CERIUM (IV) AMMONIUM NITRATE (CAN) AS A CATALYST IN WATER: A SIMPLE, PROFICIENT AND GREEN APPROACH FOR THE SYNTHESIS OF TETRAHYDROPYRIMIDINE QUINOLONES

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ABSTRACT

We report here a facile, mild and efficient synthesis of functionalized tetrahydropyrimidine quinolones via one pot three-component condensation of aromatic aldehydes, N,N-dimethyl barbituricacid (barbituricacid), 4-hydroxy-1-methylquinolin-2(1H)-one and using a cerium ammonium nitrate (CAN) as a green catalyst in aqueous media-water (as a green ideal solvent) is described. The significant advantages of this protocol are short reaction time, simple work up procedure and reduced environmental impact, wide substrate scope; generally very good to excellent yields and starting materials are inexpensive and commercially available. The structures of these compounds were established on the basis of IR, 1H NMR, 13C NMR spectra.

Key words: Tetrahydropyrimidine quinolones, One-pot, Multi-component, Green chemistry, Cerium ammonium nitrate.

INTRODUCTION

Multi-component reactions (MCRs) are important chemical transformations because of high atom economy, high yield, usable simplicity, structural variety, and complexity of the molecules, development of three and four-component reactions, in which have been used extensively of the carbon–carbon bonds in the organic chemistry, to give a final product in a one-pot procedure. Multi-component reactions are the main approaches for synthesis of special products with molecular diversity which have attracted much attention as a facial means by synthetic chemists. Therefore, the development of novel multi–component reactions is of interest for chemists [1-8].

Pyrimidine derivatives are an important series of organic compounds, because of their medicinal pedigree and the perfect activity for an effective synthesis method of heterocyclic structures. The pyrimidine showed a broad of reactivity and inexpensive, good solubility in water, etc. [27].

Tetrahydropyridines [25] not only based on its electron transfer capacity but also with its Lewis acidic property [26]. Using of CAN has many advantages like solubility in water, easy handling, non-toxic, eco-friendly nature, high reactivity and inexpensive, good solubility in water, etc. [27].

Herein, we describe a facile synthesis of tetrahydropyrimidine quinoline derivatives by the one-pot three-component reaction of 4-hydroxy-1-methyl-2-(1H)-quinolin, aromatic aldehyde, and N,N-dimethylbarbituricacid, in water using CAN as the Lewis catalyst at reflux condition (Scheme1).

EXPERIMENTAL SECTION

Melting points were measured with an Electrotherm 9200 apparatus and are not corrected. 1H NMR and 13C NMR spectra were recorded on a BRUKER AVANCE instrument using CDCl3 and DMSO-d6 as solvent and TMS as internal standard at 250 and 62.5 MHz, respectively. IR spectra were measured in JASCO FT-IR 6300 spectrometer with KBr plate.

General procedure for the synthesis of tetrahydropyrimidinequinoline derivatives (4a-j)
The mixture of aromatic aldehyde derivatives (1mmol), barbituricacid (1mmol) and 4-hydroxy-1-methyl-2-(1H)-quinoline in water at reflux conditions was stirred in the presence of CAN (25%) as a catalyst. The progress of the reaction was followed by TLC (n-hexane: ethyl acetate 7:3). After completion of the reaction the product was filtered, and washed with water to give pure product.

Spectral characterizations
5-((4-(dimethylamino)phenyl)(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (4a)

IR (KBr): ν = 3416, 2923, 1713, 1656, 1608, 1501, 1443, 1412, 1366, 1317, 1192, 1159, 1081, 831, 787, 752, 516, 474, 413 cm⁻¹; 1H NMR (CDCl3, 250 MHz): δ = 12.75 (s, 1H, enolic OH), 12.4 (s, 1H, enolic OH), 6.60-8.59 (m, 8H, ArH), 6.30 (s, 1H, CH-Ar), 3.75 (s, 3H, CH3), 3.64 (s, 3H, CH3), 3.35 (s, 6H, 2CH3), 2.92 (s, 3H, CH3); 13C NMR (62.5 MHz, CDCl3): δ = 160.6, 158.7, 154.4, 145.3, 139.5, 138.5, 133.7, 131.1, 124.8, 121.0, 114.3, 114.1, 111.0, 109.6, 78.8, 77.5, 77.1, 76.1, 76.4, 69.4, 62.1, 40.1, 34.5, 30.4, 30.0, 28.8, 28.2.

6-hydroxy-5-((4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)(4-nitrophenyl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (4b)

IR (KBr): ν = 3453, 2925, 2925, 1571, 1453, 1346, 1113, 759, 22, 494 cm⁻¹; 1H NMR (CDCl3, 250 MHz): δ = 14.92 (s, 1H, enolic OH), 11.67 (s, 1H, enolic OH), 7.20-8.67 (m, 8H, ArH), 5.90 (s, 1H, CH-Ar), 3.79 (s, 3H, CH3), 3.25 (s, 3H, CH3), 2.88 (s, 3H, CH3); 13C NMR (CDCl3, 250 MHz): δ = 161.9, 128.7, 123.4, 106.2, 77.5, 77.2, 77.0, 76.4, 70.6, 54.9, 53.3, 20.8, 17.4.

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4-hydroxy-3-((4-hydroxy-1,3-dimethyl-2-oxohexahydropyrimidin-5-yl)(3-nitrophenyl)methyl)-1-methyl-3,4-diarylquinoline (4c)

IR (KBr): δ = 3424, 1643, 1532, 1509, 1420, 1358, 1337, 1301, 1240, 1185, 1159, 1115, 1081, 856, 790, 754, 679, 533, 476 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz): δ = 14.14 (s, 1H, enolic OH), 11.06 (s, 1H, enolic OH), 7.00-8.57 (m, 8H, ArH), 5.51 (s, 1H, CH-Ar), 3.26 (s, 3H, CH₃), 2.91 (s, 3H, CH₃), 2.24 (s, 3H, CH₃), 1.29 (s, 3H, CH₃), 1.26 (s, 3H, CH₃), 1.24 (s, 3H, CH₃), 1.22 (s, 3H, CH₃), 1.21 (s, 3H, CH₃), 1.19 (s, 3H, CH₃), 1.18 (s, 3H, CH₃), 1.17 (s, 3H, CH₃), 1.15 (s, 3H, CH₃), 1.13 (s, 3H, CH₃), 1.11 (s, 3H, CH₃).

6-hydroxy-5-((4-hydroxy-1-methyl-2-oxo-1,2,6,7-tetrahydropyrimidin-3-yl)(4-hydroxyphenyl)methyl)-1,3-dimethylpyrimidine -2,4(1H,3H)-dione (4d)

IR (KBr): δ = 3451, 1686, 1607, 1569, 1529, 1455, 1346, 1261, 1214, 1169, 1098, 798, 760, 709, 676, 496 cm⁻¹; ¹H NMR (250 MHz, DMSO-d₆): δ = 11.31 (s, 1H, enolic OH), 10.81 (s, 1H, enolic OH), 8.28 (s, J = 8.4 Hz, 2H, Ar), 7.85 (d, J = 7.9 Hz, 1H, ArH), 7.59 (m, 1H, ArH), 7.43 (d, J = 8.5 Hz, 1H, ArH), 7.18 (m, 1H, ArH), 6.86 (d, J = 8.4 Hz, 2H, ArH), 5.84 (s, 1H, CH-Ar), 3.59 (s, 3H, CH₃), 3.40 (s, 1H, phenolic OH), 3.19 (s, 3H, CH₃), 3.17 (s, 3H, CH₃), 1.31 (s, 3H, CH₃). ¹C NMR (CDCl₃, 250 MHz): δ = 163.7, 136.4, 132.0, 131.6, 129.1, 128.9, 123.5, 121.5, 121.1, 114.2, 77.5, 77.2, 77.0, 76.5, 65.0, 29.2.

Further, in order to confirm the effect catalyst and optimized reaction in this transformation started the study by treating, therefore, we this reaction in mixture 4-chlorobenzaldehyde, N,N-diethylbarbituric acid and 4-hydroxy-1-methyl-2-(1H)-quinoline in the presence of different amount of CAN at reflux conditions. The resulting reaction, showed that in the presence of CAN and shorter time gave the best in yield (98%) (Table 2, entries 4-6). The using of other catalysts such as DABCO, p-TSA, L-proline were resulted poor yield. (Table 2, entry 1-3).

Table 1. Effect of solvent on the synthesis of Tetrahydro pyrimidine quinoline.

| Entry | Solvent | Time (min) | Yield (%) |
|-------|---------|------------|-----------|
| 1     | H₂O     | 45         | 92        |
| 2     | EtOH-H₂O| 45         | 92        |
| 3     | EtOH    | 60         | 90        |
| 4     | MeOH    | 60         | 73        |
| 5     | Solvent-free | 45      | 40        |
| 6     | CH₂Cl₂  | 30         | Trace     |

Table 2. Influence of catalysts in the synthesis of tetrahydro pyrimidine quinoline.

| Entry | Catalyst | Temp(°C) | Yield% |
|-------|----------|----------|--------|
| 1     | DABCO    | Reflux   | 72     |
| 2     | p-TSA    | Reflux   | 66     |
| 3     | L-proline| Reflux   | 50     |
| 4     | CAN (10 mol %) | Reflux | 85 |
| 5     | CAN (15 mol %) | Reflux | 89 |
| 6     | CAN (25 mol %) | Reflux | 98 |

Reactions are performed on a 1 mmol scale of the reactants in water under reflux condition.

To test the generality of this reaction, a group of different aromatic aldehydes with electron-donating and electron withdrawing under the optimized reaction and the results are summarized and condition reaction in Tables 3. In this regard, Results indicated that this reaction with successfully employed in the prepared product and excellent yield.

Table 3. Synthesis of compounds 4a.

| Entry | R       | R₁     | Product | Time (min) | Yield % | Mp (°C) |
|-------|---------|--------|---------|------------|---------|---------|
| 1     | CH₃     | 4-N(CH₃)₂ | 4a      | 10         | 72      | 232     |
| 2     | CH₃     | 4-NO₂   | 4b      | 5          | 98      | 216-218 |
| 3     | CH₃     | 3-NO₂   | 4c      | 15         | 90      | 234     |
| 4     | CH₃     | 4-OH    | 4d      | 35         | 82      | 218     |
| 5     | CH₃     | 4-Cl    | 4e      | 20         | 85      | 230     |
| 6     | CH₃     | 4-Br    | 4f      | 45         | 92      | 219     |
| 7     | CH₃     | 4-CN   | 4g      | 30         | 96      | 227     |
| 8     | H       | 4-N(CH₃)₂ | 4h      | 60         | 94      | 229     |

**CONCLUSION**

In conclusion, a simple and efficient three-component condensation reaction of an aldehyde, 4-hydroxy-1-methyl-2-(1H)-quinolone and N,N-dimethylbarbituric acid was developed for synthesis of phenylpyrimido pyrazinoquinolines derivatives in the presence of CAN catalyst. The simple one-pot nature of reaction, decreasing time of reaction, simple separation, along with obviating the need for any modification of conditions of the educts makes it an interesting alternative to previous approaches. Also a safe catalyst was used in this reaction.
1. (a) R. V. A. Orru, M. de Greef, Synthesis (2003) 1471. (b) D. Tejedor, D. González-Cruz, A. Santos-Expósito, J. J. Marrero-Tellado, P. de Armas, F. García-Tellado, Chem. Eur. J. 11 (2005) 3502.
2. (a) A. Dömling, Chem. Rev. 106 (2006) 17; (b) B. B. Toure, D. G Hall, Chem. Rev. 109 (2009) 4439.
3. E. Verónica, V. Mercedes, J. C. Menéndez, Chem. Soc. Rev. 39 (2010) 4402.
4. J. Zhu, H. Bienaymé; 2nd Ed.; Multicomponent Reactions; Wiley-VCH: Weinheim, 2005.
5. A. Dandia, S. L. Gupta, S. Bhaskaran, Eur. Chem. Bull. 2 (2013) 836.
6. Z. Zhou, Y. Zhang, J. Chil. Chem. Soc. 60 (2015) 2992.
7. M. Zakeri, M. M. Nasef, E. Aboouzari-Lotf, A. Moharami, M. M. Heravi, J. Ind. Eng. Chem. 29 (2015) 273.
8. M. Zakeri, M. M. Nasef, E. Abouzari-Lotf, J. Mol. Liq. 199 (2014) 267.
9. B. S. Holla, B. Kalluraya, K. R. Sridhar, E. Drake, L. M. Thomas, K. K. M. Bhandary, J. Levine, Eur. J. Med. Chem. 29 (1994) 301.
10. P. Molina, E. Aller, A. Lorenzo, P. López-Cremades, I. Rijoja, A. Ubeda, M. C. Terencio, M. J. Aicaraz, J. Med. Chem. 44 (2001) 1011.
11. A. H. Shamroukh, M. E. A. Zaki, E. M. D. Morsy, F. M. Abdel-Mott, F. M. Abdel-Meged, Arch. Pharm. 340 (2007) 236.
12. J. A. Valderama, P. Colonelli, D. Vázquez, M. F. González, J. A. Rodríguez, C. Theoduloz, Bioorg. Med. Chem. 16 (2008) 10172.
13. O. Bruno, C. Brullo, A. Ranise, S. Schenone, F. Bondavalli, E. Barocelli, V. Ballabeni, M. Chiavarini, M. Tognolini, M. Impicciatore, Bioorg. Med. Chem. Lett. 11 (2001) 1397.
14. N. R. Kamdar, D. D. Haveliwala, P. T. Mistry, S. K. Patel, Eur. J. Med. Chem. 45 (2010) 5056.
15. S. S. Chobe, B. S. Dawane, K. M. Tumbi, P. P. Nandekar, A. T. Sangamwar, Bioorg. Med. Chem. Lett. 22 (2012) 7566; (b) M. T. Di Parsia, C. Suarez, M. J. Vitolo, V. E. Marquez, B. Beyer, C. Urbina, I. Hurtado, J. Med. Chem. 24 (1981) 117.
16. M. N. Elinson, A. I. Ilovaisky, V. M. Merkulova, T. A. Zaimovskaya, G. I. Nikishin Mendeleev Commun. 21 (2011) 122.
17. A. Rahmati, Z. Khalesi, Tetrahedron 68 (2012) 8472.
18. (a) C. J. Chan, T. H. Li, 2nd Ed.; Organic Reactions in Aqueous Media; Wiley New: York, NY, 1997; (b) A. Grieco, Organic Synthesis in Water; Blackie Academic and Professional, 1998; (c) A. Chanda, V. V. Fokin, Chem. Rev. 109 (2009) 725; (d) M. C. Pirrung, K. D. Sarma, J. Am. Chem. Soc. 126 (2004) 444.
19. K. Kandhasamy, V. Gnanasambandam, Curr. Org. Chem. 13 (2009) 1820.
20. C. K. Z. Andrade, L. M. Alves, Curr. Org. Chem. 9 (2005) 195.
21. (a) V. Nair, A. Deepthi, Chem. Rev. 107 (2007) 1862; (b) V. Nair, S. B. Panicker, L. Nair G. George, A. Augustine Synlett (2003) 156.
22. V. Shivaji, M. N. V. More, S. C. Yao, Green Chem. 8 (2006) 91.
23. T. D. V. Nair, S. M Kishor, Tetrahedron Lett. 46 (2005) 3217.
24. Sh. Ko, Ch. F. Yao, Tetrahedron 62 (2006) 7293.
25. H. J. Wang, L. Hui, Zh. Zhang, ACS Comb. Sci. 13 (2011) 181.
26. P. K. Tapaswi, C. Mukhopadhyay Arkivoc (2011) 287; (b) V. Sridharan, J. C. Menendez, Org. Lett. 10 (2008) 4303; (c) M. Y. Chang, T. C. Wu, C. C. Y. Lin, Y. Hung Tetrahedron Lett. 47 (2006) 8347.
27. K. U. Sadek, A. Alnajjar, R. A. Mekheimer, N. K. Mohamed, H. A. Mohamed, Green and Sustainable Chem. 1 (2011) 92; (b) A. Mekhalifa, R. H. Mutter, W. B. Chen, Tetrahedron 62 (2006) 5617.