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Catalyst-free synthesis of benzodiazepines and benzimidazoles using glycerol as recyclable solvent

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ABSTRACT

We described herein the use of glycerol as solvent in the catalyst-free synthesis of benzodiazepines and benzimidazoles. This simple and efficient method furnishes the corresponding 1-*H*-1,5-benzodiazepines and 1,2-disubstituted benzimidazoles in good yields by the condensation of *o*-phenylenediamine with several ketones and aldehydes, respectively. In addition, glycerol can be easily re-utilized for further condensation reactions up to four times without lost of activity.

Benzodiazepines and benzimidazoles represent a significant class of biologically active nitrogen compounds and exhibit a number of important biological properties,[1,2] such as anticonvulsant, antianxiety, antiinflammatory, analgesic, hypnotic, antidepressive, antihistaminic, anti-ulcerative, antiallergic, and antipyretic. Their syntheses have received much attention in the field of medicinal and pharmaceutical chemistry.[1,2] For example, the use of 1-*H*-1,5-benzodiazepines has been extended to various diseases, such as cancer, viral infection, and cardiovascular disorders.[3] Benzimidazole derivatives are effective against the human cytomegalovirus (HCMV)[4] and are also efficient selective neuropeptide Y Y1 receptor antagonists.[5] In addition, the derivatives of benzodiazepines are used as dyes for acrylic fibers in photography[6] and benzimidazoles derivatives, because their great electron mobility, have been developed as layer materials for electron transport.[7]

Benzodiazepines and benzimidazoles are principally synthesized by the condensation of *o*-phenylenediamine with ketones[8] and aldehydes,[9] respectively, in the presence of conventional or Lewis acid catalysts. In these procedures, many reagents have been used, however, a number of these processes have some limitations, such as long reaction times, tedious work-up procedures and generation of by-products. Therefore, the search for a better reaction system for the synthesis of benzodiazepines and benzimidazoles in terms of mild reaction conditions, economic viability, and selectivity continues to attract the interest of synthetic organic chemists. In this context, synthesis of benzodiazepines and benzimidazoles using green solvents, such as, water and ionic liquids has been described.[10]

In organic synthesis, the choice of the solvent is a crucial step in a chemical reaction. The development of green methodologies from renewable resources has gained much interest recently because of the extensive uses of solvents in almost all of the chemical industries, and of the predicted disappearance of fossil oil.[11] The wanted characteristics for a green solvent include no flammability, high availability, obtaining from renewable sources, and biodegradability.[12] With the increase in biodiesel production worldwide, the market saturation of glycerol, a side product of biodiesel production, is inevitable.[13] The use of glycerol[14] and their eutetics[15] as a sustainable solvent for green chemistry were recently related. Heck and Suzuki cross-couplings, ring closing metathesis of diolefins, multicomponent reactions, asymmetrical reduction, and cycloisomerization of (*Z*)-enynols into furans, are some examples of the use of glycerol as solvent in organic reactions.[14]

The peculiar physical and chemical properties of glycerol, such as polarity, low toxicity, biodegradability, high boiling point, and ready availability from renewable feed stocks[16] prompted us to extend its use as a green solvent in organic synthesis. According to our interest in the green protocols in organic chemistry,[9f,17] we describe here the use of glycerol as green solvent in the catalyst-free synthesis of benzodiazepines and benzimidazoles by the condensation of *o*-phenylenediamine with several ketones and aldehydes (Scheme 1).

Initially, we reacted *o*-phenylenediamine **1** (1.0 mmol) with an excess of acetophenone **2a** (2.5 mmol) using glycerol as solvent at different temperatures to optimize the reaction conditions to access benzodiazepine **3a** (Table 1). When the reaction was

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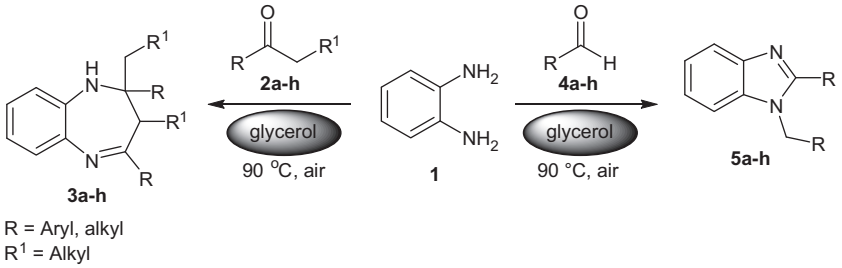
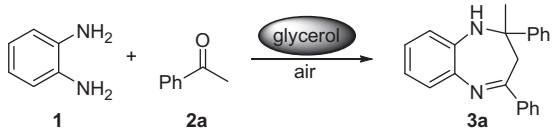


Scheme 1. General scheme of reaction.

Table 1
Reaction conditions optimization[a]



Entry	Temperature (°C)	Time (h)	Yield **3a**[b] (%)
1	rt	24	20
2	60	9	73
3	90	4	97
4[c]	90	4	96
5[d]	90	24	—
6[e]	Reflux	24	—

[a] Reactions are performed using of *o*-phenylenediamine **1a** (1.0 mmol), acetophenone **2a** (2.5 mmol) in glycerol (3 mL).
[b] Yields are given for isolated product.
[c] Reaction using 2.0 mmol of acetophenone **2a**.
[d] Reaction performed without glycerol.
[e] Reaction performed in ethanol.

Table 2
Synthesis of benzodiazepines **3a–h** using glycerol as solvent[a]

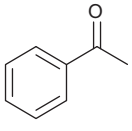
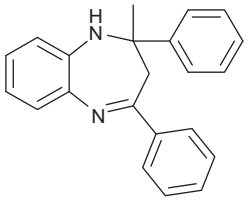
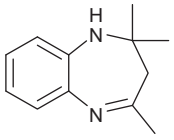
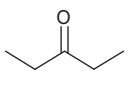
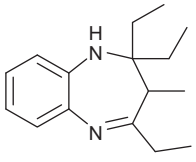
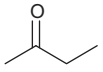
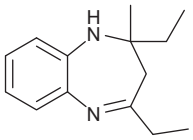
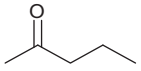
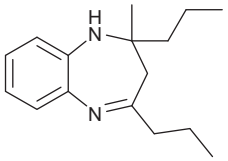
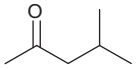
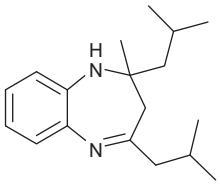
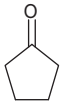
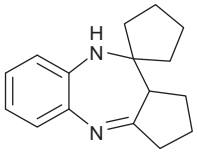
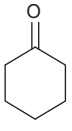
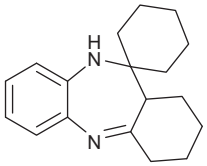
Entry	Ketone	Time (h)	Product Yield[b] (%)
1	 **2a**	4.0	 **3a** (96%)
2	 **2b**	8.0	 **3b** (45%)
3	 **2c**	4.5	 **3c** (92%)

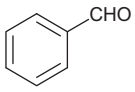
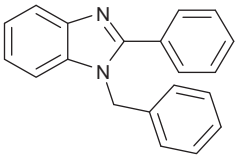
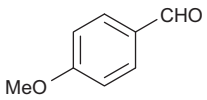
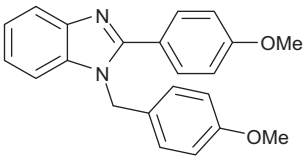
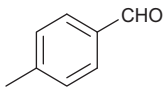
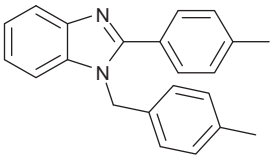
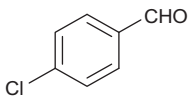
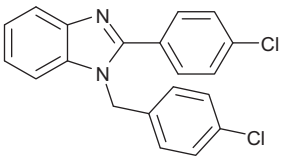
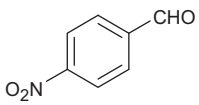
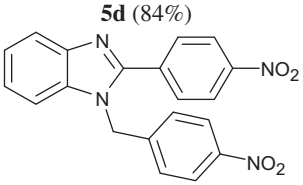
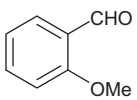
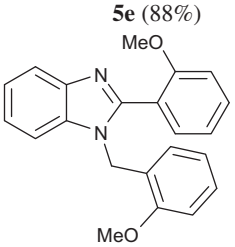
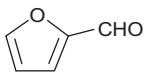
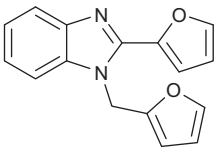
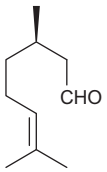
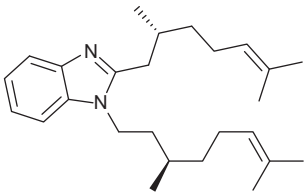
Table 2 (*continued*)

Entry	Ketone	Time (h)	Product Yield[b] (%)
4	 **2d**	5.0	 **3d** (85%)
5	 **2e**	5.0	 **3e** (84%)
6	 **2f**	7.0	 **3f** (80%)
7	 **2g**	6.0	 **3g** (89%)
8	 **2h**	5.5	 **3h** (72%)

[a] Reactions are performed using *o*-phenylenediamine **1a** (1.0 mmol), ketones **2a–h** (2.0 mmol) in glycerol (3 mL) at 90 °C.
[b] Yields are given for isolated product.

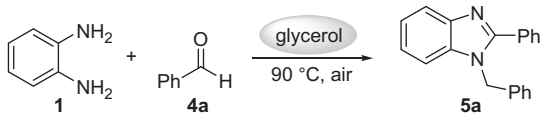
performed at room temperature, product **3a** was formed in low yield (Table 1, entry 1). To our satisfaction, by increasing the temperature, the reaction proceeds smoothly, and at 90 °C benzodiazepine **3a** was obtained in 97% (Table 1, entry 3). However, as a positive result, when the amount of acetophenone **2a** was reduced from 2.5 to 2.0 mmol, excellent yield of product **3a** was still obtained (Table 1, entry 4). It is also important to mention that when the reaction was performed without glycerol no product was

Table 3
Synthesis of benzimidazoles **5a–h** using glycerol as solvent[a]

Entry	Aldehyde	Time (h)	Product Yield[b] (%)
1	 **4a**	1.0	 **5a** (91%)
2	 **4b**	4.0	 **5b** (92%)
3	 **4c**	3.5	 **5c** (94%)
4	 **4d**	1.0	 **5d** (84%)
5	 **4e**	0.8	 **5e** (88%)
6	 **4f**	4.0	 **5f** (80%)
7	 **4g**	0.7	 **5g** (93%)
8	 **4h**	6.0	 **5h** (91%)

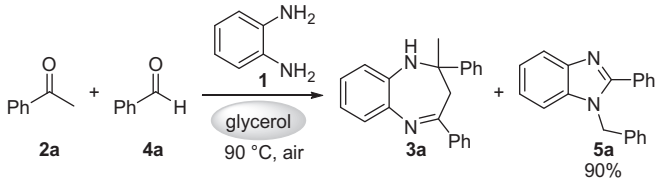
[a] Reactions are performed using *o*-phenylenediamine **1a** (1.0 mmol), aldehydes **4a–h** (2.0 mmol) in glycerol (3 mL) at 90 °C.
[b] Yields are given for isolated product.

Table 4
Reuse of glycerol in the synthesis of benzimidazole **5a**[a]



Run	Reaction time (h)	Yield **5a**[c] (%)
1	1.0	91
2[b]	1.0	91
3[b]	1.0	90
4[b]	1.5	89
5[b]	1.5	85

[a] Reaction is performed using *o*-phenylenediamine **1a** (1.0 mmol), acetophenone **2a** (2.0 mmol) in glycerol (3 mL) at 90 °C.
[b] Recovered glycerol was used.
[c] Yields are given for isolated products.



Scheme 2. Competitive condensation reaction in glycerol.

obtained (Table 1, entry 5). When we performed the reaction using other alcoholic solvents such as ethanol, no product **3a** was obtained (Table 1, entry 6). In an optimized reaction,[18] *o*-phenylenediamine **1** (1.0 mmol) was dissolved in glycerol (3 mL) and reacted with acetophenone **2a** (2.0 mmol) at 90 °C during 4 h, yielding benzodiazepine **3a** in 96% yield (Table 1, entry 4).

After reaction optimization, a study regarding the reuse of glycerol was performed. After the total consumption of reagents, the reaction mixture was diluted and extracted with a mixture of hexane/ethyl acetate 95:5 (3 × 3 mL). The upper phase was dried and the solvent evaporated. The inferior, glycerol phase, was dried under vacuum and directly reused.[19] Glycerol maintained its good level of efficiency even after being reused four times. The product **3a** was obtained in 96%, 96%, 96%, 91%, and 89% yields after successive cycles.

To demonstrate the generality of this method, we prepared a series of benzodiazepines **3a–h** using aryl, alkyl, and cyclic ketones (Table 2). In most cases, the reactions proceeded smoothly to give benzodiazepines **3a–h** in satisfactory yields. Symmetrical alkylketones **2b** and **2c** were suitable substrates for the reaction, and the respective products were obtained in satisfactory yields (Table 2, entries 2 and 3). Using unsymmetrical ketones, such as butan-2-one **2d**, pentan-2-one **2e** and 4-methylbutan-2-one **2f** as substrates, corresponding products **3d–f** were formed in good yields (Table 2, entries 4–6). It is interesting to note that the ring closure in these examples was selective from one side of the carbon chain giving a single product. Cyclic ketones **2g** and **2h** reacted to give the desired benzodiazepines **3g** and **3h** in excellent yields (Table 2, entries 7 and 8).

To extend the scope of our methodology, the possibility of the synthesis of benzimidazoles using glycerol as solvent was investigated. Thus, *o*-phenylenediamine **1** (1.0 mmol) was dissolved in glycerol (3 mL) and reacted with benzaldehyde **4a** (2.0 mmol) at 90 °C, and to our satisfaction benzimidazole **5a** was obtained in 91% isolated product yield (Table 3, entry 1). In view of this result, a variety of aryl aldehydes were condensed to corresponding benzimidazoles in good yields (Table 3, entries 2–6). Benzimidazoles containing electron donating (EDG) (Table 3, entries 2–3 and 6) and electron withdrawing groups (EWG) (Table 3, entries 4 and 5) at the benzene ring could be obtained in good yields. Excellent yield of condensation was achieved using furan-2-carbaldehyde **4g** (Table 3, entry 7). Finally, when we employed the naturally occurring aldehyde **4h**, the corresponding benzimidazole derived from (*R*)-citronellal **5h** was synthesized in 91% after 6 h (Table 3, entry 8).

After extending the scope of synthesis of benzimidazoles, we check the recyclability of glycerol in this reaction (Table 4). After completion of condensation, the reaction mixture was extracted with hexane/ethyl acetate (95:5) and the glycerol phase was dried and reused. It could then be reused for further catalytic reactions and the yields of benzimidazole **5a** after four recycles were almost the same without loss of solvent activity.

In order to investigate if glycerol could be used as a selective solvent, we carried out a competitive condensation reaction using *o*-phenylenediamine **1** (1.0 mmol) and an equimolar mixture of acetophenone **2a** (2.0 mmol) and benzaldehyde **4a** (2.0 mmol). After 12 h of reaction, only *o*-phenylenediamine **1** and benzaldehyde **4a** were totally consumed, and the product derived from *o*-phenylenediamine and benzaldehyde was formed exclusively and isolated in 90% yield (Scheme 2). The resulting acetophenone **2a** was recovered quantitatively.

In conclusion, we have presented here a simple, efficient, and catalyst-free methodology for the synthesis of benzodiazepines and benzimidazoles in good yields by the condensation of *o*-phenylenediamine with several ketones and aldehydes, respectively, using glycerol as solvent. Glycerol can be directly reused without previous purification for further condensation reactions.

Acknowledgments

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References and notes

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18. *General procedure for synthesis of benzodiazepines and benzimidazoles*: To a round-bottomed flask containing *o*-phenylenediamine **1** (1.0 mmol) and glycerol (3 mL) was added the appropriated carbonyl compound (2.0 mmol). The reaction mixture was allowed to stir at 90 °C for the time indicated in Tables 2 and 3. After that, the reaction mixture was washed with a mixture of hexane/ethyl acetate 95:5 (3 × 3 mL) and the upper organic phases were separated from glycerol, dried with $MgSO_4$, and evaporated under reduced pressure. The product was isolated by column chromatography using hexane or hexane/ethyl acetate as eluent. All the compounds were characterized by comparison of their mp and ^{1}H NMR spectra with literature. Selected spectral data for: *2-Methyl-2,4-diphenyl-2,3-dihydro-1H-1,5-benzodiazepine* (**3a**): White solid: mp 149–151 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56–7.62 (m, 4H), 7.17–7.39 (m, 7H), 7.03–7.09 (m, 2H), 6.82–6.86 (m, 1H), 3.52 (br s, 1H, NH), 3.14 (dd, 1H, J = 13.0, 4.4), 2.97 (dd, 1H, J = 13.0, 4.4), 1.76 (sd, 3H, J = 4.3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.6, 147.6, 140.1, 139.5, 138.0, 129.7, 128.6, 128.3, 127.9, 127.0, 126.3, 125.4, 121.6, 121.4, 73.7, 43.0, 29.8. IR (KBr) (cm^{-1}): 3452, 1633, 1597. MS(EI): m/z (% relative intensity) = 312 (M^+, 6), 297 (16), 194 (100), 103 (17), 77 (14). *1-Benzyl-2-phenyl-1H-1,3-benzimidazole* (**5a**): White solid: mp 132–133 °C. ^{1}H NMR (100 MHz, $CDCl_3$) δ (ppm) 7.85–7.89 (m, 1H), 7.68–7.71 (m, 2H), 7.41–7.46 (m, 3H), 7.26–7.31 (m, 4H), 7.18–7.22 (m, 2H), 7.05–7.10 (m, 2H), 5.42 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 153.7, 142.7, 136.0, 135.6, 129.6(3), 129.6(0), 128.9, 128.7, 128.4, 127.4,125.6, 122.7, 122.3, 119.5, 110.3, 47.9. IR (KBr) (cm^{-1}): 3031, 2947, 1452, 1348, 1162, 967, 697. MS (EI): m/z (% relative intensity) = 284 (M^+, 52), 207 (3), 180 (2), 92 (8), 91 (100), 77 (5), 65 (9).
19. *Recycle of glycerol*: The aforementioned procedure for condensation reaction was used with *o*-phenylenediamine **1** (1.0 mmol), appropriated carbonyl compound (2.0 mmol), and glycerol (3 mL). After the reaction was complete, the reaction mixture was washed with a mixture of hexane/ethyl acetate (95:5) (3 × 3 mL) and the upper organic phases were separated from glycerol. The product was isolated according procedure above. The glycerol was dried under vacuum and reused for further reactions without previous purification.