



Microwave-assisted Synthesis of 2-Methyl-4-Quinolinones *via* Combes Synthesis Catalyzed by Acidic Resin under Solvent-Free Condition[†]

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A simple and efficient method for the synthesis of 2-methylquinolin-4(1*H*)-one derivatives using NKC-9-resin as reusable eco-friendly catalyst *via* Combes cyclization under solvent-free and microwave irradiation conditions is described. The quinolines were obtained in high yields and in short reaction times.

Key Words: Combes, Quinoline, Microwave irradiation, NKC-9, Solvent-free.

INTRODUCTION

It is known that quinoline derivatives are important compounds in the bioorganic and medicinal chemistry, constituting the structure of interesting pharmacological properties¹. A large number of quinolines have been widely used as antimalarial², antiasthmatic³ and antiviral agent⁴. In addition, quinolines are valuable synthons used for the preparation of nano- and meso-structures with enhanced electronic and photonic properties⁵.

There are several methods for the formation of the quinoline ring system such as Skraup⁶, Knorr⁷, Conrad-Limpach⁸, Doebner-von Miller⁹, Combes¹⁰, Friedländer reactions¹¹, *etc.* Among them, although the Friedländer reaction has been studied more, the Combes reaction is still one of the most simple and straightforward approaches for the synthesis of quinolines. Traditionally, the Combes reaction is carried out in organic solvents (*e.g.*, ethanol, xylene and diphenyl ether) and heating by using H₂SO₄ as catalysts. Because of economical and environmental concerns, recently, the solid acids, such as In Cl₃,¹² NaHSO₄,¹³ used as catalysts for the Combes reaction has attracted much attention in synthesis of quinolines under solvent-free condition. However, most of the synthetic protocols reported so far suffer from high temperatures, prolonged reaction times, low yields, difficulty of separation and purification and unrenovable catalysts. Therefore, it is necessary to develop a simple, clean and efficient method for Combes reaction.

EXPERIMENTAL

All material from Aldrich and used directly as received and Flash chromatographic sheet employed was purchased

from Anhui Liangchen Silicon Material Co. Ltd., The reactions were carried out in a multimode microwave oven (frequency: 2450 Hz; maximal power: 1600 W).

To a mixture of aromatic amines (2 mmol), ethyl acetoacetate (2.4 mmol) and resin (NKC-9, 100 mg) was added. The mixture was homogenized with the help of glass rod at room temperature and irradiated in microwave oven (400 W) for 1.5 minutes by the interval of 10 sec. The reaction was monitored by TLC. After completion of the reaction, the mixture was extracted with CH₂Cl₂ and filtered, the organic phase was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The pure products were obtained by flash chromatography on silica gel eluting with petroleum ether/EtOAc (6:1, v:v) and identified by IR, ¹H, ¹³C NMR and HRMS.

All melting points were determined on a WT-melting point apparatus and are uncorrected. IR (Perkin-Elmer, 2000 FTIR), ¹H NMR (CDCl₃, 300 MHz), ¹³C NMR (CDCl₃, 75 MHz) and MS-GC (HP5890 (II)/HP 5972, EI) spectra were obtained at the Center of Analytical Configuration of University of Science and Technology of China.

2-Methyl-1*H*-quinolin-4-one (3a): IR: 3439, 3035, 1648, 1602, 1572, 1476, 1340, 701 cm⁻¹; ¹H NMR (DMSO-*d*₆, 300 MHz) δ: 2.14 (s, 3H, CH₃), 6.13 (s, 1H, CH=), 7.21-7.48 (m, 4H, Ph), 8.36 (s, 1H, NH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ: 24.17, 113.62, 120.26, 122.31, 124.33, 127.45, 134.20, 137.21, 152.40, 183.72; HRMS: calcd. for C₁₀H₉NO: 159.1845, found: 159.3195.

2,6-Dimethyl-1*H*-quinolin-4-one (3b): IR: 3342, 3032, 1647, 1621, 1574, 1472, 1342, 731 cm⁻¹; ¹H NMR (DMSO-*d*₆,

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300 MHz) δ : 2.23 (s, 3H, CH₃), 2.52 (s, 3H, CH₃), 6.09 (s, 1H, CH=), 7.24 (d, J = 7.6 Hz, 1H, Ph), 7.53 (d, J = 7.5 Hz, 1H, Ph), 7.78 (s, 1H, Ph), 9.10 (s, 1H, NH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ : 14.32, 24.28, 102.16, 116.53, 124.61, 127.11, 129.83, 133.74, 143.12, 153.62, 181.84.; HRMS: calcd. for C₁₁H₁₁NO: 173.2115, found: 173.1892.

2, 8-Dimethyl-1H-quinolin-4-one (3c): IR: 3338, 3031, 1643, 1625, 1569, 1471, 1341, 733 cm⁻¹; ¹H NMR (DMSO-*d*₆, 300 MHz) δ : 2.26 (s, 3H, CH₃), 2.54 (s, 3H, CH₃), 6.08 (s, 1H, CH=), 7.32 (m, 1H, Ph), 7.41 (d, J = 7.5 Hz, 1H, Ph), 7.68 (d, J = 7.6 Hz, 1H, Ph), 8.6 (s, 1H, NH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ : 17.21, 24.47, 104.32, 116.32, 124.54, 127.83, 130.25, 134.43, 142.20, 152.35, 184.54; HRMS: calcd. for C₁₁H₁₁NO: 173.2753, found: 173.6218.

2,7-dimethyl-1H-quinolin-4-one (3d): IR: 3345, 3037, 1646, 1620, 1568, 1463, 1338, 730 cm⁻¹; ¹H NMR (DMSO-*d*₆, 300 MHz) δ : 2.21 (s, 3H, CH₃), 2.32 (s, 3H, CH₃), 6.05 (s, 1H, CH=), 7.21 (s, 1H, Ph), 7.38 (d, J = 7.6 Hz, 1H, Ph), 7.72 (d, J = 7.5 Hz, 1H, Ph), 8.6 (s, 1H, NH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ : 15.77, 24.73, 103.25, 116.41, 124.76, 126.96, 131.54, 136.38, 142.51, 156.26, 183.43; HRMS: calcd. for C₁₁H₁₁NO: 173.7294, found: 173.3133.

2-Methyl-6-methoxy-1H-quinolin-4-one (3e): IR: 3347, 3036, 1642, 1623, 1570, 1475, 1348, 743 cm⁻¹; ¹H NMR (DMSO-*d*₆, 300 MHz) δ : 2.35 (s, 3H, CH₃), 3.73 (s, 3H, OCH₃), 6.13 (s, 1H, CH=), 7.45 (d, J = 7.7 Hz, 1H, Ph), 7.72 (d, J = 7.6 Hz, 1H, Ph), 7.89 (s, 1H, Ph), 8.70 (s, 1H, NH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ : 24.72, 57.42, 104.63, 117.33, 125.12, 127.43, 130.46, 146.71, 154.33, 167.68, 184.15; HRMS: calcd. for C₁₁H₁₁NO₂: 189.3025, found: 189.3354.

2-Methyl-8-methoxy-1H-quinolin-4-one (3f): IR: 3342, 3039, 1641, 1631, 1573, 1478, 1341, 747 cm⁻¹; ¹H NMR (DMSO-*d*₆, 300 MHz) δ : 2.52 (s, 3H, CH₃), 3.73 (s, 3H, OCH₃), 6.03 (s, 1H, CH=), 7.08 (m, 1H, Ph), 7.19 (d, J = 7.5 Hz, 1H, Ph), 7.53 (d, J = 7.5 Hz, 1H, Ph), 8.73 (s, 1H, NH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ : 24.13, 56.21, 101.48, 116.42, 122.32, 124.93, 125.62, 132.11, 148.74, 167.52, 185.71; HRMS: calcd. for C₁₁H₁₁NO₂: 189.2489, found: 189.3162.

2-Methyl-7-methoxy-1H-quinolin-4-one (3g): IR: 3351, 3034, 1647, 1633, 1575, 1471, 1358, 735 cm⁻¹; ¹H NMR (DMSO-*d*₆, 300 MHz) δ : 2.46 (s, 3H, CH₃), 3.75 (s, 3H, OCH₃), 6.10 (s, 1H, CH=), 7.12 (s, 1H, Ph), 7.27 (d, J = 7.6 Hz, 1H, Ph), 7.89 (d, J = 7.5 Hz, 1H, Ph), 8.75 (s, 1H, NH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ : 24.25, 56.72, 102.73, 114.51, 124.64, 127.78, 131.46, 147.52, 156.21, 168.31, 186.42; HRMS: calcd. for C₁₁H₁₁NO₂: 189.5547, found: 189.2396.

2-Methyl-6-chloro-1H-quinolin-4-one (3h): IR: 3345, 3033, 1646, 1617, 1571, 1470, 1341, 704 cm⁻¹; ¹H NMR (DMSO-*d*₆, 300 MHz) δ : 2.27 (s, 3H, CH₃), 6.17 (s, 1H, CH=), 7.31 (d, J = 7.6 Hz, 1H, Ph), 7.68 (d, J = 7.5 Hz, 1H, Ph), 7.83 (s, 1H, Ph), 9.11 (s, 1H, NH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ : 24.31, 103.22, 114.13, 124.76, 127.32, 131.24, 135.13, 146.43, 151.81, 182.42; HRMS: calcd for C₁₀H₈NOCl: 193.8753, found: 193.6542.

2-Methyl-8-chloro-1H-quinolin-4-one (3i): IR: 3332, 3031, 1632, 1624, 1576, 1473, 1352, 721 cm⁻¹; ¹H NMR (DMSO-*d*₆, 300 MHz) δ : 2.22 (s, 3H, CH₃), 6.13 (s, 1H, CH=),

7.25 (m, 1H, Ph), 7.34 (d, J = 7.5 Hz, 1H, Ph), 7.52 (d, J = 7.5 Hz, 1H, Ph), 9.02 (s, 1H, NH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ : 24.52, 101.89, 116.23, 125.42, 127.59, 130.82, 136.74, 146.32, 153.46, 184.37; HRMS: calcd. for C₁₀H₈NOCl: 193.5273, found: 193.2861.

2-Methyl-7-chloro-1H-quinolin-4-one (3j): IR: 3351, 3038, 1647, 1625, 1573, 1471, 1338, 733 cm⁻¹; ¹H NMR (DMSO-*d*₆, 300 MHz) δ : 2.27 (s, 3H, CH₃), 6.15 (s, 1H, CH=), 7.28 (s, 1H, Ph), 7.36 (d, J = 7.6 Hz, 1H, Ph), 7.73 (d, J = 7.5 Hz, 1H, Ph), 9.07 (s, 1H, NH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ : 24.57, 102.84, 115.62, 124.23, 127.56, 132.41, 135.28, 145.92, 153.64, 181.27; HRMS: calcd. for C₁₀H₈NOCl: 193.7468, found: 193.5396.

2-Methyl-6-nitro-1H-quinolin-4-one (3k): IR: 3336, 3031, 1641, 1627, 1568, 1462, 1345, 732 cm⁻¹; ¹H NMR (DMSO-*d*₆, 300 MHz) δ : 2.31 (s, 3H, CH₃), 6.12 (s, 1H, CH=), 7.42 (d, J = 7.6 Hz, 1H, Ph), 7.78 (d, J = 7.8 Hz, 1H, Ph), 7.97 (s, 1H, Ph), 9.13 (s, 1H, NH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ : 24.55, 104.31, 114.24, 125.11, 128.36, 132.43, 135.26, 146.35, 156.22, 186.27; HRMS: calcd. for C₁₀H₈N₂O₃: 204.1782, found: 204.4537.

2-Methyl-1H-benzo[h]quinolin-4-one (3l): IR: 3354, 3037, 1672, 1631, 1578, 1455, 1371, 753 cm⁻¹; ¹H NMR (DMSO-*d*₆, 300 MHz) δ : 2.28 (s, 3H, CH₃), 6.05 (s, 1H, CH=), 7.31-7.89 (m, 6H, Ph), 8.52 (s, 1H, NH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ : 23.92, 101.65, 113.47, 114.42, 122.33, 123.73, 124.13, 125.11, 127.93, 128.36, 132.58, 145.61, 156.72, 183.55; HRMS: calcd for C₁₄H₁₁NO: 209.3849, found: 209.7625.

RESULTS AND DISCUSSION

Herein, we wish to report our study on the synthesis of quinoline based on Combes approach by using NKC-9 as heterogeneous catalysts. It has been observed that macroporous strongly acidic styrol resin (NKC-9), which functional group is SO₃H, equals to Amberlyst-15 (USA) is an efficient catalyst for construction of quinoline derivatives from anilines and ethyl acetoacetate (Fig. 1).

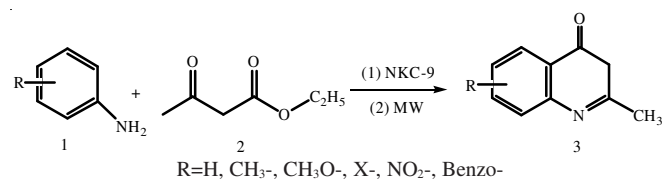


Fig. 1. Microwave Synthesis of 2-methyl-4-quinolinone under the catalyst NKC-9

Our initial study was started by reacting aniline with ethyl acetoacetate under solvent-free. The results are summarized in Table-1.

As shown in Table-1, the quinoline was not observed or in low yield in the absence of catalyst KNC-9 (entries 1, 2 Table-1). Prolonging reaction time could not increase quinoline yield (entries 3-6, Table-1). Augment of catalyst moderately helped to increase yields of quinoline (entries 7-9, Table-1). Inspiringly, using microwave irradiation could significantly shorten the reaction time and improve the reaction yields (entries 3-9, Table-1).

TABLE-1
SYNTHESIS OF QUINOLINE (3a) BY REACTING ANILINE
(2.0 mmol) WITH ETHYL ACETOACETATE
(2.4 mmol) UNDER SOLVENT-FREE

Entry	NKC-9 (g)	Time (min)	Media (SF) ^c	Yield (3a) /% ^{a, b}
1	/	120	r. t.	/
2	/	120	70 °C	53
3	0.05	0.5	MW ^d	81
4	0.05	1.0	MW	84
5	0.05	1.5	MW	89
6	0.05	2.0	MW	87
7	0.10	2.0	MW	91
8	0.15	2.0	MW	93
9	0.20	2.0	MW	92

^aProducts were identified by IR, ¹H NMR, ¹³C NMR and HRMS.

^bIsolated yields.

^cSF is Solvent-free; ^dMW is microwave irradiation (400 w)

Furthermore, we compared reaction effect by using catalyst (NKC-9) with other reported catalysts. The results are shown in Table-2.

TABLE-2
SYNTHESIS OF QUINOLINE (3a) BY REACTING ANILINE
(2.0 mmol) WITH ETHYL ACETOACETATE (2.4 mmol)
UNDER VARIOUS CATALYSTS

Entry	Catalyst	Condition	Yield (%) ^{a, b}
1	H ₂ SO ₄ (98 %)	SF / MW / 1.5 min	85
2	HF	SF / MW / 1.5 min	63
3	H ₃ PO ₄	SF / MW / 1.5 min	79
4	ZnCl ₂	SF / MW / 1.5 min	47
5	SiO ₂	SF / MW / 1.5 min	41
6	InCl ₃	SF / MW / 1.5 min	52
7	NaHSO ₄ /SiO ₂	SF / MW / 1.5 min	87
8	NKC-9	SF / MW / 1.5 min	93
9 ^c	Re-NKC-9	SF / MW / 1.5 min	90

^aProducts were identified by IR, ¹H NMR, ¹³C NMR and HRMS.

^bIsolated yields; ^cRe-NKC-9 was regenerated resin

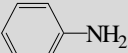

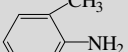
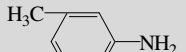
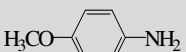
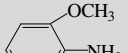
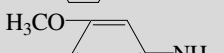
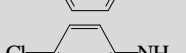
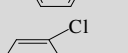
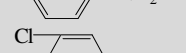
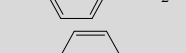
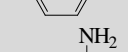
It was found that the yields of the reactions were not desired by using Lewis acids as catalysts (entries 4-6, Table-2). Although some proton acids could achieve high yields, they were difficult to recovery and reuse (entries 1-3, 7, Table-2). Besides high yield, our method has two prominent merits that the catalyst (NKC-9) can be recycled by using hydrochloric treatment and the reaction time is shorter (entries 8-9, Table-2).

After a comprehensive survey of the reaction conditions, acidic styrol resin (NKC-9) was considered as appropriate catalysis for Combes reaction and used to synthesize quinolines by reacting aniline (2.0 mmol) with ethyl acetoacetate (2.4 mmol) under microwave irradiation (400 w, 1.5 min) and solvent-free. Subsequently, a variety of amines were examined using this method (Fig. 1). The results are listed in Table-3.

The high yields of quinolines were most obtained under such reaction conditions. It was noteworthy that electronic effect on the aniline ring strong affected on the yields of quinolines. Overall, aniline bearing electron-donating group gave higher yields of quinolines than those of electron-withdraw group. Significantly, when electron-donating groups were located at *ortho*- and *para*-aniline (entries 2, 3, 5, 6, Table-3), the reaction yields were somewhat lower than at *meta*-aniline (entries 4, 7, Table-3). However, the yields of quinolines were

reduced when aniline carrying electron-withdraw groups (entries 8-11, Table-3), Moreover, other aromatic amines, such as naphthylamine, also could afford the corresponding quinoline under the same condition smoothly (entry 12, Table-3).

TABLE-3
SYNTHESIS OF QUINOLINE DERIVATIVES CATALYZED
BY RESIN (NKC-9) BETWEEN AMINES AND
ETHYL ACETOACETATE

Entry	RNH ₂	Yield/% ^{a, b}
1		3a (93)
2		3b (87)
3		3c (85)
4		3d (93)
5		3e (80)
6		3f (86)
7		3g (95)
8		3h (77)
9		3i (70)
10		3j (73)
11		3k (59)
12		3l (91)

^aProducts were identified by IR, ¹H NMR, ¹³C NMR and HRMS.

^bIsolated yields.

Conclusion

In conclusion, we have demonstrated an efficient, mild method for the synthesis of 2-methyl-4-quinolinone by employing macroporous strongly acidic styrol resin (NKC-9) as catalyst for the Combes reaction. Furthermore, catalyst (NKC-9) can be recycled by using hydrochloric treatment. Various substituted anilines underwent the above reaction with ethyl acetoacetate to produce corresponding substituted quinolines under microwave irradiation and solvent-free. The process is operationally simple and provides excellent yields to quinolines synthesis *via* Combes cyclization.

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REFERENCES

1. T.R. Verhoeven, P.J. Reider, M. Labelle, J.Y. Gauthier, Y.B. Xiang and R.J. Zamboni, *J. Org. Chem.*, **61**, 3398 (1996).
2. A. Sparatore, N. Basilico, S. Parapini, S. Romeo, F. Novelli and F. Sparatorec, *J. Biol. Med. Chem.*, **13**, 5338 (2005).
3. D. Dubé, M. Blouin, C. Brideau, C.-C. Chan, S. Desmarais, D. Ethier, J.-P. Falguyret, R.W. Friesen, M. Girard, Y. Girard, J. Guay, D. Riendeau, P. Tagari and R.N. Young, *Bioorg. Med. Chem. Lett.*, **8**, 1255 (1998).
4. T.R. Govindachari, K.R. Ravindranath and N. Viswanathan, *J. Chem. Soc., Perkin Trans. I*, 1215 (1974).
5. S.A. Jenekhe, L. Lu and M.M. Alam, *Macromolecules*, **34**, 7315 (2001).
6. Z.H. Skraup, *Chem. Ber.*, **13**, 2086 (1880).
7. R. Hauser and G.A. Reynolds, *J. Am. Chem. Soc.*, **70**, 2402 (1948).
8. M. Conrad and L. Limpach, *Chem. Ber.*, **20**, 944 (1887).
9. O. Döebner and W.V. Miller, *Chem. Ber.*, **16**, 246 (1883).
10. A. Combes, *Bull. Soc. Chim. Fr.*, **49**, 89 (1888).
11. P. Friedlander, *Chem. Ber.*, **15**, 2572 (1882).
12. K. Mogilaiah, K. Vidya and T.K. Swamy, *Indian J. Chem.*, **48B**, 599 (2009).
13. B. Sapkal, K.F. Shelke, B.B. Shingate and M.S. Shingare, *J. Korean Chem. Soc.*, **54**, 723 (2010).