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# CATALYST-FREE SYNTHESIS OF FURANO- AND PYRANOQUINOLINES BY USING GLYCEROL AS RECYCLABLE SOLVENT

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**Abstract**
We describe the use of glycerol as an efficient, safe and recyclable solvent in the one-pot imino Diels–Alder reaction of aldehydes, amines, and cyclic enol ethers to afford corresponding furano- and pyranoquinolines in excellent yields under mild conditions.

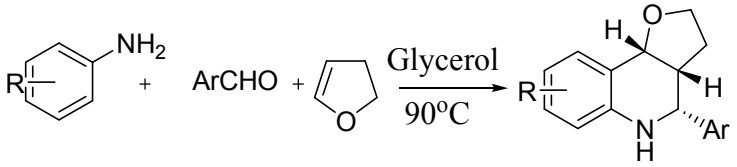
**Keywords**: Glycerol, imino Diels-Alder reaction, furano- and pyranoquinolines.

## Introduction

The development of green methodologies from renewable resources has gained much interest because of the extensive uses of solvents in chemical industries[i-vi]. Glycerol is a non-toxic, biodegradable and recyclable liquid that is highly inert, stable and also dissolves organic compounds that are poorly miscible in water. It has many advantages like low toxicity, low price, wide availability, highly boiling point and low vapour pressure[vii, viii]. These advantages make glycerol ideal sustainable solvent in organic synthesis[ix-xix].
On the other hand, Furano- and pyranoquinolines possess a wide spectrum of biological activities such as psychotropic, anti-allergic, anti-inflammatory, and estrogenic activity[xx, xxi]. Generally, they are prepared by means of imino Diels–Alder reaction[xxii-xlvii]. However, some of them require strongly acidic conditions, unsatisfactory yields, require dry reaction conditions, and also involve tedious product-isolation procedures. Therefore, the development of mild, convenient, and efficient procedure would extend the scope of this methodology to synthesis of highly functionalized quinoline derivatives. As part of our ongoing research, herein we report, a simple and efficient process for the synthesis of furano and pyranoquinolines under catalyst-free conditions using glycerol as recyclable reaction medium.

## Results and Discussion

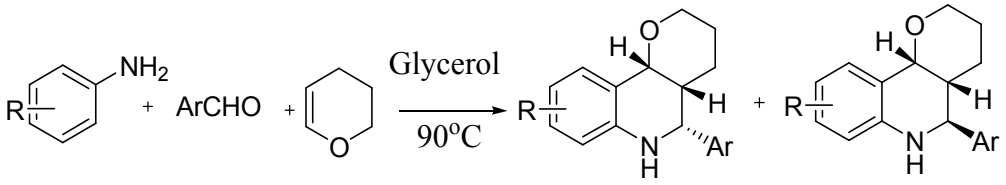
In a first attempt the reaction of aniline and benzaldehyde with 2, 3- dihydrofuran(DHF) in glycerol as solvent to access the furanoquinoline **3a** was studied at different temperatures. At room temperature, no reaction was observed after stirring for 24 h. Increase of the reaction temperature to 90$^{o}$C the respective furanoquinoline **3a** was obtained with a yield of 91%.




3a-3f

**Scheme 1**. Synthesis of furano tetrahydroquinolines

Several aromatic aldehydes and anilines reacted successfully with 2, 3-dihydrofuran in glycerol at 90°C to afford the corresponding furanoquinolines in excellent yields (Table 1). In all the cases, the products were obtained exclusively as endo-isomers (Scheme 1). Like dihydrofuran, 3,4-dihydro-2H-pyran (DHP) also reacted effectively with aromatic aldehydes and anilines under similar conditions to provide pyranoquinolines in excellent yields (Scheme 2). In the case of 3, 4-dihydro-2H-pyran, the products were obtained as a mixture of endo- and exo-isomers, favouring endo-diastereomers . Enhanced reaction rates, excellent yields, and high *cis*-selectivity are the features observed in this protocol. After completion of reaction, the reactants were extracted with ethyl acetate and the glycerol was used for further reactions without any problem.




major
4g-4n

minor
5g-5n

**Scheme 2.** Synthesis of pyrano tetrahydroquinolines

**Experimental**

Melting points were recorded on Buchi R-535 apparatus. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr disk. $^1$H-NMR Spectra were recorded on Gemini-200 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

**General procedure:** 3, 4-Dihydro-2H-pyran or 2, 3-dihydrofuran (1.5 mmol) was added to a mixture of aldehyde (1 mmol) and aryl amine (1 mmol) in glycerol (3 mL). The mixture was stirred at 90°C. After completion of the reaction as indicated by TLC, ethyl acetate (2x10 mL) was added and stirred well. The ethyl acetate layer was separated by simple decantation. The ethyl acetate extract was washed with brine, dried over $Na_2SO_4$ and concentrated under reduced pressure. The crude compound was purified by column chromatography using silica gel 60-120 mesh. All the pure products were identified by their spectroscopy data.

**Spectral data for selected compounds**

***Cis*-4-Phenyl-2, 3, 3a, 4, 5, 9b-hexahydrofuro 3, 2-c. quinoline (3a):** Solid, m.p. 92-95 $^0$C (lit-95$^0$C[(xxix)]),IR (KBr): ν 3322, 3026, 2974, 2877, 1608, 1489, 1453, 1362, 1365, 1337, 1297, 1259, 1062, 1031, 994, 920, 756 cm$^{-1}$; $^1$H NMR ($CDCl_3$). δ 1.52-1.57 (m, 1H), 2.20-2.30 (m, 1H), 2.70-2.80 (m, 1H), 3.75-3.85 (m, 3H), 4.72 (d, 1H, *J* = 2.8 Hz), 5.24 (d, 1H, *J* = 8.0 Hz), 6.56 (d, 1H, *J* = 8.0 Hz), 6.81 (t, 1H, *J* = 8.0 Hz), 7.03 (t, 1H, *J* = 8.0 Hz), 7.35-7.55 (m, 6H) ; EIMS *m/z*: 251 m$^+$, 207, 174, 130, 117, 91, 71, 43.

***Cis*-4-(4-fluorophenyl)-8-methoxy-2, 3, 3a, 4, 5, 9b-hexahydrofuro 3, 2-*c*. quinoline (3e):** Solid, m.p. 135-138 $^0$C. (lit-136-138 $^0$C[(xxvii)]), IR (KBr): ν 3014, 1662, 1577, 1503, 1220, 1108, 1036, 1012, 986, 864, 812, 726 cm$^{-1}$; $^1$H NMR ($CDCl_3$). δ 1.33-1.55 (m, 1H), 2.09-2.25 (m, 1H), 2.57-2.76 (m, 1H), 3.62-3.80 (m, 3H), 3.76 (s, 3H), 4.63 (d, 1H, *J* = 2.8Hz), 5.20 (d, 1H, *J* = 8.0 Hz), 6.46 (d, 1H, *J* = 8.4 Hz), 6.70 (dd, 1H, *J* = 8.4 & 2.8 Hz), 6.90 (d, 1H, *J* = 2.8 Hz), 7.00-7.10 (m, 2H), 7.20-7.30 (m, 2H); EIMS *m/z*: 299 m$^+$, 272, 255, 205, 150, 109, 77, 51, 43.

***cis*-9-Methyl-5-phenyl-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano3,2-*c*.quinoline (4k)**: White solid m.p. 129-130$^o$C; (lit-129-130$^o$C[(xxxvii)]), IR (KBr): ν 3374, 2924, 2855, 1733, 1619, 1503, 1457, 1375, 1348, 1305, 1270, 1070, 910, 812, 703 cm$^{-1}$; 1H NMR (200 MHz, $CDCl_3$): δ 1.14-1.26 (m, 1H), 1.30-1.60 (m, 3H), 2.02-2.12 (m, 4H), 3.36 (dt, *J* = 11.4, 2.7 Hz, 1H), 3.48 (dd, *J* = 11.4, 2.7 Hz, 1H), 3.54 (brs, NH, 1H), 4.62 (d, *J* = 2.7 Hz, 1H), 5.24 (d, *J* = 5.6 Hz, 1H), 6.50 (d, *J* = 8.0 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 7.25-7.42 (m, 6H); EIMS *m/z*: 279 M+, 247, 221, 194, 175, 145, 98, 91, 92,57.

***trans*-9-Methyl-5-phenyl-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano3,2-*c*.quinoline (5k):** Pale yellow oil; IR (KBr): ν 3332, 2931, 2835, 1622, 1509, 1453, 1361, 1316, 1258, 1064, 1032, 907, 815, 701 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): δ 1.30-1.42 (m, 1H), 1.42-1.52 (m, 1H), 1.58-1.70 (m, 1H), 1.80- 1.94 (m, 1H), 2.02-2.14 (m, 4H), 3.72 (dt, *J* = 11.5, 2.4 Hz, 1H), 3.90 (brs, NH, 1H), 4.14 (dd, *J* = 11.5, 2.4 Hz, 1H), 4.34 (d, *J* = 2.8 Hz, 1H), 4.64 (d, *J* = 10.5 Hz, 1H), 6.40 (d, *J* = 8.0 Hz, 1H), 6.96 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.00 (d, *J* = 1.2 Hz, 1H), 7.32-7.48 (m, 5H). EIMS *m/z*: 279 M+, 235, 221, 194, 175, 145, 98, 91, 43.

***cis*-5-(4-Chloro-phenyl)-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano3,2-*c*.quinoline(4n):** White solid, m.p. 167-170$^o$C (lit-169-170$^o$C[(xxxvii)]); IR (KBr): ν 3321, 3024, 2925, 2854, 1740, 1608, 1484, 1371, 1274, 1214, 1089, 927, 753 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): δ 1.20-1.36 (m, 1H), 1.42-1.63 (m, 3H), 2.08-2.20 (m, 1H), 3.43 (dt, *J* = 11.5, 2.5 Hz, 1H), 3.62 (dd, *J* = 11.5, 2.5 Hz, 1H), 3.78 (brs, NH, 1H), 4.72 (d, *J* = 2.8 Hz, 1H), 5.28 (d, *J* = 5.7 Hz, 1H), 6.62 (d, *J* = 8.2 Hz, 1H), 6.80 (t,*J* = 7.9 Hz, 1H), 7.12 (t, *J* = 7.9 Hz, 1H), 7.30-7.48 (m, 5H); EIMS *m/z*: 299 M+, 268,240, 211, 105, 91, 85, 57.

***trans*-5-(4-Chloro-phenyl)-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano3,2-*c*.quinoline (5n):** White solid, m.p.121-123$^o$C (lit-121-123$^o$C[(xxxvii)]); IR (KBr): ν 3386, 2925, 2854, 1897, 1739, 1601, 1315, 1271, 1085, 1011, 839, 747, 703 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): δ 1.22-1.50 (m, 2H), 1.58-1.72 (m, 1H), 1.82-1.90 (m, 1H), 1.98-2.10 (m, 1H), 3.73 (dt, *J* = 11.5, 2.5 Hz, 1H), 3.92 (brs, NH, 1H), 4.05- 4.08 (m, 1H), 4.36 (d, *J* = 2.7 Hz, 1H), 4.72 (d, *J* = 10.8 Hz, 1H), 6.48 (d, *J* = 8.2 Hz, 1H), 6.72 (t, *J* = 8.0 Hz, 1H), 7.12 (t, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 8.2 Hz, 1H), 7.28-7.40 (m 4H); EIMS *m/z*: 299 M+, 297, 240, 211, 203, 166, 125, 111, 97, 85, 71, 57, 43.

## Conclusion

In summary, It was shown that glycerol can be used as an efficient green solvent for the catalyst-free imino Diels–Alder reaction between aldehydes, amines, and cyclic enol ethers to afford furano- and pyranoquinolines. The reactions proceed easily even in the absence of any acid catalyst. The present method offers significant advantages such as mild reaction conditions, no catalyst, high conversions, cleaner reaction profiles, recyclability of the solvent and excellent yields.

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**Table 1.** Glycerol promoted synthesis of furano- and pyranoquinolines.

| S.No. | R | Ar | olefin | product | time(h) | yield(%) | exo:endo |
|---|---|---|---|---|---|---|---|
| A | H | $C_6H_5$ | 2,4-DHF | 3a | 2.5 | 91 | - |
| B | 3,5-$(MeO)_2$ | 4-$FC_6H_4$ | 2,4-DHF | 3b | 3.0 | 87 | - |
| C | H | 4-$MeOC_6H_4$ | 2,4-DHF | 3c | 2.5 | 90 | - |
| D | 4-Me | 4-$ClC_6H_4$ | 2,4-DHF | 3d | 3.0 | 85 | - |
| E | 4-MeO | 4-$FC_6H_4$ | 2,4-DHF | 3e | 3.5 | 82 | - |
| F | H | 4-$FC_6H_4$ | 2,4-DHF | 3f | 3.0 | 92 | - |
| G | H | $C_6H_5$ | 2,4-DHP | 4g : 5g | 2.6 | 90 | 92:8 |
| H | 4-MeO | $C_6H_5$ | 2,4-DHP | 4h : 5h | 3.0 | 90 | 86:14 |
| I | 2-Me | $C_6H_5$ | 2,4-DHP | 4i : 5i | 2.8 | 87 | 85:15 |
| J | 4-F | $C_6H_5$ | 2,4-DHP | 4j : 5j | 3.2 | 86 | 85:15 |
| K | 4-Me | $C_6H_5$ | 2,4-DHP | 4k : 5k | 3.5 | 86 | 87:13 |
| L | 1-Napthyl | $C_6H_5$ | 2,4-DHP | 4l : 5l | 3.6 | 82 | 82:18 |
| M | 1-Napthyl | 4-$FC_6H_4$ | 2,4-DHP | 4m : 5m | 4.0 | 81 | 80:20 |
| N | H | 4-$ClC_6H_4$ | 2,4-DHP | 4n : 5n | 3.8 | 85 | 86:14 |

a: Isolated and unoptimized yields.
b: Separated using column chromatography.

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