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ORIGINAL PAPER

DBU-catalyzed expeditious and facile multicomponent synthesis of *N*-arylquinolines under microwave irradiation

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Abstract *N*-Arylquinoline derivatives are obtained in excellent yields by a rapid, easy, and efficient one-pot multicomponent reaction of aromatic aldehydes, 3-arylamino-5,5-dimethylcyclohex-2-enone, and active methylene compounds utilizing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a catalyst in ethanol under microwave irradiation.

Keywords Microwave-assisted synthesis · Multicomponent reaction · One-pot synthesis · Quinoline · DBU

Introduction

Heteroaromatic rings containing nitrogen atoms often play an important role as the scaffolds of bioactive substances. Quinoline is one of the most popular *N*-heteroaromatic frameworks present in many pharmaceuticals and exhibits a wide spectrum of pharmacological effects, such as antiplasmodial [1], intrinsic [2], cytotoxic [3], functional [4], antibacterial [5], antiproliferative [6], antimalarial [7], and anticancer activities [8]. Therefore, the synthesis of quinolines has attracted much attention in organic synthesis. The classical methods for the preparation of quinoline derivatives include the Skraup, Doebner–Von Miller, Conrad–Limbach, Combes, and Pfitzinger syntheses [9–13]. Owing to the remarkable potential of these compounds as a source of valuable drugs, various synthetic methods have also been reported [14–19]. Most of these processes, however, suffer from one or other drawbacks such as long reaction times, poor product yields, harsh conditions, high costs, and use of hazardous catalysts. Further, there are few examples of syntheses of *N*-substituted quinoline derivatives in the literature [20–22]. Microwave (MW) irradiation has evolved as a powerful method to perform organic synthesis with great success, particularly in the light of the current paradigm shift to green chemistry [23, 24]. The environmental acceptability of the process is further improved if a multicomponent approach is adopted under microwave irradiation [25, 26]. The multicomponent syntheses of such *N*-arylquinoline derivatives has been recently effected by employing catalysts such as [Bmim]BF_4 (1-butyl-3-methylimidazolium tetrafluoroborate) [27] and TBAF (tetrabutylammonium fluoride) [28].

Results and discussion

In view of the above, we have investigated a 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 5 mol%) catalyzed, one-pot, simple, and efficient procedure for the rapid construction of *N*-substituted quinolines via a three-component reaction of 3-arylamino-5,5-dimethylcyclohex-2-enones, aromatic aldehydes, and active methylene compounds such as malononitrile or ethyl cyanoacetate in ethanol under controlled microwave irradiation (Scheme 1).

In order to optimize the effect of catalyst, MW power, and temperature, we investigated the model reaction of 3-phenylamino-5,5-dimethylcyclohex-2-enone (**1a**), *p*-anisaldehyde (**2c**), and malononitrile (**3a**). The reaction was carried out in the presence of different organic bases such as DBU, Et_3N, piperidine, and pyridine under microwave irradiation at different power, temperature, and time in ethanol. It is evident from the results presented in

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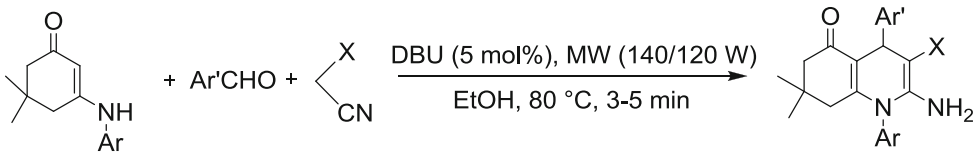
Scheme 1



1 **2** **3** **4**

X = -CN, -COOEt (92-99%)

Ar = C_6H_5, *p*-$CH_3C_6H_4$, *p*-BrC_6H_4; Ar' = C_6H_5, *p*-$CH_3C_6H_4$, *p*-$CH_3OC_6H_4$, *p*-ClC_6H_4, *m*-ClC_6H_4, *p*-BrC_6H_4, *p*-FC_6H_4, *p*-OHC_6H_4, *p*-$NO_2C_6H_4$, *m*-$NO_2C_6H_4$

Table 1 that DBU (5 mol%) as catalyst accomplishes the reaction successfully and the use of the microwave irradiation further enhances the yield of the product considerably with dramatic reduction in the reaction time, the best result being obtained using 140 W at 80 °C in 3 min (entry 6).

Under the optimized reaction conditions (entry 6), a number of 3-arylamino-5,5-dimethylcyclohex-2-enones **1** undergo multicomponent reaction with different aromatic aldehydes **2** and malononitrile in a molar ratio of 1:1:1 in ethanol under microwave heating (140 W, 80 °C). When malononitrile was replaced by ethyl cyanoacetate, another series of 4-arylquinoline derivatives **4s–4w** were obtained in excellent yields (92–95%) under similar reaction conditions at 120 W microwave power and 80 °C in ethanol. All the reactions were completed in 3–5 min (TLC monitoring) and the results are given in Table 2. Both electron-rich and electron-deficient aldehydes afforded excellent yields of the products **4a–4w** (92–99%). All products were crystalline and fully characterized on the basis of their melting points, elemental analyses, and spectral data (IR, ^{1}H NMR, and ^{13}C NMR).

Table 1 Optimization of reaction conditions for the synthesis of **4d**

Entry	Base/mol%	Microwave			Yield/%
		MW/W	Temp/°C	Time/min	
1	–	180	80	10	–
2	DBU (3)	120	80	5	67
3	DBU (3)	120	100	5	71
4	DBU (3)	140	80	5	73
5	DBU (5)	120	80	3	92
6	**DBU (5)**	**140**	**80**	**3**	**98**
7	DBU (5)	180	80	3	98
8	DBU (7)	140	80	3	97
9	DBU (10)	140	80	3	95
10	Et_3N (5)	140	80	5	56
11	Et_3N (10)	140	80	5	70
12	Piperidine (5)	140	80	7	45
13	Piperidine (10)	140	80	5	58
14	Pyridine (5)	180	80	10	20
15	Pyridine (10)	180	80	10	28

The bold entry signifies the best result obtained during the optimization

Conclusion

We have developed a new, facile, and efficient methodology for the DBU-catalyzed rapid preparation of *N*-substituted quinoline derivatives via one-pot three-component condensation of 3-arylamino-5,5-dimethylcyclohex-2-enone, aromatic aldehyde, and active methylene compounds including malononitrile and ethyl cyanoacetate in ethanol. The mildness of the conversion, its experimental simplicity, compatibility with various functional groups, excellent product yields, short reaction times, and the easy workup procedure make this approach attractive for synthesizing a variety of such derivatives.

Experimental

All chemicals were procured from Aldrich, USA, and E. Merck, Germany, and were purified prior to their use. IR spectra were recorded on a JASCO FT-IR-5300 spectrophotometer. NMR spectra were run on a JEOL AL300 FT-NMR spectrometer; chemical shifts are given as δ (ppm) relative to TMS as internal standard. Elemental microanalysis was performed on an Exeter Analytical Inc model CE-440 CHN analyzer. Melting points were measured in open capillaries. The microwave irradiation was effected using CEM's Discover BenchMate single-mode microwave synthesis system using safe pressure regulation 10-cm^3 pressurized vials with "snap-on" caps. 3-Arylamino-5,5-dimethylcyclohex-2-enones **1** were synthesized according to the procedure described in Ref. [29].

*General procedure for the synthesis of N-substituted quinolines **4a–4w***

A mixture of 3-arylamino-5,5-dimethylcyclohex-2-enone **1** (1 mmol), aromatic aldehyde **2** (1 mmol), 0.066 g malono-

Table 2 DBU-catalyzed synthesis of *N*-substituted quinolines under MW

Entry	Ar	Ar′	X	Product	Time/min	Yield/%[a]	M.p./°C	
							Observed	Refs. [21, 27, 28]
1	C_6H_5	C_6H_5	CN	**4a**	3	97	223–225	246–247
2	C_6H_5	4-$CH_3C_6H_4$	CN	**4b**	3	98	231–232	–
3	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	CN	**4c**	3	99	252	252–254
4	C_6H_5	4-$CH_3OC_6H_4$	CN	**4d**	3	98	245–246	244–245
5	4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	CN	**4e**	3	99	240–241	239–241
6	4-$CH_3C_6H_4$	4-ClC_6H_4	CN	**4f**	4	97	258–260	260–262
7	C_6H_5	4-ClC_6H_4	CN	**4g**	4	96	268–269	268–269
8	C_6H_5	3-ClC_6H_4	CN	**4h**	4	94	230–232	–
9	4-$CH_3C_6H_4$	3-ClC_6H_4	CN	**4i**	4	95	232–234	233–234
10	C_6H_5	4-BrC_6H_4	CN	**4j**	4	94	254–256	275–277
11	4-BrC_6H_4	4-BrC_6H_4	CN	**4k**	5	93	276–277	276–278
12	4-$CH_3C_6H_4$	4-BrC_6H_4	CN	**4l**	4	95	259–261	261–263
13	C_6H_5	4-FC_6H_4	CN	**4m**	3	95	259–260	260–261
14	C_6H_5	4-$NO_2C_6H_4$	CN	**4n**	5	93	276–277	275–276
15	C_6H_5	3-$NO_2C_6H_4$	CN	**4o**	5	93	267–268	268–269
16	4-$CH_3C_6H_4$	3-$NO_2C_6H_4$	CN	**4p**	4	94	280	281–283
17	4-BrC_6H_4	3-$NO_2C_6H_4$	CN	**4q**	5	92	272–274	271–274
18	C_6H_5	4-OHC_6H_4	CN	**4r**	3	96	266–268	267–268
19	C_6H_5	4-$CH_3C_6H_4$	COOEt	**4s**	5	94	176–178	–
20	C_6H_5	4-ClC_6H_4	COOEt	**4t**	5	93	204–205	204–206
21	4-$CH_3C_6H_4$	4-ClC_6H_4	COOEt	**4u**	5	95	201–203	198–200
22	4-$CH_3C_6H_4$	3-ClC_6H_4	COOEt	**4v**	5	94	220–222	219–221
23	4-$CH_3C_6H_4$	3-$NO_2C_6H_4$	COOEt	**4w**	5	92	236–237	236–237

Microwave heating using 140 W (120 W for entries 19–23) at 80 °C

[a] Isolated yield

nitrile **3a** (1 mmol) or 0.113 g ethyl cyanoacetate **3b** (1 mmol), 0.0076 g DBU (5 mol%), and 1.5 cm^3 ethanol was placed in a sealed pressure regulation 10-cm^3 pressurized vial with "snap-on" cap and was irradiated in the single-mode microwave synthesis system at 140 W/120 W at 80 °C for 3–5 min. After completion of reaction (TLC), the mixture was cooled and the resulting product was filtered, dried, and recrystallized from ethanol to afford the pure products **4a**–**4w**.

2-Amino-1,4,5,6,7,8-hexahydro-7,7-dimethyl-4-(4-methylphenyl)-5-oxo-1-phenylquinoline-3-carbonitrile
(**4b**, $C_{25}H_{25}N_3O$)
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.85$ (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 1.80 (d, $J = 17.4$ Hz, 1H, CH), 2.04 (d, $J = 17.1$ Hz, 1H, CH), 2.16–2.18 (m, 2H, CH_2), 2.31 (s, 3H, CH_3), 3.99 (s, 2H, NH_2), 4.72 (s, 1H, CH), 7.12 (d, $J = 7.8$ Hz, 2H, ArH), 7.23–7.58 (m, 7H, ArH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 195.2$, 150.1, 149.2, 145.4, 136.2, 130.6, 130.2, 129.8, 128.7, 127.2, 126.4, 120.7, 113.2, 62.8, 49.7, 41.2, 35.9, 32.4, 29.3, 26.7, 21.2 ppm; IR (KBr): $\bar{\nu} = 3{,}458$, 3,334, 3,038, 2,954, 2,178, 1,653, 1,575, 1,488, 1,411, 1,371, 1,256, 1,147, 1,043, 848, 793, 670 cm^{-1}.

2-Amino-4-(3-chlorophenyl)-1,4,5,6,7,8-hexahydro-7,7-dimethyl-5-oxo-1-phenylquinoline-3-carbonitrile
(**4h**, $C_{24}H_{22}ClN_3O$)
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.85$ (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 1.82 (d, $J = 17.4$ Hz, 1H, CH), 2.05 (d, $J = 17.4$ Hz, 1H, CH), 2.17–2.19 (m, 2H, CH_2), 4.07 (s, 2H, NH_2), 4.74 (s, 1H, CH), 7.16–7.29 (m, 6H, ArH), 7.59–7.61 (m, 3H, ArH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 195.6$, 149.8, 149.3, 144.7, 136.1, 133.5, 130.1, 129.3, 128.4, 127.2, 126.2, 120.4, 112.8, 62.7, 49.5, 41.3, 36.1, 32.3, 29.1, 26.5 ppm; IR (KBr): $\bar{\nu} = 3{,}461$, 3,329, 3,218, 3,065, 2,959, 2,180, 1,653, 1,592, 1,566, 1,494, 1,416, 1,372, 1,257, 1,148, 1,044, 879, 758, 699 cm^{-1}.

Ethyl 2-amino-1,4,5,6,7,8-hexahydro-7,7-dimethyl-4-(4-methylphenyl)-5-oxo-1-phenylquinoline-3-carboxylate
(**4s**, $C_{27}H_{30}N_2O_3$)
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.78$ (s, 3H, CH_3), 0.94 (s, 3H, CH_3), 1.22 (t, $J = 6.9$ Hz, 3H, CH_3), 1.65–1.77

(m, 2H, CH_2), 2.02–2.18 (m, 2H, CH_2), 2.28 (s, 3H, CH_3), 4.04 (q, $J = 7.2$ Hz, 2H, CH_2), 5.10 (s, 1H, CH), 6.18 (s, 2H, NH_2), 7.05 (d, $J = 7.8$ Hz, 2H, ArH), 7.26–7.34 (m, 4H, ArH), 7.56–7.59 (m, 3H, ArH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 195.2$, 167.4, 149.8, 145.2, 136.1, 130.7, 130.0, 129.6, 128.6, 127.2, 126.5, 113.1, 105.9, 59.8, 50.7, 40.8, 36.5, 32.6, 29.4, 27.1, 19.8, 14.2 ppm; IR (KBr): $\bar{\nu} = 3{,}464$, 3,329, 3,063, 2,963, 1,656, 1,596, 1,505, 1,363, 1,275, 1,210, 1,187, 1,074, 1,021, 816, 763 cm^{-1}.

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