Lithium Perchlorate/Diethylether Catalyzed Aza-Diels-Alder Reaction: An Expeditious Synthesis of Pyrano, Indeno Quinolines and Phenanthridines[#]

J. S. Yadav,* B. V. Subba Reddy, R. Srinivas, Ch. Madhuri, T. Ramalingam

Organic Division-I, Indian Institute of Chemical Technology, Hyderabad- 500 007, India

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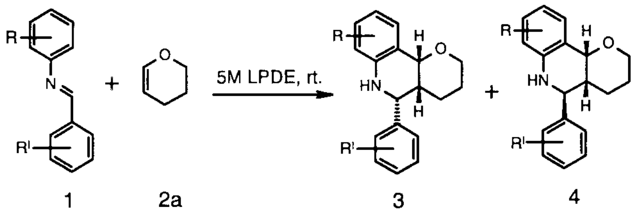
Abstract: Lithium perchlorate in diethylether (LPDE) is found to catalyze imino-Diels-Alder reactions of N-aryl aldimines with 3,4-dihydro-2H-pyran (DHP), indene, and cyclohexenone to afford the corresponding pyrano, indeno quinolines and phenanthridinone derivatives in high yields.

Key words: lithium perchlorate, aza-Diels-Alder reaction, quinoline derivatives

Aza-Diels-Alder is one of the most powerful synthetic routes for constructing nitrogen containing six-membered heterocycles.[1] Pyrano quinoline derivatives are found to possess a wide spectrum of biological activities[2] such as psychotropic, antiallergic, anti-inflammatory and estrogenic activity. Indeno quinolines are also known to exhibit a vast range of pharmacological activities[3] such as 5HT-receptor binding, anti-inflammatory and anti-tumor. The imino-Diels-Alder provides an easy access to pyrano, indeno quinolines and phenanthridine derivatives. Imines derived from aromatic amines act as heterodienes and undergo imino-Diels-Alder reaction with various dienophiles. Lewis acids[4-6] are known to catalyze these reactions. Also, lanthanide triflates[7] are found to be effective. However, many Lewis acids are deactivated or sometimes decomposed by nitrogen containing reactants; even when the desired reactions proceed, more than stoichiometric amounts of the Lewis acids are required because the acids are trapped by nitrogen.[1] Lithium perchlorate in diethylether (5M LPDE) is found to retain its activity even in the presence of amines[8]. Although, aza-Diels-Alder reaction is an important synthetic route for the construction of a variety of heterocycles, the usage of expensive reagents[7], strongly acidic conditions[9] and stoichiometric amounts of the acids[1] always demands newer and efficient reagents which can effect the transformation under mild and neutral reaction conditions.

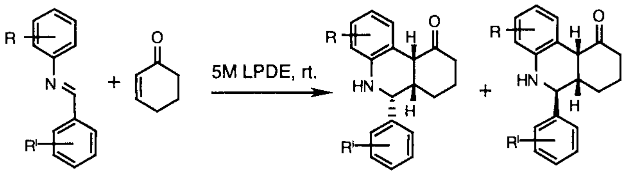
In recent years, lithium perchlorate in diethyl ether has received considerable attention as a powerful reaction medium for effecting various organic transformations[10] such as cycloaddition reactions, sigmatropic rearrangements, ring opening reactions of epoxides, glycoside synthesis, selective carbonyl protection as dithioacetals, Michael addition and aldol condensation reactions. The lithium ion acts as a mild Lewis acid in diethylether and shows enhanced rates and selectivity in cycloaddition reactions. In addition, LPDE medium offers a convenient procedure to carry out the reactions under essentially neutral reaction and work-up conditions. These special properties inherent to LPDE medium prompted us to disclose a mild and efficient procedure for the synthesis of pyrano, indeno quinolines and phenanthridine derivatives.

In this communication, we wish to report the 5M ethereal $LiClO_4$ catalyzed imino-Diels-Alder reaction of aldimines with various olefins like 3,4-dihydro-2H-pyran, indene, and cyclohexenone to afford corresponding quinoline derivatives. The reactions proceeded smoothly at ambient temperature to give the products in high yields in a short reaction time with high diastereoselectivity. The enhanced reaction rates and selectivity was observed in imino-Diels-Alder reaction in 5M LPDE medium. The mild Lewis acidity of the lithium ion in diethylether activates the imines (Schiff's bases) to behave as heterodienes in this reaction. Several aldimines (formed in situ from aromatic aldehydes and anilines in the presence of sodium sulphate in diethylether) were treated with 3,4-dihydro-2H-pyran in 5M LPDE medium to afford corresponding pyrano [3,2-c] quinolines in 80-95% yield. The products were obtained as a mixture of *cis*- and *trans*- isomers, which were separated by column chromatography on silica gel. The product ratio was determined by ^{1}H NMR spectrum of crude product.



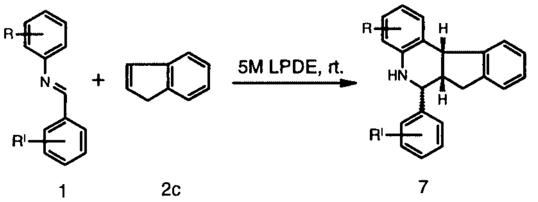
Scheme 1

Similarly, N-benzylidineanilines were treated with cyclohexenone in 5M LPDE medium at ambient temperature to afford corresponding phenanthridinone derivatives in good yields. 2-Cyclohexenone is a dienophile of low reactivity. The coordination of the carbonyl function of the cyclohexenone with LPDE increases the reactivity of dienophile and enhances the yield. The reaction of cyclohexenone with Schiff's base gave the product as a mixture of *cis*- and *trans*- isomers, which were separated by column chromatography.



Scheme 2

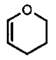
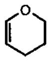
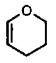
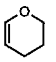
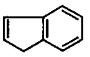
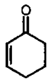
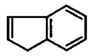
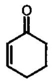
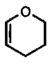
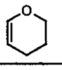
The reaction of indene with aldimines gave only a single isomer, which was confirmed by ^{1}H NMR spectra and is also in agreement with earlier observation.[5b]



Scheme 3

The reaction of aldimines with indene and cyclohexenone took longer reaction time to afford corresponding indeno quinolines and phenanthridinone derivatives in comparable yields with pyrano quinolines. Similarly various aldimines were treated with different dienophiles in 5M LPDE medium to give the corresponding quinoline derivatives and the results are presented in the Table.

Table 5M LPDE mediated aza-Diels-Alder reaction

Entry	Imine R (1)	R^I	Olefin (2)	Reaction time (h)	Yield (%)[a]	Product ratio[b]
a	H	H		2	95	70:30
b	2-CH3	H		3.5	93	60:40
c	4-Br	H		3	91	85:15
d	4-Cl	H		3	88	80:20
e	4-OCH$_3$	H		2.5	90	75:25
f	H	H		6	80	100:0
g	H	H		8	78	70:30
h	2-Naphthyl	H		4	80	60:40
i	H	4-Cl		7	82	100:0
j	H	4-CH$_3$		9	75	70:30
k	H	3, 4-Cl$_2$		3	92	85:15
l	4-Me	H		3.5	92	90:10
m	4-CN	H		4	88	80:20
n	H	4-OCH$_3$		3.5	93	75:25

[a] Isolated yields after purification; all the products were characterized by ^{1}H NMR, ^{13}C NMR, IR and Mass spectra.

[b] Product ratio was determined by the ^{1}H NMR spectrum of the crude product.

In conclusion, we have described 5M LPDE to be an excellent medium for the synthesis of pyrano, indeno quinolines and phenanthridinone derivatives through imino-Diels-Alder reaction of aldimines with 3,4-dihydro-2H-pyran, indene and cyclohexenone, respectively. The procedure offers several advantages like mild/neutral reaction conditions, high yields of products, low cost of the reagents, enhanced rates & selectivity, operational simplicity and ease of isolation of the products which makes it a useful procedure for the synthesis of these compounds.

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References and Notes

[#] IICT Communication: 4574

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(11) **Experimental:** A mixture of aldimine (5 mmol), olefin (5 mmol) and 5M Lithium perchlorate in diethylether[10] (5 mL) was stirred at ambient temperature for an appropriate time (Table). After complete conversion, as indicated by TLC, the reaction mixture was quenched by addition of water (20 mL) and extracted twice with dichloromethane (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and purified by column chromatography on silica gel (Merck, 100-200 mesh, ethyl acetate-hexane, 0.5-9.5) gave pure quinoline derivative. Spectroscopic data for compound **3a:** solid, mp 129-131 °C, 0.88 g (70% yield), ^{1}H NMR ($CDCl_3$) δ : 1.25-1.55 (m, 4H), 2.15 (m, 1H), 3.35-3.65 (m, 3H), 4.70 (d, *J* = 2.8 Hz, 1H), 5.34 (d, *J* = 5.6 Hz, 1H), 6.55 (d, *J* = 7.8 Hz, 1H), 6.75 (t, *J* = 7.8 Hz, 1H), 7.05 (t, *J* = 7.8 Hz, 1H), 7.25-7.45 (m, 6H). EIMS: (m/z) : 265M$^+$, 206, 194, 129, 91, 77. IR (KBr) ν : 3335. Analysis calculated for $C_{18}H_{19}NO$: C 81.5; H 7.16; N 5.28. Found: C 81.56; H 7.20; N 5.31. HRMS: Calculated for $C_{18}H_{19}NO$: 265.14. Found: 265.16.

4a: Viscous oil, 0.38 g (30% yield), ^{1}H NMR ($CDCl_3$) δ : 1.25 (m, 1H), 1.50 (m, 1H), 1.65 (m, 1H), 1.85 (m, 1H), 2.15 (m, 1H), 3.75 (t, *J* = 11.7 Hz, 1H), 3.95 (m, 2H), 4.40 (d, *J* = 2.8 Hz, 1H), 4.75 (d, *J* = 10.5 Hz, 1H), 6.50 (d, *J* = 7.8 Hz, 1H), 6.80 (t, *J* = 7.8 Hz, 1H), 7.05 (t, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 7.8 Hz, 1H), 7.35-7.45 (m, 5H). EIMS (m/z): 265 M$^+$, 206, 194, 129, 91, 77. IR (KBr) ν: 3340.

5g: Viscous oil**,** 0.76 g (70% yield), ^{1}H NMR ($CDCl_3$) δ: 1.75 (m, 2H), 2.05 (m, 1H), 2.35 (m, 1H), 2.05 (m, 1H), 2.65 (m, 1H), 2.75 (m, 1H), 4.70 (d, *J* = 2.1 Hz, 1H), 4.85 (d, *J* = 2.5 Hz, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 6.80 (t, *J* = 8.0 Hz, 1H), 7.15 (t, *J* = 8.0 Hz, 1H), 7.20-7.40 (m, 6H). EIMS (m/z) : 277M$^+$, 206, 91, 77. IR (KBr) ν: 3370, 2950, 1740, 1590. Analysis calculated for $C_{19}H_{19}NO$: C 82.28; H 6.90; N 5.05. Found: C 82.30; H 6.92; N 5.10. HRMS: Calculated for $C_{19}H_{19}NO$: 277.37. Found: 277.41.

6g: semi-solid, 0.32 g (30% yield), ^{1}H NMR ($CDCl_3$) δ: 1.80 (m, 2H), 2.18 (m, 2H), 2.50 (m, 1H), 2.75 (m, 1H), 2.85 (m, 1H), 4.65 (m, 1H), 4.80 (d, *J* = 2.5 Hz, 1H), 6.60 (d, *J* = 8.0 Hz, 1H), 6.75 (t, *J* = 8.0 Hz, 1H), 7.10 (t, *J* = 8.0 Hz, 1H), 7.25-7.35 (m, 6H). EIMS (m/z): 227 M$^+$, 206, 91, 77. IR (KBr) ν: 3368, 2975, 1738, 1587.

7f: Viscous oil**,** 1.19 g (80% yield), ^{1}H NMR ($CDCl_3$) δ: 2.35 (m, 1H), 3.15 (m, 1H), 3.35 (m, 1H), 3.85 (brs, 1H), 4.5 (d, *J* = 6.5 Hz, 1H), 4.70 (d, *J* = 2.8 Hz, 1H), 6.55 (d, *J* = 8.0 Hz, 1H), 6.70 (t, *J* = 8.0 Hz, 1H), 6.95 (t, *J* = 8.0 Hz, 1H), 7.15-7.65 (m, 9H), 7.85 (d, *J* = 8.0 Hz, 1H). EIMS (m/z): 297M$^+$, 206, 91, 77. IR (KBr) ν: 3345, 3050, 1570. Analysis calculated for $C_{22}H_{19}N$: C 88.85; H 6.44; N 4.71. Found: C 88.83; H 6.45; N 4.73. HRMS: Calculated for $C_{22}H_{19}N$: 297.15. Found: 297.18.

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