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Synthesis of quinoline derivatives by acid catalyzed microwave-assisted approach

V.Nadaraj*[#1], S.Thamarai Selvi[1]

[#]Department of Chemistry, Tamilnadu College of Engineering, Karumathampatti, Coimbatore-641659, (INDIA)

[1]Department of Chemistry (PG and Research), Kongunadu Arts and Science College, G.N. Mills (PO), Coimbatore, 641029, (INDIA)

E-mail: vnraj303@yahoo.com; thamaraimohan@yahoo.co.in

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ABSTRACT

Acid catalyzed microwave-assisted synthesis of quinoline intermediates from anilines and diethyl-1,3-acetonedicarboxylate is described. The cyclocondensation reaction in a matter of minutes and provided excellent yields. The structures of the synthesized compounds were confirmed by analytical and spectral (IR, NMR, and Mass) data.

KEYWORDS

Quinoline;
Microwave;
Aniline;
Cyclocondensation;
Acid.

INTRODUCTION

The synthesis of nitrogen heterocycles has been of considerable interest to organic and medicinal chemistry for many years as large number of natural product and drugs contain this hetero atom[1-5]. The obvious applications of compound derived from heterocyclic rings in pharmacy, medicine, agriculture and other fields. Among them, the nitrogen heterocyclic compounds, quinolines find valuable applications in medicinal field.

The quinolines skeleton is a common structural motif in a broad range of biologically active compounds. Quinoline derivatives are utilised as anti-malarial,[6] antibacterial,[7,8] antifungal[9,10] and antitumour[11]. Due to their importance, the synthesis of quinolines attracted widespread attention. It is well known that, the major synthetic routes leading to the formation of pyrano-, pyrido- pyrimidioquinolines and acridines invariably involved some common intermediates. Several methods such as skraup, Doebner-Miller, Friedlander and Combes synthesis were developed which provide quinolines derivatives efficiently, but so in multiple steps and using harmful reagents and harsh conditions. However many of these methods suffer from the needs of high temperature prolonged reaction time and drastic reaction conditions and also the unsatisfied yields. Therefore, the design of improved and environmentally benign approaches for their preparation is great demand.

Now-a-day "Microwave-induced organic reaction enhancement" (MORE) chemistry result in accelerated reactions[12-14] conducted safely in open vessels (such as Erlenmeyer flasks or beakers) in commercial microwave ovens key elements of these techniques are the choice of low volatility solvents which can serve as efficient microwave energy transfer regents and control of energy input to prevent boiling of the reaction mixture. Recently[15-17] we employed different basic and acidic catalyst under microwave irradiation, promoting both yield and rates of the reaction greatly.

Microwave-induced rate acceleration technology has becomes a powerful tool in organic synthesis be-

cause, the high beating efficiency gaining remarkable rate, enhancement and dramatic reduction in reaction time[18-20]. Herein, we describe an environmentally benign one-pot domino approach for the synthesis of quinolines intermediates. The major benefits of the microwave assisted heterogeneous catalytic reaction are fast reaction, solvent free and improve yield.

EXPERIMENTAL

Melting points were recorded on Boetieus microheating table and are uncorrected. IR (KBr) spectra were recorded on a Shimadzu-8201 FT spectrophotometer. ^{1}H NMR spectra were recorded on AMX-400 (400 MHz) spectrometer, using TMS as an internal reference, and mass spectra were recorded at 70eV on a Joel JMS-D-300 instrument. The reactions were carried out in a domestic microwave oven (KENSTAR–OM-20ESP, 2450 MHz).

Synthesis of ethyl (1,4-dihyroquinolin-4-one-2-yl)acetate derivatives (3a-e) from anilines with diethyl-1,3-acetonedicrboxylate

General procedure: Anilines (0.005 mole), diethyl-1,3-acetonedicarboxylate (0.007 mole) and catalytic amount of *p*-Toulene Sulphonic acid (PTSA) were taken in a 100 mL beaker and mixed well with the help of a glass rod and covered with a watch glass. The reaction mixture was irradiated in the microwave oven at 320 W for the specified times (TABLE 2). The progress of reaction was monitored at 30 s intervals by TLC. After completion of the reaction, the mixture was poured into boiling water. The solid obtained was boiled with sodium carbonate solution, filtered, dried and purified.

3a: IR (KBr) νcm^{-1}: 3500-3200 (NH), 1715 (C = O), 1621 (4-quinoline); ^{1}H NMR (DMSO-d_6) δ ppm : 1.22 (t, 3H, CH_3), 3.79 (s, 2H, CH_2), 3.93-3.95 (q, 2H, OCH_2), 5.39 (s, 1H, C_3-H), 7.09-7.65 (m, 4H, Ar-H), 9.09 (s, 1H, NH); MS (70 eV): 231 (M^+, 100%), 202 (24 %) and 187 (58 %). Anald. Calculated for $C_{13}H_{13}NO_3$; C 63.53, H 5.67, N 6.06%, Found C 63.50, H 5.62, N 6.01%.

3b: IR (KBr) νcm^{-1}: 3560-3200 (NH), 1712 (C=O), 1620 (4-quinoline); ^{1}H NMR (DMSO-d_6) δ ppm : 1.25 (t, 3H, CH_2CH_3), 2.52 (s, 3H, 6-CH_3), 3.76 (s, 2H, CH_2), 3.93-3.95 (q, 2H, CH_2CH_3), 5.33 (s, 1H, C_3-H), 7.03-7.55 (m, 3H, Ar-H), 7.60 (s, 1H, C_6-H) 9.12 (s, 1H, NH); MS (70 eV): 245 (M^+, 100%). Anald. Calculated for $C_{14}H_{15}NO_3$; C 68.57, H 6.17, N 5.71%, Found C 68.51, H 6.12, N 5.68%.

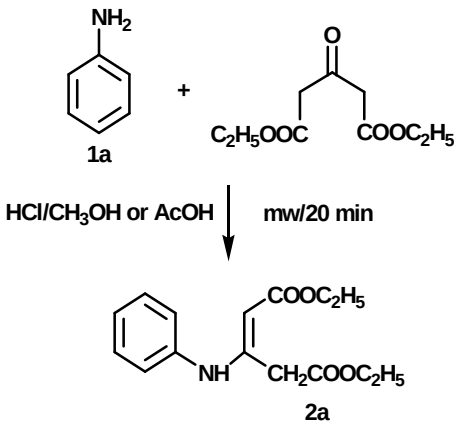
3c: IR (KBr) νcm^{-1}: 3500-3180 (NH), 1718 (C = O), 1630 (4-quinoline); ^{1}H NMR (DMSO-d_6) δ ppm : 1.18 (t, 3H, CH_2CH_3), 2.56 (s, 3H, 8-CH_3), 3.66 (s, 2H, CH_2), 3.88-3.93 (m, 2H, CH_2CH_3), 5.40 (s, 1H, C_3-H), 7.11-7.58 (m, 3H, Ar-H), 9.22 (s, 1H, NH); MS (70 eV): 245 (M^+, 100%).

3d: IR (KBr) νcm^{-1}: 3550-3300 (NH), 1715 (C = O), 1624 (4-quinoline); ^{1}H NMR (DMSO-d_6) δ ppm : 1.22 (t, 3H, CH_2CH_3), 3.97 (s, 3H, 6-OCH_3), 3.70 (s, 2H, CH_2), 3.88-3.92 (q, 2H, CH_2CH_3), 5.36 (s, 1H, C_3-H), 7.11-7.50 (m, 3H, Ar-H), 7.58 (s, 1H, C_6-H) 9.22 (s, 1H, NH); MS (70 eV): 261 (M^+, 100%).

3e: IR (KBr) νcm^{-1}: 3550-3330 (NH), 1712 (C = O), 1620 (4-quinoline); ^{1}H NMR (DMSO-d_6) δ ppm : 1.25 (t, 3H, CH_2CH_3), 3.99 (s, 3H, 8-OCH_3), 3.70 (s, 2H, CH_2), 3.92-3.98 (q, 2H, CH_2CH_3), 5.32 (s, 1H, C_3-H), 7.15-7.60 (m, 3H, Ar-H), 9.20 (s, 1H, NH); MS (70 eV): 261 (M^+, 100%).

RESULTS AND DISCUSSION

To develop our new approach, we have chosen the cyclisation of aniline **(1a)** with diethyl-1,3-acetonedicarboxylate as reaction sequence. The reactions have been tried out by irradiation of aniline with diethyl-1,3-acetonedicarboxylate in presence of HCl/CH_3OH. But unfortunately, now cyclisation could not be observed even at high power of microwave irradiation and maximum time (20 min). In contrast, HCl, a



Scheme 1

traditional liquid acid while providing the intermediate uncyclised product **(2a)** (Scheme 1). In order to optimize the reaction parameter, we carried out several test reaction and studied the effect of temperature (Watt) and various catalyst and time.

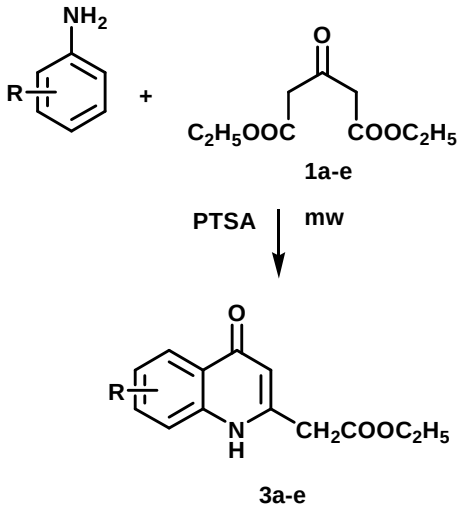
Different catalyst including acetic acid, silica gel, acidic alumina, PTSA, Lewis acid like $ZnCl_2$, $AlCl_3$ and PPA were characterized to define the most effective (TABLE 1) catalyst and varying the reaction time and power of microwave irradiation. In a typical procedure, cyclic condensation of aniline with diethyl-1,3-acetonedicarboxylate in presence of respective catalyst under various power of microwave irradiation. After completion of the reaction the obtained solid was washed with hot sodium carbonate solution, filtered, dried and purified.

TABLE 1 : Effect of catalyst for synthesis of (3a) under microwave irradiation

Catalyst	Reaction Time (min)	Power (W)	Yield (%)
HCl	20	160	Nil
Acetic acid	20	160	Nil
Acidic alumina	12	320	15
K_{10} Clay	12	320	60
Silica gel	10	320	10
PTSA	8	320	89
$ZnCl_2$	10	160	68
$AlCl_3$	12	160	82
PPA	14	160	66

Thus IR Spectrum of solid **(3a)** show characteristic absorption band in the region 3500-3200 cm^{-1} for NH group and 1715 cm^{-1} for ester carbonyl group and peak at 1621 cm^{-1} for 4-quinoline moiety. ^1H NMR spectrum predicted three singlets at δ 5.39, 3.79 and 9.09 for C_3-H, -CH_2- and NH protons and also revolved triplet at δ 1.22 for methyl prontons and quartet at δ 3.93-3.95 for OCH_2 protons. The unresolved multiplet appeared in the region δ 7.09-7.65 for aromatic protons. The mass spectrum shows the molecular peak at *m/z* 231 and other peak at 202, 187. The elemental analysis of **(3a)** corroborated the propose molecular formula $C_{13}H_{13}NO_3$; Calcd.: C 63.53, H 5.67, N 6.06%; Found: C 63.50, H 5.62, N 6.01%. All the above spectral data, the obtained compound **(3a)** confirmed as ethyl (1,4-dihyroquinolin-4-one-2-yl)acetate.

From the results obtained by using different solid supports, it is obvious that PTSA is the most suitable catalyst for the synthesis of ethyl (1,4-dihyroquinolin-4-one-2-yl)acetate **(3a)**, as it reduces the reaction time to minimum and increases the yield of the product to maximum (TABLE 1). These conditions have thus been extended to the synthesis of other ethyl (1,4-dihyroquinolin-4-one-2-yl)acetate derivatives **(3b-e)** (Scheme 2) with very good results (TABLE 2).



1a R = H **3a R = H**
1b R = 4-CH_3 **3b R = 6-CH_3**
1c R = 2-CH_3 **3c R = 8-CH_3**
1d R = 4-OCH_3 **3d R = 6-OCH_3**
1e R = 2-OCH_3 **3e R = 8-OCH_3**

Scheme 2

TABLE 2 : Physical data of quinolines derivaives (3a-g) from (1a-g) under microwaves

Compound	Reaction Time (min)	Yield (%)	mp °C
2a	8	89	202
2b	6	90	196
2c	7	80	200
2d	9	82	184
2e	8	89	175

CONCLUSION

In conclusion, we have elaborated a convenient solid acid catalyzed synthetic path way to substituted quinolines based on cyclic condensation of anilines with diethyl-1,3-acetonedicarboxylate is described. This method provides the products in good to excellent yields

and very short reaction time. In addition to efficient, solvent-free, environmentally free and waste free nature make the process an alternative green synthesis of quinolines derivatives.

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