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Research Article

One Pot Three Components Synthesis of Pyrazolo[3,4-*b*] Quinoline Derivatives Catalyzed By DBU.

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ABSTRACT
Multicomponent reactions (MCRs) are one of the most important processes for the preparation of highly functionalized organic compounds in modern synthetic chemistry. A simple, efficient and green protocol has been developed for the synthesis of pyrazolo[3,4-*b*] quinoline derivatives from a one-pot three-component condensation of methyl-1H-pyrazol-5-amine, dimedone, and different substituted aromatic aldehydes were refluxed independently in ethanol using 1, 8-diazabicyclo [*5.4.0*] undec-7-ene (DBU) as an efficient and green catalyst. DBU can play catalytic role in the organic reactions. This methodology has several advantages such as the use of a very small amount of catalyst, easy workup, short reaction times, high yields, easy access, use of non-toxic and hazardous catalysts and solvents.

KEYWORD
Aromatic aldehydes, Dimedone, methyl-1H-pyrazol-5-amine, DBU, green protocol.

1. INTRODUCTION

Heterocyclic compounds are very widely distributed in nature and are particularly important because of the wide variety of physiological activities associated with this class of substances. Quinazolines are reported to have a broad range of biological and medicinal activities such as anti-inflammatory [1], anticancer [2], antidepressant [3], anticonculsant [4], fungicide, antineoplastic, antiplasmodial [5], antibacterial [6], anticonculgant [7], AIDS treatment, and cognition disorder activities [8]. They are also building blocks of many alkaloid molecules [8-10]. On the other hand, pyrazole is an important part ofnitrogen heterocyclic compound and displays various chemical, biological [11-12], agrochemical and pharmacological properties. Several drugs have been developed from the pyrazole mother nucleus. Pyrazolo[3,4-*f*]quinoline, a novel member of this family, is also an important class of tricycle fused heterocycles, and its derivatives produce remarkable effects as pharmaceuticals including antifungal, antibacterial and antagonistic activities.

Friedlander prepared pyrazolo [3, 4-*b*] quinoline by the condensation of o-amino benzaldehyde with suitable pyrazoline-5-one. This reaction affords several by-products along with pyrazolo quinoline. To overcome shortcomings, several methods are reported for the synthesis of pyrazolo[3,4-b]quinolines. Recently Shi and Yang synthesized pyrazolo quinolines by using ionic liquid and Chebanovco-workers prepared these derivatives in the presence of microwave irradiation. However, these reported protocols suffer from one or more drawbacks such as the use of expensive reagents, prolonged reaction times, low yields, cumber some product isolation procedures, and harsh reaction conditions. Exploring a mild, efficient and environmentally benign protocol for the synthesis of pyrazolo[3,4-*b*]quinoline derivatives is highly desirable.

2. MATERIALS AND METHODS

A mixture of methyl-1H-pyrazol-5-amine (10 mmol) (01), Dimedone (10 mmol) (02) and different substituted aromatic aldehydes (10 mmol) (03a-e), was refluxed using 1, 8-diazabicyclo [*5.4.0*] undec-7-ene (DBU) 10 mmol % as an efficient and green catalyst in ethanol for certain period of time to afford the respective products (04a-e). The reaction mixture was cooled to room temperature and poured into ice-cold water. The solid obtained was filtered, washed with water and recrystallized by ethanol to give (04a-e). The reaction was monitored by TLC. These synthesized compounds (04a-e) were completely characterized by IR, ^{1}H-NMR, Mass and ^{13}C-NMR spectroscopic technique and also elemental analysis.

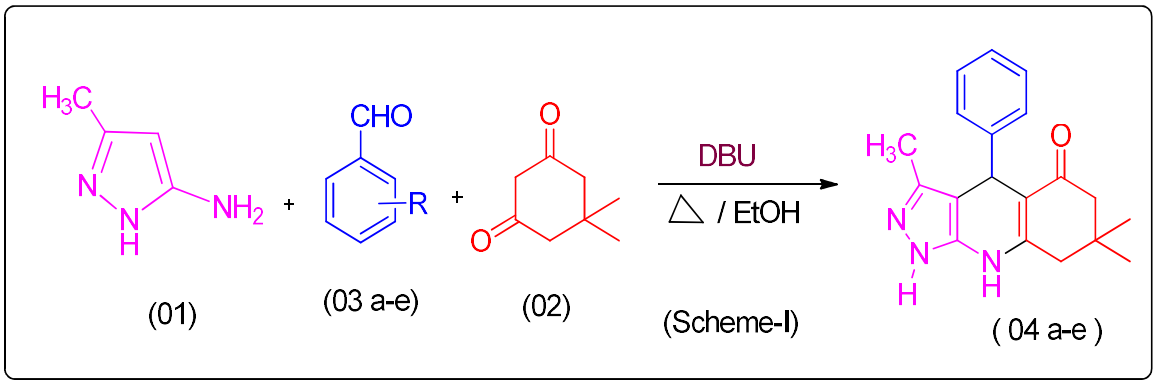
2.1. Experimental

Open capillary tubes were used for melting points of isolated synthesized compounds and are uncorrected. Perkin-Elmer FTIR spectrophotometer was used for IR (KBr) spectra of compounds. Mass spectral data were recorded on a liquid chromatography-mass spectrometer (Shimadzu 2010Ev) using the ESI probe. The ^{1}H and ^{13}C NMR spectra were recorded on spectrometer at 400MHz using TMS as an internal standard.

2.2. General procedure for the synthesis of pyrazolo[3,4-b]quinoline derivatives(04a-e)

A mixture of methyl-1H-pyrazol-5-amine(10 mmol) (01), dimedone (10 mmol) (02) and different substituted aromatic aldehydes (10 mmol) (03a-e) was refluxed using 1, 8-diazabicyclo [*5.4.0*] undec-7-ene (DBU)10 mmol % as an efficient and green catalyst in ethanol for certain period of time to afford the respective products (04a-e). The reaction mixture was cooled to room temperature and poured into ice-cold water. The solid obtained was filtered, washed with water and recrystallized by ethanol to give (04a-e). The reaction was monitored by TLC. These synthesized compounds (04a-e) were completely characterized by IR, ^{1}H-NMR, Mass and ^{13}C-NMR spectroscopic technique and also elemental analysis.

3. RESULTS AND DISCUSSION



Scheme 1. Synthesis of Pyrazolo[3,4-*b*] Quinoline Derivatives.

We initially focused on optimization reaction conditions. The reaction mixture of 3-methyl-1H-pyrazol-5-amine, Dimedone, and different substituted aromatic aldehydes was refluxed independently in ethanol using 1, 8-diazabicyclo [*5.4.0*] undec-7-ene (DBU) 10 mmol % as an efficient and green catalyst, It was considered as a model reaction (Scheme 1) for investigating the effectiveness of different polar and non-polar solvent using catalytic amount of DBU 10 mmol %. Solvent optimization clearly noted that ethanol is the best solvent for the desired transformation due to the fast reaction rate and high yield (Table 1, entry 6). While other aprotic solvents like DMF, Ethylene glycol, Acetonitrile, THF, DCM displayed slow reaction rates leading to lower yield (Table 1, entry 1-4).

We have carried out the model reaction using different stoichiometric amount of catalyst. The catalyst screening result are summarized in Table 2. It was observed that the excellent yield was achieved by using 10mmol % of DBU (Table 2, entry 5).

Further investigating the influence of different parameters on the model reaction, we turned our attention towards the pyrazolo[3,4-*b*]quinoline derivatives (04a-e) using reaction of methyl-1H-pyrazol-5-amine (01), Dimedone (02) and different substituted aromatic aldehydes (03a-e), was refluxed independently in ethanol using 1, 8-diazabicyclo [*5.4.0*] undec-7-ene (DBU) and the results are summarized in Table 3. With the both electron-poor and electron-rich benzaldehydes (Table 3, entries 1-5), the corresponding pyrazolo[3,4-*b*]quinoline derivatives (04a-e), were

obtained to excellent yields. These synthesized products (04a-e) were characterized by IR, ^{1}H-NMR, Mass and ^{13}C-NMR spectroscopic technique and also elemental analysis.

Table 1. Optimization of the reaction conditions using different solvents.[b]

Entry	Solvent	Reaction Time (h)	Yield (%)[b]
1	DMF	6.5	30
2	Ethylene glycol	6.0	40
3	Acetonitrile	5.5	50
4	THF	5.0	60
5	DCM	6.0	70
6	Ethanol	3.0	82

[a]***Reaction conditions:*** Methyl-1H-pyrazol-5-amine(10 mmol), Dimedone (10 mmol) and aromatic aldehyde (10 mmol) was refluxed at 80^{o}C; [b] Isolated yields.

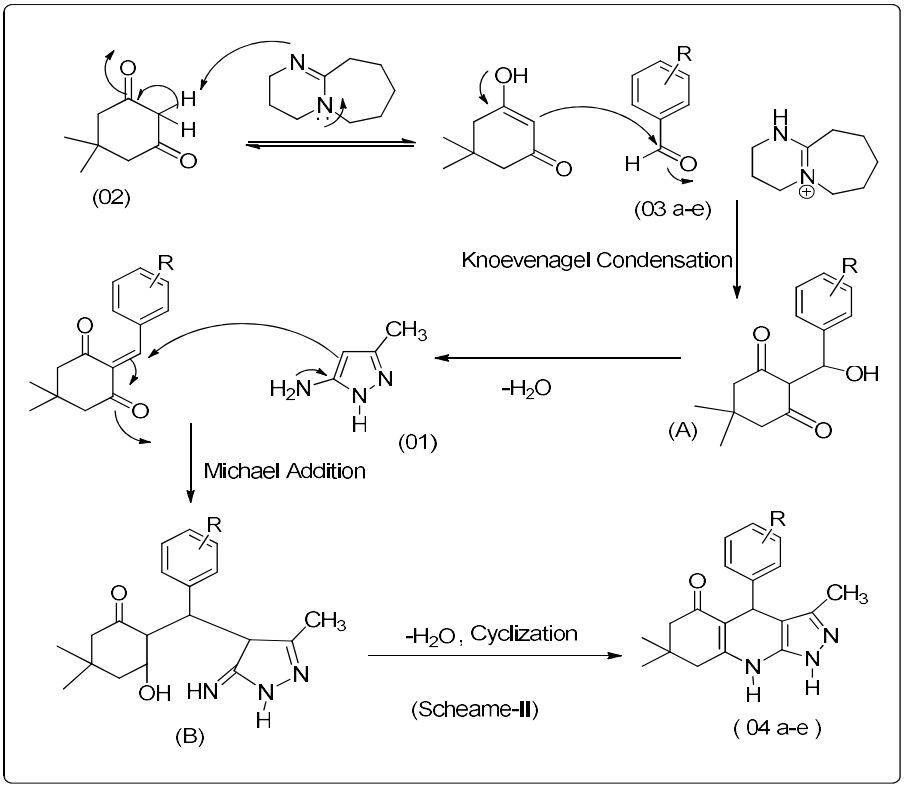
Table 2. Optimization Study for the amount 1, 8-diazabicyclo [*5.4.0*] undec-7-ene (DBU)[b]

Entry	Catalyst (mole %)	Temperature (^{0}C)	Reaction Time (h)	Yield %[b]
1	01	80	5.0	35
2	02	80	5.0	40
3	05	80	5.0	50
4	08	80	5.0	65
5	10	80	5.0	82
6	15	80	5.0	84

[a]***Reaction conditions:*** Methyl-1H-pyrazol-5-amine(10 mmol), Dimedone (10 mmol) and aromatic aldehyde (10 mmol) was refluxed at 80^{0}C; [b] Isolated yields.

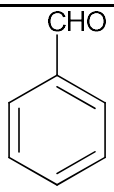
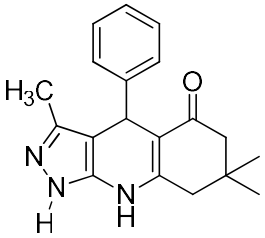
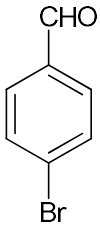
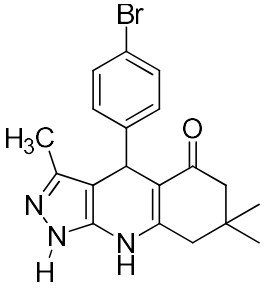
3.1. Plausible Mechanism of Parent Compound (04 a-e)

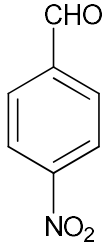
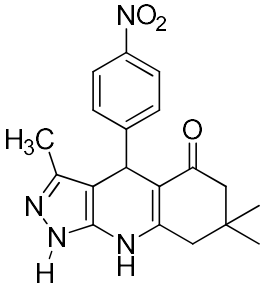
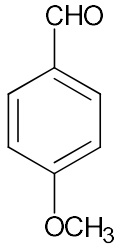
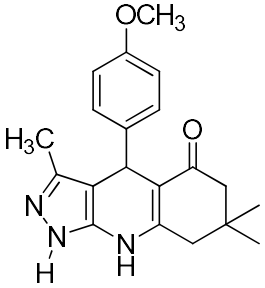
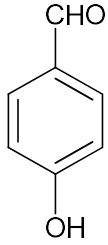
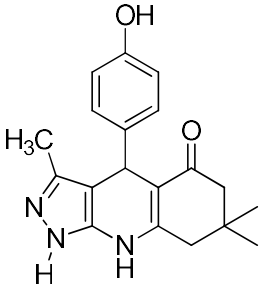
The possible mechanism is described in Scheme 2. Initially, Knoevenagel condensation occurs between substituted aromatic aldehydes and dimedone, resulting in the adduct (A), which upon nucleophiles attack by methyl-1H-pyrazol-5-amineproduces the Michael adduct, as an intermediate (B). This intermediate on further cyclization and dehydration yields the final product.



Scheme 2. Plausible mechanism.

Table 3. Four component reaction of methyl-1H-pyrazol-5-amine (01), dimedone (02), aromatic aldehydes (03a-e) and for the synthesis of (04a-e).[a]

Entry	Aldehyde (02a-e)	Products (04 a-e)	Time (h)	Yield (%)[b]	M.P. (^{0}C)
1			3.0	75	233-235
2			3.0	82	318-320

3			3.5	80	300-302
4			3.0	80	298-300
5			3.5	76	274-276

[a]***Reaction conditions:*** (01) (1 mmol), (02) (1 mmol),(03) (1 mmol) and ethanol in DBU were refluxed at 70^0.[b] Isolated yields.

3.2. Spectral Analysis

3,7,7-Trimethyl-4-phenyl-6,7,8,9-tetrahydro-1H-pyrazolo[3,4-b]quinolin-5(4H)-one (04a)

M.P. 233-235^{0}C; Yield 75 %; IR (KBr, *v*max, cm^{-1}) 3245, 3010, 2980, 1592, 1550, 1260,760, ; ^{1}H NMR (400MHz, DMSO-d$_6$, ppm) δ 0.96-1.02 (s, 6H, CH_3),1.94 (s, 3H, CH_3),1.96-2.01 (s, 2H, CH_2), 2.22-2.30 (s, 2H, CH_2), 4.98 (s, 1H, *CH*), 6.40(s, 1H, NH), 7.20-7.45 (m, 5H, Ar-H),10.95 (s, 1H, NH);^{13}C NMR (400 MHz, DMSO-d$_6$, ppm): 13.40, 27.80, 30.10, 32.50, 35.15, 41.35, 50.50, 108.30, 117.45, 127.10,130.90, 138.10, 145.60, 145.14, 159.20, 196.45; EI-MS (m/z: RA %): 307 ($M^{+\cdot}$, 100%). Elemental analysis Calculated data for $C_{19}H_{21}N_3O$; C, 74.24; H, 06.89; N, 13.67 Found: C, 74.20; H, 06.90; N,13.70.

4-(4-Bromophenyl)-3,7,7-trimethyl-6,7,8,9-tetrahydro-1H-pyrazolo[3,4-b]quinoline 5(4H)-one (04b)

M.P. 318-320^{0}C, Yield 82 %. IR (KBr, *v*max, cm^{-1}) 3240, 3122, 2960, 1580, 1552, 1250, 790; ^{1}H NMR (400MHz, DMSO-d$_6$, ppm, 0.99-1.05 (s, 6H, CH_3), 2.08 (s, 3H, CH_3), 2.10-2.15(m,2H, CH_2), 2.24-2.38 (s, 2H, CH_2), 4.90 (s, 1H, 4*H*), 6.42 (s, 1H, NH), 7.10 (d, 2H, Ar-H), 7.70 (d, 2H, Ar-H), 11.75 (s, 1H, NH); ^{13}C NMR (400 MHz, DMSO–d$_6$, ppm): δ 15.10, 27.05, 28.22,

32.20, 34.10, 40.98, 55.60, 110.40, 113.76, 118.20, 129.30, 132.60, 134.20, 145.50, 146.88, 151.32, 197.60 ; EI-MS (m/z: RA %): 385 ($M^{+\cdot}$, 100%). Elemental analysis Calculated data for$C_{19}H_{20}BrN_3O$; C, 59.08.34; H, 05.22; N, 10.88. Found: C, 59.10; H, 05.20; N, 10.90.

3,7,7-Trimethyl-4-(4-nitrophenyl)-6,7,8,9-tetrahydro-1H-pyrazolo[3,4-b]quinoline 5(4H)-one (04c)

M.P. 300-302^{0}C, Yield 80 %. IR (KBr, *v*max, cm^{-1}) 3270, 3080, 2950, 1596, 1510, 1250, 735; ^{1}H NMR (400MHz, DMSO-d_6 , ppm, 0.98-1.15 (s, 6H, CH_3), 2.20 (s, 3H, CH_3), 2.10-2.15(s,2H, CH_2), 2.30-2.40 (s, 2H, CH_2), 4.98 (s, 1H, 4*H*), 6.94 (s, 1H, NH), 7.40 (d, 2H, Ar-H), 8.20 (d, 2H, Ar-H), 12.15 (s, 1H, NH); ^{13}C NMR (400 MHz, DMSO–d_6, ppm): δ 12.98, 27.45, 29.22, 32.02, 33.60, 41.40, 52.90, 108.15, 114.50, 122.45, 128.89, 133.55, 139.44, 146.64, 146.74, 165.66, 195.55; EI-MS (m/z: RA %): 352 ($M^{+\cdot}$, 100%). Elemental analysis Calculated data for $C_{19}H_{20}N_4O_3$; C, 64.76; H, 05.72; N, 15.90; Found: C, 64.80; H, 05.70; N, 15.88.

4-(4-Methoxyphenyl)-3,7,7-trimethyl-6,7,8,9-tetrahydro-1H-pyrazolo[3,4-b]quinolin-5(4H)-one (04d)

M.P. 298-300^{0}C, Yield 80 %. IR (KBr, *v*max , cm^{-1}) 3240, 3060, 2970, 1592, 1549, 1250, 760; ^{1}H NMR (400MHz, DMSO-d_6, ppm, 0.96-1.08 (s, 6H, CH_3), 2.02 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 2.10-2.15(s, 2H, CH_2), 2.25-2.35 (s, 2H, CH_2), 4.76 (s, 1H, 4*H*), 7.60 (s, 1H, NH), 6.92 (d, 2H, Ar-H), 7.18 (d, 2H, Ar-H), 10.70 (s, 1H, NH); ^{13}C NMR (400 MHz, DMSO–d_6, ppm): δ 14.60, 27.20, 30.20, 32.02, 34.60, 40.30, 54.94, 60.54, 110.20, 113.80, 120.45, 130.86, 134.66, 140.60, 146.20, 152.78, 160.25, 197.55 ; EI-MS (m/z: RA %): 337 ($M^{+\cdot}$, 100%). Elemental analysis Calculated data for $C_{20}H_{23}N_3O_2$; C, 71.39; H, 06.87; N, 12.45; Found: C, 71.40; H, 06.90; N, 12.50.

4. CONCLUSION

In conclusion, we have developed efficient, simple and convenient etiquette for the synthesis of pyrazolo[3,4-*b*]quinoline derivatives via the condensation of methyl-1H-pyrazol-5-amine, Dimedone and different substituted aromatic aldehydes using DBU as an efficient and green catalyst in ethanol as solvent. These methods provide several advantages over reported methods such as high yield, short reaction time, safety, use of non-toxic solvent and environmentally favorable. Overall, the reaction strategy carried out from Knoevenagel-Michael's reaction.

5. ACKNOWLEDGMENTS

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