C), 122.0 (1C), 125.0 (1C), 127.8 (1C), 128.8-128.9 (4C),129.3 (1C), 133.4 (1C), 137.7 (1C), 138.2 (1C), 139.9 (1C), 157.4 (1C), 157.8 (1C), 161.8-161.9 (2C),Mass Spectra: m/z 348.30 $(M + H)^{+}$

Entry	Comp.	Ketone	Time	Yield
1			2	91
2			2	93
3			5	96
3			4	85
4			2	98
5			2	95
6			2	92
			7	79
8			7	90
9			4	92
10			5	92
11			4	95
12			3	97
13			3	90
14			3	97

Experimental

All used materials buy from HPLC Mumbai and Glycerol from local vendor, Ultrasonication probe made by Nanbai-Chaina.

Preparation of green solvent composite: A 100 ml round-bottom flask (RBF) and the initial mixture were prepared by combining glycerol and Dimethyl Carbonate (DMC) in specified proportions. The quantity of each solvent utilized is contingent upon the desired viscosity, solubility, and application. Typically, a 1:1 ratio (Glycerol: DMC) serves as the initial reference point, although modifications can be made based on the characteristics of the materials employed. The two solvents were subsequently mixed by stirring at room temperature. If necessary, the mixture was gently heated to facilitate the dissolution process, ensuring the temperature remained below 60°C to prevent excessive evaporation of DMC. Various ratios, such as (3:7), (5:5), and (7:3), can be employed.

Note: Check the boiling point of the solvent and store it in a dry and cool environment.

3.2 General procedure for the preparation: o-Phenylenediamine (1 mmol) and Acetophenone (2.20 mmol) were introduced into a 20 ml test tube equipped with a stopper, along with various green solvents, and subjected to ultrasonic agitation for appropriate minutes. Upon completion of the reaction, which was monitored using thin-layer chromatography (TLC) with CHCl3 and MeOH (9.5:0.5 mL) as the eluents, the reaction mixture was filtered under vacuum. The resulting solid was subsequently recrystallized from ethanol.

Recovery of Solvent: The reaction mixture was subjected to vacuum filtration, after which the receiver was cooled and subsequently washed with n-hexane to recover the solvent and eliminate n-hexane at ambient temperature. In the absence of any observable impurity or product spot in the recovered solvent, the process was repeated for subsequent cycles, achieving a consistent yield after up to three cycles.

CONCLUSION:

The utilization of a Glycerol and DMC solvent mixture as a green solvent under sonochemical reaction conditions presents a sustainable and efficient methodology for chemical synthesis. This combination capitalizes on the recyclability and biocompatibility of Glycerol, alongside the low toxicity and versatility of DMC, while sonochemistry enhances reaction kinetics and reduces energy consumption. Collectively, they offer a promising green alternative to traditional solvents and methods, potentially resulting in cleaner reaction profiles, higher yields, and diminished environmental impacts. Nevertheless, the specific efficacy is contingent upon the reaction type, substrate compatibility, and optimization of the Glycerol:DMC ratio, indicating that further experimental validation is necessary to substantiate these benefits in practice. The remarkable results achieved in a short time with high yield and clean reaction conditions highlight the potential of this green solvent system. Further investigations could examine the applicability of this approach across a broader spectrum of chemical reactions and industries. Optimization of the Glycerol:DMC ratio and sonochemical parameters could potentially lead to even greater enhancements in efficiency and sustainability.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

REFERENCES:

1. Vaithiyalingam, M., Kumar, R. M., Khagar, P., Sabarathinam, S., Alghazwani, Y., & Chidambaram, K. (2024). Isolation of 6-gingerol and semi-synthesis of 1, 4-benzodiazepines derivatives: An in-situ pharmacokinetics properties, molecular docking and molecular dynamics simulation assessments. Saudi Journal of Biological Sciences, 31(8), 104048.
2. 2.Teli, S., Teli, P., Soni, S., Sahiba, N., & Agarwal, S. (2024). Synthetic aspects of 1, 4-and 1, 5-benzodiazepines using o-phenylenediamine: A study of past quinquennial. *RSC advances*, *13*(6), 3694-3714.
3. Teli, S., Sethiya, A., & Agarwal, S. (2024). Pioneering synthetic strategies of 2-substituted benzothiazoles using 2-aminothiophenol. *Chemistry*, *6*(1), 165-206.
4. Junkes, L., Mendlowicz, M. V., Shader, R., & Nardi, A. E. (2024). Leo Sternbach and the benzodiazepines 60 years on: A revolutionary treatment for anxiety disorders. *Pharmacological Research*, *207*, 107310.
5. Cheremnykh, K. P., Bryzgalov, A. O., Baev, D. S., Borisov, S. A., Sotnikova, Y. S., Savelyev, V. A., ... & Shults, E. E.

(2023). Synthesis, pharmacological evaluation, and molecular modeling of lappaconitine–1, 5-benzodiazepine hybrids. *Molecules*, *28*(10), 4234.

6. Kusuma, S., Patil, K. N., Srinivasappa, P. M., Chaudhari, N., Soni, A., Nabgan, W., & Jadhav, A. H. (2022). Ferrocene anchored activated carbon as a versatile catalyst for the synthesis of 1, 5-benzodiazepines via one-pot environmentally benign conditions. *RSC advances*, *12*(23), 14740-14756.

7. 7.Poonia, S. S., Prakash, O., & Choudhary, A. Adsorption Behavior of Lead (II) and Chromium (VI) by Chitosan Functionalized Iron Oxide-Biochar Composites in Single and Binary Metal Ion Systems.

8. Nitone, U., Mahida, J., & Agrawal, S. (2022). ONE-POT MCR REACTION VIA DIFFERENT BASE USED AS CATALYST ANDGLYCEROL AS A SOLVENT. *Rasayan Journal of Chemistry*, *15*(4).

9. Majid, S. A., Khanday, W. A., & Tomar, R. (2012). Synthesis of 1, 5-benzodiazepine and its derivatives by condensation reaction using H-MCM-22 as catalyst. *BioMed Research International*, *2012*

10. solvent free oxalic acid catalyzed synthesis of 1,5-benzodiazepinesaniket p. sarkate,a jaiprakash n. sangshetti,b nanasaheb b. dharbale,c ajinkya p. sarkate,d pravin s. wakte,a devanand b. shinde

11. Jeganathan, M., & Pitchumani, K. (2014). Solvent-Free syntheses of 1, 5-Benzodiazepines using HY Zeolite as a green solid acid catalyst. ACS Sustainable Chemistry & Engineering, 2(5), 1169-1176.

12. Jeganathan, M., & Pitchumani, K. (2014). 1. Singh, A., Palakollu, V., Pandey, A., Kanvah, S., & Sharma, S. (2016). Green synthesis of 1, 4-benzodiazepines over La 2 O 3 and La (OH) 3 catalysts: Possibility of Langmuir–Hinshelwood adsorption. *RSC Advances*, *6*(105), 103455-103462.

13. Jamatia, R., Gupta, A., Dam, B., Saha, M., & Pal, A. K. (2017). Graphite oxide: a metal free highly efficient carbocatalyst for the synthesis of 1, 5-benzodiazepines under room temperature and solvent free heating conditions. *Green Chemistry*, *19*(6), 1576-1585.

14. Harsha, K. B., Kavitha, C. V., Swaroop, T. R., Shobith, R., & Rangappa, K. S. (2021). A green synthesis of 1, 5-benzodiazepines using reusable-heterogeneous silica sulfuric acid catalyst under solvent-free conditions and their antileukemic activity. *Asian Journal of Chemistry*, *33*(5), 1006-1012.

15. Isaeva, V. I., Timofeeva, M. N., Panchenko, V. N., Lukoyanov, I. A., Chernyshev, V. V., Kapustin, G. I., ... & Kustov, L. M. (2019). Design of novel catalysts for synthesis of 1, 5-benzodiazepines from 1, 2-phenylenediamine and ketones: NH2-MIL-101 (Al) as integrated structural scaffold for catalytic materials based on calix [4] arenes. *Journal of Catalysis*, *369*, 60-71.

16. Kusuma, S., Patil, K. N., Srinivasappa, P. M., Chaudhari, N., Soni, A., Nabgan, W., & Jadhav, A. H. (2022). Ferrocene anchored activated carbon as a versatile catalyst for the synthesis of 1, 5-benzodiazepines via one-pot environmentally benign conditions. *RSC advances*, *12*(23), 14740-14756.

17. Fereydooni, M., Ghorbani-Vaghei, R., & Alavinia, S. (2025). An economical synthesis of benzodiazepines using ACT@ IRMOF core–shell as a potential eco-friendly catalyst through the activated carbon of thymus plant (ACT). *Nanoscale Advances*.

18. Singh, R. K., Sharda, S., Sharma, S., Kumar, S., & Prasad, D. N. (2020). Multicomponent catalytic synthesis of 1, 5-benzodiazepines: an update. *Mini-Reviews in Organic Chemistry*, *17*(4), 465-484.

19. A. P. Singh and A. Singh, Advanced Organic Chemistry Letters, 2016, 3(1), 1–3; R. E. Reeves, J. Am. Chem. Soc., 1951, 73, 957–959..

20. Mahida, J., & Patel, R. B. (2019). Application of Silica Supported Aluminium Hydroxide as a Low Cost Green Catalyst for the One Pot MCR Sythesis via Thermal Method. *Journal of Drug Delivery and Therapeutics*, *9*, 43-47.

21. Mahida, J., & Patel, R. B. Green Reusable Catalyst For The Formation Diastereo Selective Synthesis Of Cyclohexanones By Condensation Reaction Acetoacetanilide With Different Aromatic Aldehydes At Variety Method Of Reaction.