*Heterocyclic Letters*
*Vol. 7| No.1|141-146|Nov-Jan| 2017*
*ISSN : (print) 2231–3087 / (online) 2230-9632*
*CODEN: HLEEAI*
*http://heteroletters.org*

# SYNTHESIS OF QUINAZOLINONES *VIA* TANDEM CYCLIZATION OF 2-HALOBENZOIC ACIDS WITH AMIDINES USING CERIUM(III) CHLORIDE AS A CATALYST

**B. Yedukondalu,[1] B. Lalitha kumari,[2] M. Hari Krishna,[3] P. Thriveni.[3]**

*Department of Chemistry, Vignan's University, Guntur -522 213, Andhra Pradesh, India.*
*Department of Biotechnology, Srimaharshi Research Institute of Vedic Technology, Guntur, A.P., India*
*Department of Chemistry, Vikrama Simhapuri University, Nellore-524001, Andhra Pradesh, India.*
**Corresponding Author E-mail: Chemkondavigna@gmail.com*

## ABSTRACT
Tandem cyclization of 2-halobenzoic acids with amidines provides a new facile protocol for the synthesis of 2-substituted quinazolinones using Cerium(III) chloride as effective catalyst. This protocol is very simple and provides moderate yields.

**KEYWORDS:** Quinazolin-4(3H)-ones, Cerium(III) chloride.

## INTRODUCTION
Heterocycles has drawn a special focuses on organic chemistry due to its availability in natural products and their biological properties.[1] Efforts have been taken to design the synthesize and utilize the unreported heterocyclic moiety for therapeutic applications. Their interest is to provide an account of synthetize, chemical and biological properties of nitrogen compounds. Generally, quinazolinone nucleus were an important scaffold that was found in a wide range of biologically active compounds including natural product and synthetic drugs.[2-4] Camptothecin and Mappicine have been approved as a drug by FDA. Both the drugs having nitroen motif. It has an attracted growing interest due to their certain synthetic methodology. Further they have been provided with an importance, significance in a biological field such as anti–parasitic, antimicrobial, anticancer and antibiotic action.[5-7]
Quinazolinones are prevalent in a wide range of both natural and non-natural products. For example, febrifugine, fumiquinaoline A, luotonin A and (-)-asperlicin have all been found to display noteworthy biological activities including anti-malarial and anti-cancer properties.[8-11] With a high occurrence of quinazolinone derivatives displaying broad and diverse biological profiles, efficient routes for the synthesis of these heteroaromatic structures has attracted significant attention over many years.[12]
These compounds exhibit remarkable antitubercular, antifungal, antimalarial, antidiabetic, anti-inflammatory, and antitumor activities.[13,14] In addition, some quinazolinone derivatives are already being used and some are being tested in clinical trials for the treatment of cancer, which are expected to be promising candidates for facile and practical approaches for the synthesis of cancer therapy in the future.[15]

Generally, quinazolinone derivatives are synthesized using *ortho*-amino or *ortho*-nitro benzoic acid derivatives as starting materials.[13] The first synthesis of a quinazolinone scaffold from anthranilic acid and cyanogens was carried out by Griess,[7]and later, von Niementowski optimized the reaction involving the fusion (130–150$^0$C) of anthranilic acid analogs with amides.[16] Vanelle *et al.* reported the microwave-assisted synthesis of new quinazoline derivatives from 2-aminobenzamide and chloroacetyl chloride. However, the feasibility of this method was limited due to the difficult preparation of the starting materials.[17] Recently, CuI-catalyzed coupling of 2-bromobenzoic and 2-iodobenzoic derivatives with amidines to form quinazoline derivatives has been reported.[18] Despite the efficiency of the above mentioned protocols in terms of conversion, the development of less expensive and environmentally more benign catalysts is a major goal for organic synthesis. However, these conventional and microwave methodologies are associated with various drawbacks, like the reaction conditions, availability of reagents and chemical hazards. Among the developed procedures, most of the synthetic routes suffering from low yields, multistep reactions and relatively harsh reaction conditions. Therefore new methodologies for quinazolinones synthesis are still under request. As a result, we herein report a practical method for the selective synthesis of quinazolin-4(3H)-ones by Cerium(III) chloride as a catalyst.

## MATERIALS AND METHODS

Laboratory chemicals were provided by Rankem India Ltd. and Ficher Scientific Ltd. Melting points were determined by the open tube capillary method and are not correct. The purity of the compounds was determined by thin layer chromatography (TLC) plates (silica gel G) in the solvent system toluene: ethyl acetate (8:2). The spots were observed by exposure to iodine Vapours or by UV light or P-Anisaldehyde Stain Solution. The IR spectra were received by Perkine Elmer 1720 FT-IR spectrometer (KBr pellets). The $^1$H NMR and $^{13}$C NMR spectra were obtained by Bruker Advance II 400 spectrometer using TMS because the internal standard in $CDCl_3$. Elemental analysis of the synthesized compounds were obtained by Carlo Erba 1108 analyzer. General Information. Commercial chemicals were treated as follows: THF, ether, hexanes distilled from Na/ benzophenone.

The synthesis of the compounds and synthetic route was depicted in **scheme I** is given below**.** The title compounds **3(a-j)** were synthesised using reagent and reaction conditions, the **3(a-j)** were obtained in moderate yields (**Table-1**). The structure were established by spectral (IR, $^1$H-NMR, $^{13}$C-NMR and mass).

**Scheme I**

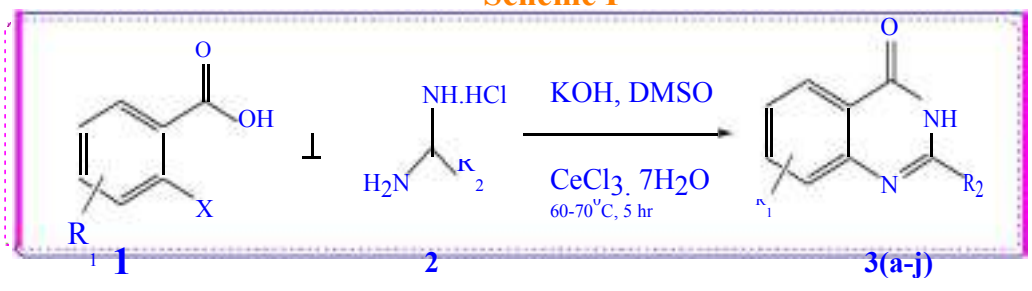
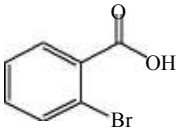
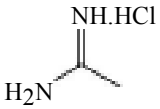
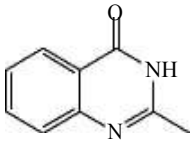
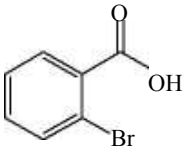
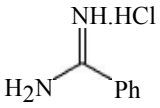
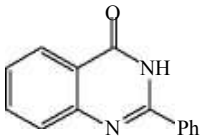
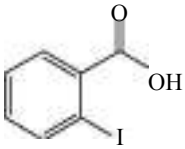
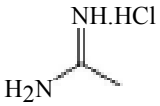
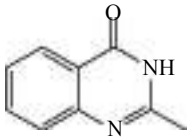
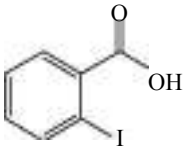
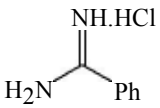
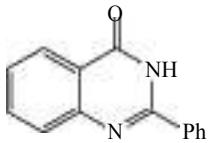
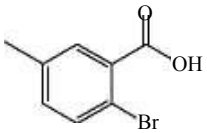
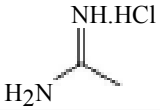
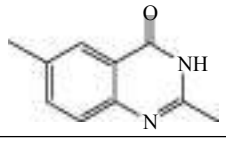
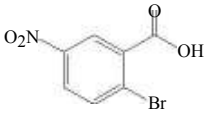
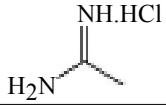
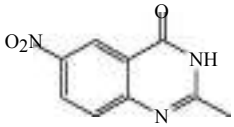
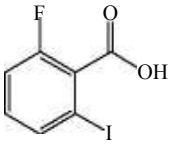
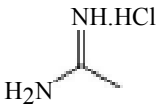
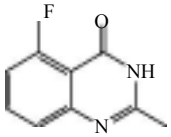
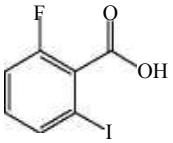
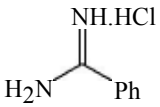
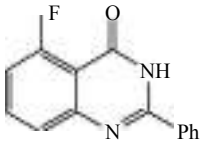
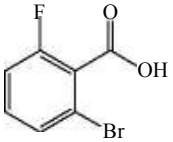
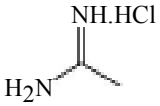
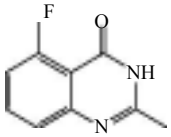
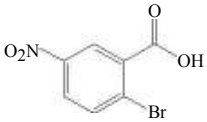
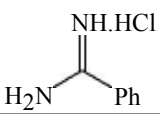
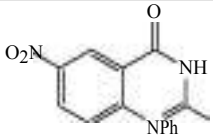


**Table 1**: Synthesis of quinazolinone derivatives **3(a-j)**

| **Entry** | **1** | **2** | **Product** | **Yield(%)** |
|---|---|---|---|---|
| 1 |  |  |  | 83 |
| 2 |  |  |  | 79 |
| 3 |  |  |  | 82 |
| 4 |  |  |  | 80 |
| 5 |  |  |  | 80 |
| 6 |  |  |  | 78 |
| 7 |  |  |  | 76 |
| 8 |  |  |  | 78 |
| 9 |  |  |  | 81 |
| 10 |  |  |  | 79 |

## EXPERIMENTAL SECTION

All reactions were carried out under argon in oven-dried glassware with magnetic stirring. Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. All solvents were reagent grade. THF was distilled from sodium benzophenone ketyl and degassed thoroughly with dry argon directly before use. Unless otherwise noted, organic extracts were dried with anhydrous $Na_2SO_4$, filtered through a fitted glass funnel, and concentrated with a rotary evaporator (20–30 Torr). Flash chromatography was performed with silica gel (200–300 mesh) by using the mobile phase indicated. The NMR spectra were measured with a 400 MHz Bruker Avance spectrometer at 400.1 and 100.6 MHz for $^{1}H$ for $^{13}C$, respectively, in $CDCl_3$ solution with tetra methyl silane as internal standard. Chemical shifts are given in ppm (δ) and are referenced to the residual proton resonances of the solvents. Proton and carbon magnetic resonance spectra ($^{1}H$ NMR and $^{13}C$ NMR) were recorded using tetramethylsilane (TMS) in the solvent of CDCl3-d or DMSO-d6 as the internal standard ($^{1}H$ NMR: TMS at 0.00 ppm, $CDCl_3$ at 7.26 ppm, DMSO at 2.50 ppm; $^{13}C$ NMR: $CDCl_3$ at 77.16 ppm, DMSO at 40.00 ppm).

### General procedure for synthesis of quinazolinone derivatives 3(a-j):

To a mixture of Substituted 2-halobenzoic acid (**1**, 1.0 mmol), amidines hydrochloride (**2**, 1.1 mmol) and KOH (2.0 equiv) in DMSO (4 mL), catalyst Cerium(III) chloride heptahydrate (2.0 equiv) were added. The reaction mixture was stirred at room temperature for 10 min, then heated at 60-70°C for 5 h. After completion of the reaction, the mixture was cooled to room temperature and water (4 mL) and ethyl acetate (6 mL) were added. The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 x 4 mL). The combined organic layers were washed with brine (4 mL), dried with anhydrous $Na_2SO_4$, filtered and concentrated under reduced pressure. The product was purified by silica gel column chromatography by using petroleum ether/ethyl acetate.

### Spectral data for selected compounds:

**2-methylquinazolin-4(*3H*)-one (3a):**

White solid, mp: 176-177°C.

$^{1}H$ NMR ($CDCl_3$, 400 MHz): δ 12.19 (s, 1H), 8.28 (dd, *J*1 =8.0 Hz, *J*2 = 1.2 Hz, 1H), 7.75 (dt, *J1* = 8.4 Hz, *J2* = 1.6 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.47 (dt, *J1* = 8.4Hz, *J2* = 1.2 Hz, 1H), 2.61 (s, 3H).

$^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 22.1, 120.2, 126.2, 126.4, 127.0, 134.9, 149.4, 153.3, 164.4.

**2-phenylquinazolin-4(*3H*)-one (3b):**

White solid, mp: 122-123°C.

$^{1}H$ NMR ($CDCl_3$, 400 MHz): δ 10.66 (s, 1H ), 8.34 (d, *J*=7.6 Hz, 1H), 8.15 -8.17 (m, 2H ), 7.78-7.87 (m, 2H ), 7.59-7.60 (m, 3H ), 7.53 (dt, *J1* = 8.0 Hz, *J2* = 1.6 Hz, 1H).

$^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 126.5, 126.9, 127.1, 128.1, 129.2, 131.8, 132.8, 134.9, 149.4,151.4, 163.1.

**6-Nitro-2-Methylquinazolin-4(3*H*)-one (3f):**

Light yellow solid, mp: 270-279 $^{0}C$.

$^{1}H$ NMR ($CDCl_3$, 400 MHz): δ 12. 65 (s, br, 1H), 8.70 (s, 1H), 8.44 - 8.41 (dd, 1H, *J* = 8, 4 Hz), 7.67 (d, 1H, *J* = 8 Hz), 2.36 (s, 3H) ppm.

$^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 161.3, 158.8, 153.6, 144.7, 128.7, 128.6, 122.3, 121, 22 ppm.

**5-fluoro-2-methylquinazolin-4(*3H*)-one (3g):**

White solid, mp: 252-253°C.

$^{1}H$ NMR ($CDCl_3$, 400 MHz): δ 2.56 (s, 3H), 7.10 (t, *J* = 9.2 Hz, 1H), 7.47 (d, *J* =8.4 Hz, 1H), 7.67-7.72 (m, 1H), 11.22 (s, 1H).

$^{13}$C NMR ($CDCl_3$, 100 MHz): δ 22.0, 110.2, 113.0, 123.0, 135.2, 151.3, 154.2, 160.1, 162.6.

**6-Nitro-2-phenylquinazolin-4(3*H*)-one (3j):**

Yellow solid, mp: 297-299$^0$C.

$^1$H NMR ($CDCl_3$, 400 MHz): δ 13.00 (s, br, 1H), 8.18 (d, 1H, *J* = 7.60 Hz), 8.81 (s, 1H), 8.54 (d, 2H, *J*= 8.52 Hz), 8.20 (d, 1H), 7.59 (m, 3H).

$^{13}$C NMR ($CDCl_3$, 100 MHz): δ 162.1, 156.2, 153.5, 145.2, 132.8, 132.5, 129.7, 129.3, 129.1, 128.8, 122.6, 121.5.

## RESULTS AND DISCUSSION

As expected, this reaction provides desired products in moderate yields. A series of 2-substituted Quinazolinone derivatives **3(a-j)** from 2-halobenzoic acids and amidines using Cerium(III) chloride at 60-70$^0$C. Electron-donating or electron withdrawing groups attaching to aromatic ring were investigated. The substitution groups on the aromatic ring had no obvious effect on the yield (**Table 1**).

## CONCLUSION

In summary, a new efficient facile protocol for the synthesis of 2-substituted Quinazolinone derivatives from 2-halobenzoic acids and amidines has been developed under simpler condition using Cerium(III) chloride. The intermolecular tandem cyclization is mediated by easily available KOH base in DMSO at 60-70°C. The advantage of this method are extremely mild reaction conditions, short reaction time, moderate yield. Thus, the developed methodology could be an alternative for the academic as well as industrial applications.

## ACKNOWLEDGEMENT

Authors are thankful to our Research Supervisor Dr. B. Lalitha kumari for providing us required facilities and motivation for completion of the research work. We also extend our gratitude towards Vignan's university, A.P, India for providing us facilities of IR Spectra, $^1$H NMR for characterization of synthesized compounds.

## REFERENCES

[1] M. Jha, S. Guy, Y.C. Ting, *Tetrahedron Lett.* **2011**, 52, 4337- 4371.

[2] A. Salgado, C. Varela, A.M.G. Collazo, P. Pevarello, *Magn. Reson. Chem,* **2010**, 48, 614–622.

[3] G. Fischer, *Adv. Heterocycl.Chem,* **2008,** 95, 143–219.

[4] M.R. Shaaban, T.S. Saleh, A.M. Farag, *Heterocycles.* **2007**, 71,1765-1777.

[5] S.B. Charki, C.Marin, C.R. Maldonado, M.J. Rosales, J.Urbano, R.Guitierrez-Sanchez, M.Quiros, J.M. Salas, M. Sanchez- Moreno, *Drug. Metab.Lett.***2009**, 3, 35– 44.

[6] G. Ruisi, L. Canfora, G. Bruno, A. Rotondo, T.F. Mastropietro, E.A. Debbia, M.A. Girasolo, B. Megna, *J. Organomet. Chem.* **2010**, 695, 546–551.

[7] M.M.A. El-Gendy, M. Shaaban, K.A. Shaaban, A.M. El-Bondkly, H. Laatsch, *J. Antibiot.***2008**, 61, 149–157.

[8] N. P. McLaughlin, P. Evans, M. Pines, *Biorg. Med. Chem.***2014**, 22, 1993.

[9] B. B. Snider, H. Zeng, *Org. Lett.* **2000,** 2, 4103.

[10] F. He, B. M. Foxman, B. B. Snider. *J. Am. Chem. Soc.* **1998**, 120, 6417.

[11] A. Cagir, S. H. Jones, R. Gao, B. M. Eisenhauer, S. M. Hecht, *J. Am. Chem. Soc.* **2003,** 125, 13628.

[12] D. J. Connolly, D. Cusack, T. P. O'Sullivan, P. J. Guiry. *Tetrahedron.* **2005**, 61, 10153.

[13] (*a*) A. Witt and J. Bergman, *Curr. Org. Chem.*, 2003, **7**, 659. (*b*) S. B. Mhaske and N. P. Argade, *Tetrahedron*, 2006, **62**, 9787.

[14] D. J. Connolly, D. Cusack, T. P. O. Sullivan, P. J. Guiry, *Tetrahedron*, **2005**, 61, 10153.

[15] Z.-Z. Ma, Y. Hano, T. Nomura, *Heterocycles***, 2005,** 65, 2203

[16] S. von Niementowski, *J. Prakt. Chem.*, **1895,** 51, 564.

[17] (*a*) J.-F. Liu, P. Ye, B. Zhang, G. Bi, K. Sargent, L. Yu, D. Yohannes, C. M. Baldino, *J. Org. Chem*, **2005**, 70, 6339. (*b*) J.-F. Liu, M. Kaselj, Y. Isome, P. Ye, K. Sargent, K. Sprague, D. Cherrak, C. J. Wilson, Y. Si, D. Yohannes, S.-C. Ng. *J. Comb. Chem.*, **2006,** 8, 7. (*c*) A. D. Roy, A. Subramanian, R. Roy. *J. Org. Chem.* **2006**, 71, 382. (*d*) C. L. Yoo, J. C. Fettinger, M. J. Kurth. *J. Org. Chem.*, **2005**, 70, 6941.

[18] (*a*) X.-W. Liu, H. Fu, F. Zhao, *Angew. Chem., Int. Ed.*, **2009**, 48, 348. (*b*) C. Huang, Y. Fu, H. Fu, F. Zhao. *Chem. Commun.*, **2008**, 49, 6333.

Received on December17, 2016.