International Journal of Chemical and Biological Sciences

E-ISSN: 2664-6773
P-ISSN: 2664-6765
Impact Factor: RJIF 5.72
IJCBS 2025; 7(2): 64-68
www.chemicaljournal.org
Received: 12-06-2025
Accepted: 18-07-2025

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1, 4-diazabicyclo [2.2.2] octane (DABCO) catalyzed one-pot three-component synthesis of polyhydroquinoline derivatives

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DOI: https://www.doi.org/10.33545/26646765.2025.v7.i2a.150

Abstract

The study investigates the synthesis of substituted quinoline derivatives known for their biological activities and structural versatility which serve as pivotal building blocks in organic synthesis. A series of substituted quinoline derivatives were synthesized by one-pot three-component cyclocondensation between substituted aldehyde, dimedone, ethylacetoacetate and ammonium acetate in presence of 1, 4-diazabicyclo [2.2.2] octane (DABCO) by conventional reflux in ethanol for 8 hrs. The newly synthesized compounds were characterized by ^{1}HNMR, ^{13}CNMR and mass spectra. The reaction proceeds via Knoevenagel condensation, Michael addition and intramolecular cyclization. The used techniques provides the practical benefits of facile isolation, high yields and cascading one pot condensation.

Keywords: Knoevenagel condensation, substituted quinoline derivatives, 1,4-diazabicyclo[2.2.2]octane (DABCO)

Introduction

The majority of Multicomponent reactions (MCRs) follow a convergent reaction pathway, where two or more starting elements reacts in a single pot to generate a single product without the need of any intermediary synthesis [1]. Multicomponent reactions are crucial to organic chemistry because of their high yields, perfect atom economy, convergence, exploratory power that makes some heterocyclic compounds simple to synthesize and their numerous uses in combinatorial synthesis [2-4]. The quinoline core has drawn a lot of interest from chemists and biologists in this sector as one of the fundamental building blocks for many medicinal drugs. Quinoline is one of the many nitrogen heterocycles and a scaffold that is very significant for application in biomedicine. Chemists and biologists working in this sector are very interested in the quinoline core because it is one of the fundamental building blocks for many medicinal drugs.

Numerous quinoline derivatives with diverse biological activity have been obtained from natural resources or synthesized. It is commonly recognized that compounds containing quinoline have a wide range of medicinal applications including effects against cancer [5], inflammation [6], bacteria [7], viruses [8], and tuberculosis [9-11]. Quinoline nucleus containing some of the anticancer drugs is available in market those are foretinib [12] Figure 1 and cabozantinib [13] Figure 2.

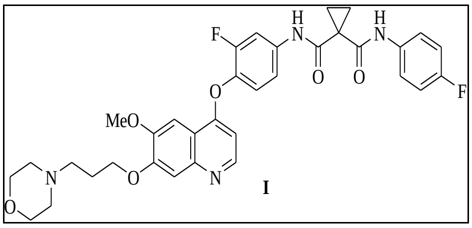


Fig 1: Chemical structure of Foretinib, a quinoline-based anticancer drug.

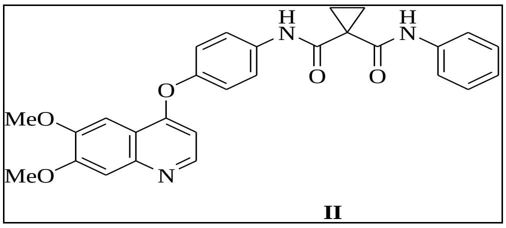


Fig 2: Chemical structure of Cabozantinib, another quinoline derivative used as an anticancer agent.

Numerous techniques for the synthesis of derivatives of polyhydroquinolines have been reported.

The process of cyclocondensation of aldehyde, β-ketoester, and ammonia in acetic acid at room temperature or refluxing in alcohol for a longer time is the usual method used to synthesize 1,4-dihydropyridines [14-15]. Molecular iodine was used to illustrate the utilization of cyclic 1,3-diketone in the Hantzsch process for the synthesis of polyhydroquinoline [16-17], TMS-NaI [18] and expensive metal triflates such as $Yb(OTF)_3$, $Se(OTF)_3$ [19-20], Cerium (IV) ammonium nitrate [21], HY-zeolite [22] and ionic liquid [23].

These techniques have their limitations nevertheless, by the need for costly metal precursors, high reaction temperatures, environmentally hazardous catalysts, and lengthy reaction times. As a result, research is currently being conducted to develop straightforward and effective procedures for producing polyhydroquinoline derivatives, and there is room for additional development that could involve softer reaction conditions and higher product yields.

A inexpensive, non-toxic, and readily available catalyst called DABCO (1, 4-diazabicyclo[2.2.2]octane) has been used widely in the synthesis of fused heterocyclic compounds. The field of Multicomponent reactions has increased its importance in the last few years because of novelty of concept, efficiency and selectivity in many reactions, which meet the standards of well-established framework. The wide range of examples demonstrates how Multicomponent reactions have become their own field in recent years. A cage-like molecule with moderate basic characteristics and medium impediment, DABCO (1,4-diazabicyclo[2.2.2]octane) is commonly utilized in chemical synthesis [24] Figure 3.

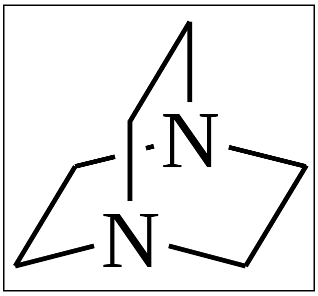


Fig 3: Structure of 1,4-diazabicyclo[2.2.2]octane (DABCO), a cage-like organic base catalyst.

1,4-Diazabicyclo [2.2.2] octane (DABCO), one of the organ catalysts, works well as a solid catalyst in a variety of processes. In several processes used in the production of heterocycles, it also functions well as a base and nucleophile. A wide variety of reactions, including ring opening, cycloaddition, coupling, Henry, and Baylis-Hillman reactions, are catalyzed by DABCO.

Materials and Methods.

All chemicals and solvents were purchased commercially and used exactly as supplied. Melting points were determined in open capillary and are uncorrected. Using CDCl3 solvent, NMR spectra were obtained at 500 MHz using a BrukerAvance III HD.

General procedure for the synthesis of 1, 4-dihydropyridnes and polyhydroquinoline

DABCO (5 mol%) was added to a mixture of 1 mmol of Benz aldehyde, 1 mmol of dimedone, 1 mmol of ethyl acetoacetate, and 1 mmol of ammonium acetate in 10 mL of ethanol. After refluxing the reaction mixture for almost eight hours, a solid product started to form. TLC was used to track the reaction's development. Under lower pressure, the solid vaporised once the reaction was finished. Through recrystallisation from ethanol and water, the pure product was refined.

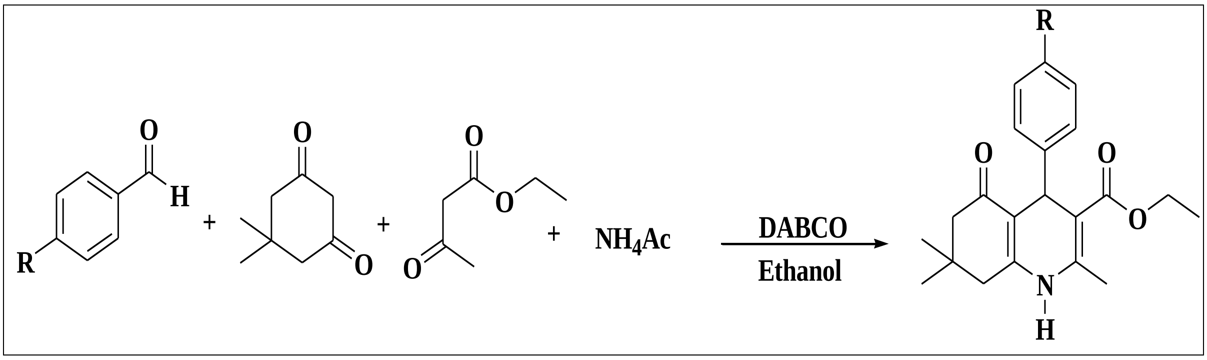


Fig 4: General reaction scheme for the synthesis of polyhydroquinoline derivatives catalyzed by DABCO.

Results and Discussion

The reaction between aldehyde, dimedone, ethyl acetoacetate, and ammonium acetate at room temperature has been regarded as a standard model reaction in a search for an effective solid acid catalyst. Initially, the model reaction in ethanol has been used to screen a number of catalysts (table I). It was discovered that the ideal catalyst in these conditions was DABCO.

Optimization of reaction conditions

Initially, the model reaction was carried out in a solvent-free condition to determine the efficiency of various solvents; this resulted in a poor yield of the desired product. Every single time, the substrate was combined with 5 mol% DBU and agitated with 8-10 millilitres of solvent. Table 2 shows that EtOH produced the highest yield of all these solvents; as a result, EtOH was chosen as the ideal solvent.

Table 1: Effect of various catalysts on synthesis of polyhydroquinoline

Entry	Catalyst	Time (h)	Yield (%) [b]
1	No Catalyst	24	22
2	K_2CO_3	18	36
3	Trimethyl amine	18	45
4	Morpholine	18	52
5	Pyridine	12	54
6	DBU	12	58
7	CAN	12	67
8	L-Proline	12	78
9	I_2	12	82
10	DABCO	6	92

[a]**Reaction conditions:** Benzaldehyde (1mmol), dimedone (1mmol), ethyl acetoacetate (1mmol), ammonium acetate (1mmol), various catalysts were stirred at room temp, [b]Isolated Yield

Table 2: Solvent effect for the synthesis

Entry	Solvent	Time (h)	Yield (%)
1	Ethanol	8	92
2	Methanol	8	89
3	Acetonitrile	8	81
4	t-BuOH	10	60
5	1,4-Dioxane	10	58
6	Toluene	18	45
7	DCM	18	40
8	cyclohexane	18	30

[a]**Reaction conditions:** Benzaldehyde (1mmol), dimedone (1mmol), ethyl acetoacetate (1mmol), ammonium acetate (1mmol), various catalysts were stirred at room temp, [b]Isolated Yield

Optimization of catalyst loading

We studied the model reaction using different concentrations of DABCO to determine the role of catalyst in the synthesis of polyhydroquinoline. The yield of the product was extremely poor in the absence of catalyst, but it significantly increased once catalyst was added, demonstrating the catalyst's critical role in the synthesis of polyhydroquinolines. Table 3 shows that as catalyst concentration increases to 15 mol%, product yield increases as well.

Table 3: Optimization study for the amount of DABCO as catalyst[a]

Entry	Catalyst (mol%)	Time (h)	Yield%[b]
1	0	8	10
2	2	8	30
3	5	8	45
4	10	8	65
5	15	8	92

[a]**Reaction conditions:** Benzaldehyde(1mmol), dimedone (1mmol), ethyl acetoacetate (1mmol), ammonium acetate (1mmol), various catalysts were stirred at room temp, [b]Isolated Yield

Spectral analysis

Ethyl-4-(4-chlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydrquinoline-3-carboxylate: MP: 243-245 °C; **IR(KBr):** 3276, 3199, 3077, 2964, 1716, 1738 cm^{-1}; ^{1}H-NMR: (500MHz, DMSO, δppm) δ=0.94 (s, 3H) 1.08 (s,3H), 1.18 (t,3H), 2.12-2.34 (m,4H), 2.37(s, 3H), 4.04(q, 2H), 5.04(s, 1H), 7.15-7.19(d, 2H), 7.24-7.26(d, 2H); ^{13}CNMR: (DMSO, 125MHz, ppm) δ=12.09, 18.0, 25.8, 28.1, 31.3, 34.9, 39.6, 49.4, 58.6, 104.4, 110.4, 126.4, 128.1, 130.3, 142.4, 144.3, 147.2, 165.9, 194.3

Ethyl-4-(4-hydroxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydrquinoline-3-carboxylate: MP: 232-233 °C; IR(KBr): 3331, 3132, 1718, 1737, 1495, 1234, 730 cm^{-1}; ^{1}**H-NMR:** (500MHz, DMSO, δppm) δ=0.94 (s, 3H) 1.08 (s, 3H), 1.20 (t, 3H), 2.08-2.18 (m, 4H), 2.20-2.35(s, 3H), 4.07(q, 2H), 4.98(s, 1H), 6.65(d, 2H),7.16(d, 2H); ^{13}CNMR: (DMSO,125MHz, ppm) δ=15.1, 19.1, 19.1, 27.4, 33.4, 36.7, 41.1, 51.7, 54.9, 60.2, 106.2, 112.6, 115.5, 130.1, 131.3, 140.4, 145.3, 149.7, 156.6, 168.4, 195.3.

Ethyl-4-(4-methoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydrquinoline-3-carboxylate: MP: 260-261 °C; IR(KBr): 3292, 3224, 3087, 2958, 1716, 1735, 1491 cm^{-1}; ^{1}H-NMR: (500MHz, DMSO, δppm) δ=0.94 (s, 3H) 1.07 (s, 3H), 1.21 (t, 3H), 2.13-2.36 (m, 4H), 3.74(s, 3H), 4.06(q, 2H), 5.00(s, 1H), 6.74(d, 2H),7.22(d, 2H); ^{13}CNMR: (DMSO, 125MHz, ppm) δ=14.2, 19.4, 27.1, 29.4, 32.6, 35.6, 41.1, 50.7, 55.1, 59.7, 106.3, 112.4, 113.2, 128.9, 139.5, 139.5, 143.1, 147.7, 157.7, 167.4, 195.5.

Ethyl-4-(4-nitrophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydrquinoline-3-carboxylate: MP: 240-242 °C; IR(KBr): 3506, 3285, 3193, 2447, 1720, 1740, 1518, 1484, 1306, 1284, 1166, 870, 755 cm^{-1}; ^{1}H-NMR: (500MHz, DMSO, δppm) δ=0.89 (s, 3H) 1.09 (s, 3H), 1.08 (t, 3H), 2.05-2.25 (m, 4H), 2.37(s, 3H), 4.00(q, 2H), 5.05(s, 1H), 7.42(d, 2H),8.05(d, 2H); ^{13}CNMR: (DMSO, 125MHz, ppm) δ=12.9, 18.1, 25.7, 28.1, 31.4, 35.7, 39.5, 49.3, 58.7, 103.7, 109.7, 119.9, 121.5, 127.3, 133.5, 143.4, 146.9, 148.1, 165.7, 194.3.

Synthesis of various polyhydroquinoline derivatives

To perform the Hantzsch reaction with a catalytic quantity of DABCO in room temperature ethanol, a range of aromatic aldehydes were used. Table 4 provides an overview of the study's results.

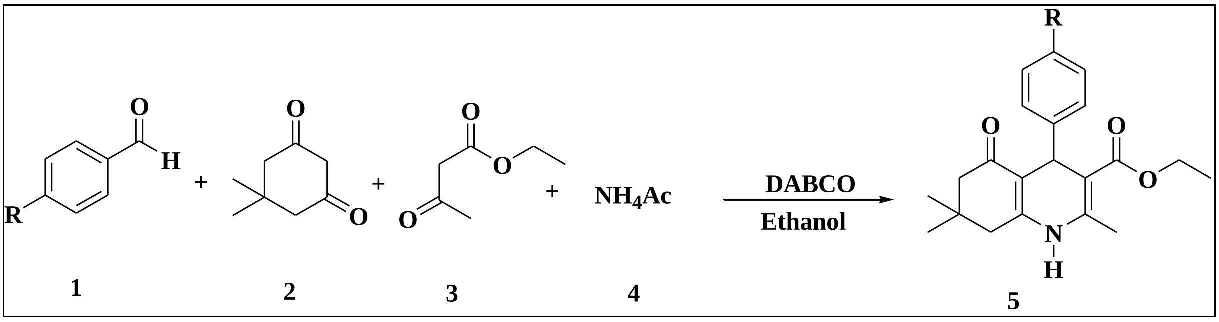
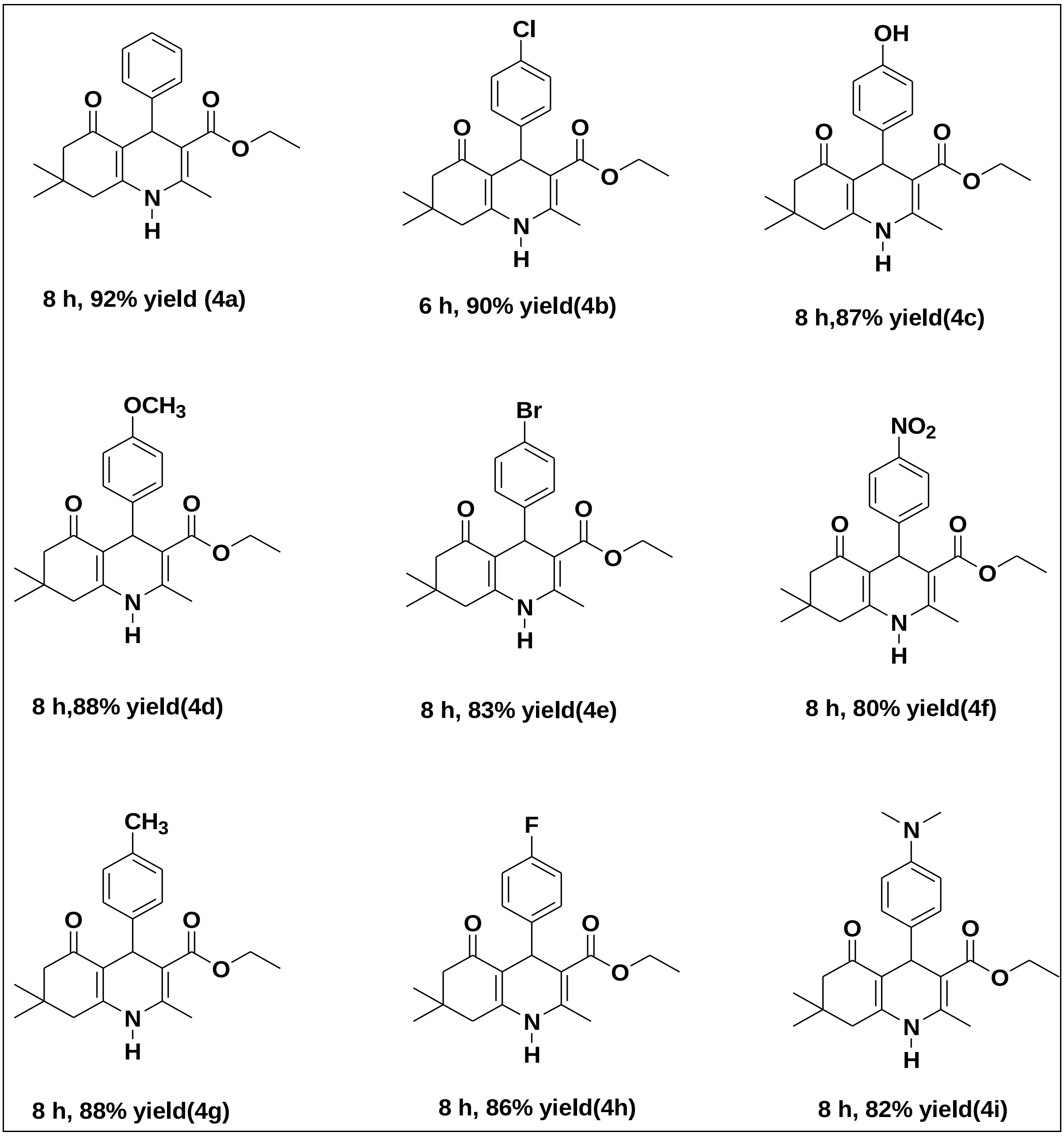


Fig 5: Hantzsch reaction pathway for the preparation of polyhydroquinoline derivatives using aromatic aldehydes and DABCO



8 h, 92% yield (4a)

6 h, 90% yield(4b)

8 h,87% yield(4c)

8 h,88% yield(4d)

8 h, 83% yield(4e)

8 h, 80% yield(4f)

8 h, 88% yield(4g)

8 h, 86% yield(4h)

8 h, 82% yield(4i)

Fig 6: Structures and yields of various synthesized polyhydroquinoline derivatives (4a–4i)

Conclusion

To sum up, we were able to create a simple and effective procedure for creating a range of derivatives of polyhydroquinolines. The use of effective, ecologically safe, commercially accessible DABCO as a catalyst in the synthesis of polyhydroquinoline derivatives in good yield is noteworthy, as is the catalytic activity of this extraordinary material. In comparison to methods documented in literature, the current approach offers numerous benefits, such as quick reaction times, comfortable conditions, elevated yields, and effortless setup.

Acknowledgement

Authors are thankful to Central instrumental facility, Savitribai Phule University Pune for structural characterization and Department of Chemistry, Sant Dnyaneshwar Mahavidyalaya, Soegaon, Chhatrapati Sambhajinagar.

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