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An improved synthesis of 2-amino-3-formylquinoline derivatives under phase transfer condition

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ABSTRACT

2-Amino-3-formylquinoline intermediates were synthesised by microwave enhanced reaction in a time-efficient manner with high yield starting from 2-cholor-3-formyl quinoline and ammonium acetate as constituent synthons using tetra butyl ammonium bromide (TBAB) as a catalyst.

KEYWORDS

Quinoline;
Microwave;
Phase transfer catalysts;
Ammonium acetate;
2- chloro-3-formylquinoline.

INTRODUCTION

The synthesis of nitrogen heterocycles has been of considerable interest to organic and medicinal products and drugs contain this heteoatom[1-4]. Among, the nitrogen heerocyclic compouonds, quinolines find valuable applications in medicinal field. Quinoline derivatives are found to possess a broad spectrum of biological activities such as antimalarial[5-7], antibacterial[8-10], antifungal[11,12] and anticancer[13,14]. Due to their importance, the synthesis of quinoline attracted widespread attention. It is well known that, the major synthetic routes leading to the formation of pyrano-, pyrido- and pyrimidioquinolines invariably involved some common intermediates.

Among them, 2-chloro-3-formylqunoline and 2-amino-3-formylquinoline occupy a prominent position, as they are key intermediates for further [*b*]-annelation of wide variety of rings and for various functional group interconversion. 2-Amino-3-formylquinolines are used for synthesis of various naphthyridine systems[15,16]. Conventionally[15], 2-amino-3-formylquinolines are prepared from respective 2-chloro-3-formylquinoine by passing dry ammonia in ethanol for 4-hr at 0-20º C and then kept at room temperature for 12 hr. The time taken for the classical method is nearly 16 hr and temperature control in necessary.

Microwave irradiation using commercial domestic oven has been recently used to accelerate organic reactions, the high heating efficiency giving remarkable rate enhancement and dramatic reduction in reaction time[17,18]. As a part of a research project to develop environmentally benign organic reactions, we have recently reported the synthesis of simple quinolines, pyrimido- and pyrazoloquinolines under microwaves[19,20].

Herein, we describe an environmentally benign one-pot domino approach for the synthesis of quinolines. The major benefits of the microwave assisted phase transfer processes are the fast reaction, solvent free, environment and improve yield.

EXPERIMENTAL

Melting points (mp) were determined using Boetieus micro heating table and are uncorrected.

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IR (KBr, cm^{-1}) spectra were obtained on Shimadzu-8201 spectrophotometer. ^1H NMR spectra were recorded on Bruker AMX-400 (400 MHz) spectrometer using TMS as an internal reference (Chemical shift in δppm). Elemental analyses were performed on Perking Elmer CHN-analyzer. Mass spectra were recorded on Shimadzu GCMS-QP5050A (70eV) mass spectrometer. For microwave irradiation a Ken star domestic microwave oven was used.

Synthesis of 2-amino-3-formylquinolines (2a-e) from 2-chloro-3-formylquinolines (1a-e)

General procedure

The respective 2-chloro-3-formylquinoline (1 mmol), ammonium acetate (1 mmol) and 100 mg of TBAB and few drops of water were taken in a 100 mL beaker and irradiated using microwave for specific time (TABLE-1). After the completion, the reaction mixture poured into ice and the precipitate formed was filter and purified using column chromatography.

2-amino-3-formylquinoline (2a)

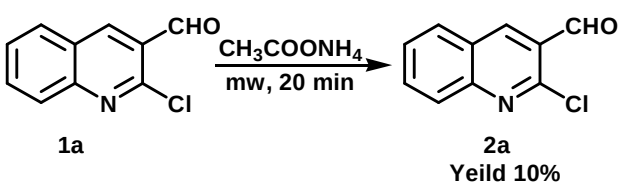
IR (KBr) νcm^{-1}: 3448 (NH_2), 1685 (C = O), 1571 (CN); ^1H NMR (DMSO-d_6) δppm : 3.91 (s, 2H; NH_2), 7.74-8.29 (m, 4H; Ar-H), 8.89 (s, 1H; C_4-H), 8.99 (s, 1H; C_5-H), 10.28 (s, 1H; CHO); MS (70 eV): 172 (M^+, 100%).

6-methyl-2-amino-3-formylquinoline (2b)

IR (KBr) νcm^{-1}: 3400 (NH_2), 1680 (C = O), 1570 (CN); ^1H NMR (DMSO-d_6) δppm : 2.42 (s, 3H; CH_3), 3.88 (s, 2H; NH_2), 8.22 (s, 1H; C_6-H), 8.91 (s, 1H; C_5-H), 7.82 (d, 1H; C_7-H), 7.94 (d, 1H; C_8-H), 10.22 (s, 1H; CHO); MS (70 eV): 186 (M^+, 100%).

8-methyl-2-amino-3-formylquinoline (2c)

IR (KBr) νcm^{-1}: 3440 (NH_2), 1685 (C = O), 1568 (CN); ^1H NMR (DMSO-d_6) δppm : 2.48 (s, 3H; CH_3), 3.90 (s, 3H; NH_2), 7.80-8.10 (m, 3H; $C_{5,6}$ & $_7$-H), 10.28 (s, 1H, CHO).



Scheme 1

6-methoxy-2-amino-3-formylquinoline (2d)

IR (KBr) νcm^{-1}: 3445 (NH_2), 1683 (C = O), 1568 (CN); ^1H NMR (DMSO-d_6) δppm : 3.80 (s, 2H; NH_2), 3.99 (s, 3H; OCH_3), 7.70-8.89 (m, 3H; $C_{5,6}$ & $_8$-H), 10.30 (s, 1H, CHO).

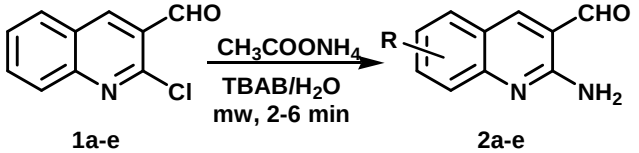
8-methoxy-2-amino-3-formylquinoline (2e)

IR (KBr) νcm^{-1}: 3448 cm^{-1} (NH_2), 1685 cm^{-1} (C = O), 1560 cm^{-1} (CN); ^1H NMR (DMSO-d_6) δppm : 3.82 (s, 2H; NH_2), 3.98 (s, 3H; OCH3), 7.78-8.68 (m, 3H; $C_{6,7}$ & $_8$-H), 10.32 (s, 1H, CHO).

RESULTS AND DISCUSSION

To develop our new approach, we have synthesis 2-amino-3-formylquinoline have been prepared from 2-chloro-3-formylquinoline by nucleophilic reaction in good yield. The starting material 2-chloro-3-formylquinoline has been prepared by Villsmeyer-Hack reaction of substituted acetanilide using DMF/$POCl_3$. For this purpose, a equimolar mixture of 2-chloro-3-formylquinoline and ammonium acetate (100mg) taken in a 100mL beaker and irradiated at 160W up to 20 min. [TLC Check]. The obtained solid was mixture of product. The obtained mixture was isolated using column chromatography. The target product obtained only in low yield (10%) (Scheme 1) and remaining as starting material 2-chloro-3-formylquinoline. Next we improve the yield of target product using effect of catalyst.

Based on our recent studies[21,22], we have chosen Tetra-butyl ammonium bromide (TBAB) as the catalyst. Tetra-butyl ammonium bromide (TBAB) was an alternative catalyst with various substrates. The cost availability and compatibility across phases in biphasic organic-aqueous layer heterogeneous reaction system, with water as solvent, TBAB was found to be a better catalyst. It was a commercially available, stable, environmentally benign, inexpensive, and active under microwave conditions and can be used without any pre-



R= H, 6-CH_3, 8-CH_3, 6-OCH_3, 8-OCH_3

Scheme 2

TABLE 1 : Synthesis of 2-amino-3-formylquinolines (2a-e) from 2-chloro-3-formylquinolines (1a-e) under microwave irradiation

Compound	Time (min)	mp (°C)	Yield (%)
2a	3	124	81
2b	2	172	88
2c	3	162	89
2d	4	145	89
2e	6	148	84

treatment. Its features and synthetic applications have been the topic of many reviews. The combination of phase transfer catalyst and microwave irradiation provided as extensive number of successful process[23-26].

Next, we explored the same reaction carried out in presence of TBAB and water under microwave irradiation for 3 min. at 160 W. The single yellowish product **(2a)** was obtained (TLC Check) in 83% yield. IR spectrum of obtained **(2a)** showed a peak at 3448 cm^{-1} for NH_2 group. The ^1H NMR spectrum of compound **(2a)** showed singlet at ä 3.91 for NH_2 protons and also showed three singlets at δ 8.89, 8.99 & 10.28 for C_4, C_5 & CHO protons. The mass spectrum showed molecular ion peak *m/z* at 172 (M^+, 100%). From these spectral data the obtained compound **(2a)** as 2-amino-3-formylquinoline. The quinoline derivatives with substitutions in the aromatic ring with 6-methyl, 8 - methyl, 6-mthoxy and 8-methoxy to furnish a series of products **(2a-e)** (TABLE 1).

The general synthetic scheme for 2-amino-3-formylquinolines **(2a-e)** has been depicted in Scheme 2. The Structure of all the synthesised compound were established on the basis of their spectral (IR, ^1H NMR, and Mass spectrum) and elemental analysis data. The melting point, time required for preparation and yield percentage of all the products have been summarised in TABLE 1.

CONCLUSION

The procedures described above provide a useful, clean, fast and efficient alternative for the preparation of 2-amino-3-formylquinoline from 2-chloro-3-formylquinolin under microwave irradiation. The use of TBAB preserves the classical simplicity of one-pot synthesis and remarkably improved the yield profile and short reaction time (2-6 min) than conventional method (16 hr). The major benefits of the microwave assisted phase transfer processes are the fast reaction, solvent free, environment and improve yield.

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REFERENCES

[1] E.Ritchie; Pure Appl.Chem., **14**, 561 (**1964**).
[2] M.F.Grundon; Alkaloids (London), **6**, 103 (**1976**).
[3] M.N.S.Nayar, C.V.Sutar, M.K.Bhan; Phytochemistry, **10**, 2843 (**1971**).
[4] R.Storer, D.W.Young, D.R.Taylor, J.M.Wrner; Tetrahedron, **29**, 721 (**1973**).
[5] O.Bilker, V.Lindo, M.Panico, A.E.Etiene, T.Paxton, A.Dell, M.Rogers, R.E.Sinden, H.R.Morris; Nature, **392**, 289 (**1998**).
[6] G.Roma, M.D.Braccio, G.Grossi, F.Mattioli, H.Ghiz; Eur.J.Med.Chem., **35**, 1021 (**2000**).
[7] Y.L.Chen, K.C.Fang, J.Y.Sheu, S.L.Hsu, C.C.Tzeny; J.Med.Chem., **44**, 2374 (**2001**).
[8] K.C.Fang, Y.L.Chen, J.Y.Sheu, T.C.Wang, C.C. Tzeny; J.Med.Chem., **43**, 3809 (**2000**).
[9] J.Chevalier, S.Atifi, A.Eyraud, A.Mahamoad, J.Barbe, J.M.Pages; J.Med.Chem., **44**, 4023 (**2001**).
[10] L.T.Phan, T.Jian, Z.Chen, Y.L.Qiu, Z.Wang, T.Beach, A.Plemeropoulos, Y.S.Or; J.Med.Chem., **47**, 2965 (**2004**).
[11] L.Y.Vargas, M.V.Castelli, V.V.Kouzetsov, J.M.Urbina, S.N.Lopez, M.Sortino, R.D.Enriz, J.C.Ribas, S.Zacchino; Bioorg.Med.Chem., **11**, 1531 (**2003**).
[12] M.Singh, M.P.Singh, S.Y.Ablodeppey; Drug Dev.Ind.Pharm., **22**, 377 (**1996**).
[13] L.Dassonneville, A.Lansiaux, A.Wattelet, N.Wattez, C.Mahieu, S.Van Miert, L.Pieters, C.Billy; Eur.J. Pharmcol., **409**, 9 (**2000**).
[14] L.Dassonneville, K.Bongean, M.C.DePauwgillet, P.Colson, C.Houssier, J.Quetin-Leclercg, L.Angenot, S.Y.Ablordeppey; Bioorg.Med.Chem., **10**, 1337 (**2002**).

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[15] G.Arul Prakash, S.P.Rajendran; Heterocylic Commun., **6**, 63 (**2000**).
[16] R.P.Thummel, D.K.Kohli; J.Heterocyclic Chem., **14**, 685 (**1977**).
[17] B.A.Roberts, C.R.Strauss; Acc.Chem.Res., **38,** 653 (**2005**).
[18] S.Jolivet, L.Toupet, F.Texior-Boullet, J.Hamelin; Tetrahedron, **52,** 5819, **(1996)**.
[19] S.Thamarai Selvi, V.Nadaraj, S.Mohan, R.Sasi, M.Hema; Bioorg.Med.Chem., **14**, 3896, **(2006)**.
[20] V.Nadaraj, S.Thamarai Selvi, R.Sasi; Arkivoc, 82 (**2006**).
[21] V.Nadaraj, S.Thamarai Selvi; Indian J.Chem.B, **46**, 1203 (**2007**).
[22] V.Nadaraj, S.Thamarai Selvi; Oriental J.Chem., **25**, 549 (**2009**).
[23] R.S.Varma, R.K.Saini; Synlett, **7**, 857 **(1997)**.
[24] R.S.Varma, D.Kumar; Tetrahedron Lett., **40,** 7665 (**1999**).
[25] A.Vass, J.Dudas, R.S.Varma; Tetrahedron Lett., **40**, 495 (**1999**).
[26] B.Ahmeed, R.A.Khan, Habibullah, M.Keshari; Tetrahenron Lett., **50**, 2889 **(2009)**.