

**MULTICOMPONENT SYNTHESIS AND CHARACTERIZATION OF
NEW 2-SUBSTITUTED DERIVATIVES OF 3-AMINO-4-IMINO-8-
NITRO-2H-PYRAZOLO [3,4-e]PYRIMIDO[2,3-
b][1,3]BENZOTHIAZOLE**

Anil B. Chidrawar* and Rajkumar U. Pokalwar

Department of Chemistry, Degloor College, Degloor-431717, S.R.T.M.U. Nanded.
Maharashtra, India.

Article Received on
03 Jan 2016.

Revised on 24 Jan 2016,
Accepted on 15 Feb 2016

***Correspondence for
Author**

Dr. Anil B. Chidrawar

Department of Chemistry,
Degloor College, Degloor-
431717, S.R.T.M.U.

Nanded. Maharashtra,
India.

ABSTRACT

A simple and efficient method have been used for the synthesis of 2-substituted derivatives of 3-amino-4-imino-8-nitro-pyrazolo [3,4-e] pyrimido [2,3-b] [1,3] benzothiazole (**III**) obtained by the multicomponent reaction of 2-amino-6-nitro benzothiazole (**I**) and bis methylthio methylene malononitrile (**II**) on refluxed with hydrazine hydrate in the presence of 5 ml of dimethyl formamide with a pinch of anhydrous K_2CO_3 . The structures for the synthesized compounds are assigned on the basis of IR, 1H NMR and Mass spectral studies.

KEYWORDS: 2-amino-6-nitrobenzothiazole, bismethylthio methylene malononitrile, hydrazine hydrate, dimethyl formamide,

potassium carbonate.

INTRODUCTION

Heterocycles containing sulphur and nitrogen atoms in the core structure shows number of pharmacologically and biologically active compounds. So, various fused pyrimidines like purines, pteridines, quinazolines, pyridopyrimidines, triazolopyrimidines, pyrazolopyrimidines, pyrimido-azepines, furopyrimidines and pyrrolopyrimidines were studied in the past decade and were found to possess remarkable pharmacological properties.^[1-6]

Garin Javier *et. al.*^[7] also reported the synthesis of 1-H, 4-H-4-oxo-1-phenyl pyrazolo [3',4':4,5] pyrimido [2,1-b] benzothiazole from pyrazolo [3,4-d] pyrimidine in the presence

of NBS/ sulphuric acid and NCS/ sulphuric acid. In the presence of NBS/ sulphuric acid, the varying by-products were obtained along with pyrazolo pyrimido benzothiazole, but in the presence of NCS/ sulphuric acid, the pyrazolo pyrimido benzothiazole was obtained in good yield. The synthesis of 3-amino-4-oxo-(2H)-pyrazolo [3',4':4,5] pyrimido [2,1-*b*] benzothiazole and its 2- and 3-substituted derivatives starting from 3-cyano-2-methylthio-4-oxo-4H-pyrimido[2,1-*b*] benzothiazole has been reported by Baheti K.G. and Kuberkar S.V.^[8-10] Kamal F.M. Atta *et.al*^[11] reported The formation of (*E*)-3-{2-(2,5-diphenylpyrazolo[1,5-*c*]pyrimidin-7yl)hydrazono} indolin-2-ones has been achieved by condensation of equimolar amounts of 7-hydrazino-2,5-diphenylpyrazolo[1,5-*c*]pyrimidine and isatin (or isatin derivatives) at room temperature. Dehydrative cyclisation of the hydrazones using phosphorus oxychloride afforded the 2,5-diphenyl-indolo[2,3-*e*] pyrazolo [1',5':3",4"] pyrimido[2",1"-*c*][1,2,4] triazines which exhibit antibacterial activity. Wageeh S.El-Hamouly *et al*^[12] reported synthesis and antitumor activity of some new 1,3,4-oxadiazole, pyrazole and pyrazolo[3,4-*d*]pyrimidine derivatives attached to 4-benzothiazol-2-yl phenyl moiety. Some 1,3,4-oxadiazole, pyrazole and pyrazolo[3,4-*d*] pyrimidine derivatives were synthesized starting from *o*-amino thiophenol by reacting with different electrophilic and nucleophilic reagents. Some of the newly synthesized compounds have been evaluated for their potential cytotoxicity against breast cancer cell line (MCF7). Saman Damavandi, Reza Sandaroos^[13] reported Synthesis of Pyrazolo [4,3-*f*] pyrimido [4,5-*b*] quinoline-8, 10-dione derivatives .Pyrazolo [4,3-*f*] pyrimido [4,5-*b*]quinoline-8,10-dione derivatives have been synthesized from one-pot condensation of 1-methyl barbituric acid, aromatic aldehydes and 5-aminoindazole utilizing bis[7-*tert*-butyl-2-anilino]tropone] Ti complex in toluene under reflux condition.

MATERIALS AND METHODS

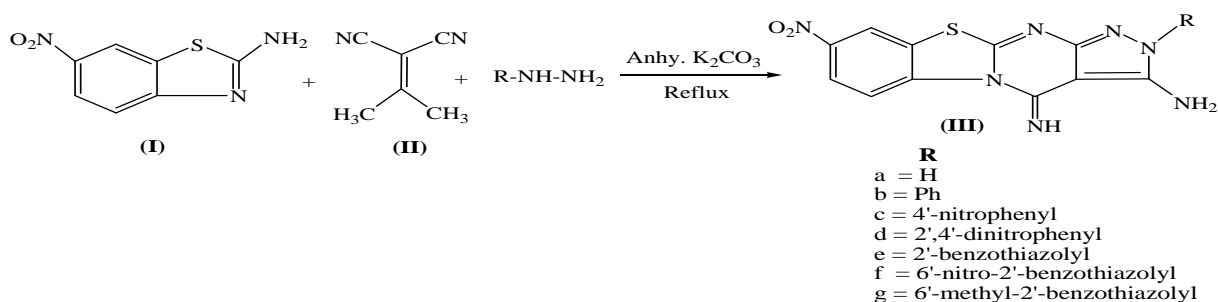
Experimental Section

All melting points were determined in open capillary tube and were uncorrected. IR spectra were recorded with potassium bromide pellets technique, ¹H NMR spectra were recorded on AVANCE 300 MHz Spectrometer in DMSO using TMS as internal standard. Mass spectra were recorded on a FT VG-7070 H Mass Spectrometer using EI technique at 70 eV. All the reactions were monitored by Thin layer chromatography.

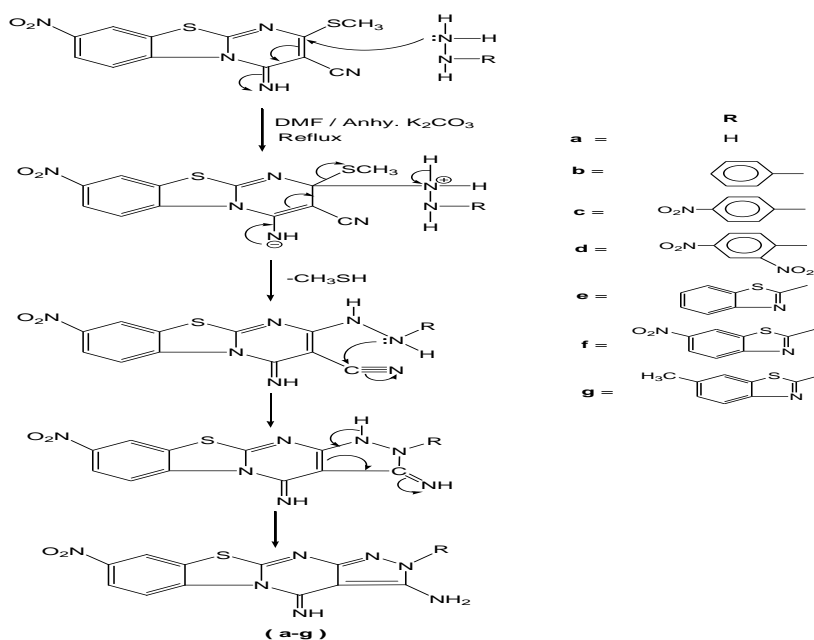
Synthesis of 2-substituted derivatives of 3-amino-4-imino-8-nitro-2H-pyrazolo[3,4-*e*] pyrimido[2,3-*b*] [1,3]benzothiazole (III): In the present work, we report multicomponent

synthesis of 2-substituted derivatives of 3-amino-4-imino-8-nitropyrazolo [3,4-*e*] pyrimido [2,3-*b*] [1,3] benzothiazole (III) by refluxing 2-Amino-6-nitro benzothiazole (I), bis methylthio methylene malononitrile (II) independently with hydrazine hydrate, phenyl hydrazine/ 4-nitro phenyl hydrazine /2,4-dinitro phenyl hydrazine /2-hydrazino benzothiazole /6-nitro-2-hydrazino benzothiazole /6-methyl-2-hydrazino benzothiazole in the presence of dimethyl formamide and catalytic amount of potassium carbonate afforded 2-substituted compounds, 3-amino-4-imino-8-nitro-2-H (a), 3-amino-4-imino-8-nitro-2-phenyl (b) /2-(4'-nitro phenyl) (c) /2-(2',4'-dinitro phenyl) (d) /2-(2'-benzothiazolyl) (e) /2-(6'-nitro-2'-benzothiazolyl) (f) /2-(6'-methyl-2'-benzothiazolyl)(g)/ pyrazolo [3,4-*e*] pyrimido [2,3-*b*] [1,3] benzothiazole respectively. Structures to these compounds are assigned on the basis of elemental analysis and spectral data.

Reaction



A tentative mechanism for the formation of compound (a-g) can be adducted as shown in Scheme-1 as follows.



Scheme-1 : Mechanism for the formation of compound (a-g)

1) Synthesis of 3-amino-4-imino-8-nitro-2H-pyrazolo[3,4-*e*]pyrimido[2,3-*b*][1,3] benzothiazole (a): A mixture of 2-Amino-6-nitro benzothiazole [0.195 gm, 0.001 mole], bis methylthio methylene malononitrile [0.170 gm, 0.001 mole] and Hydrazine hydrate [0.096gm 0.001mole] was refluxed in the presence of 5ml of dimethyl formamide and a pinch of anhydrous potassium carbonate (0.2 gm) for five hours. The reaction mixture was cooled to room temperature and poured in ice cold water. The separated solid product was filtered, washed with water and recrystallized from DMF-ethanol mixture to give 0.212 gm of crystalline solid of 3-amino-4-imino-8-nitro-2H-pyrazolo[3,4-*e*] pyrimido [2,3-*b*] [1,3] benzothiazole (a).

Yield: 70 %, M.P : 251 °C, IR:(KBr/cm⁻¹) : 3440 (=NH), 3386 (-NH), 3274 (-NH₂), 1620 (C=N), 1515 & 1338 (-NO₂, asymmetric and symmetric stretching), ¹H-NMR: (DMSO) : δ □4.2 (broad, 2H NH₂), δ 7.2 to δ □8.5 (m 3H Ar-H), δ 9.15 (s 1H =NH), δ 11.8 (s 1H NH), EI-MS: (m/z:RA%) : 302 (M+1, 15%), 273, 244, 218, 191, 153, 107. Elemental analysis : C₁₁H₇N₇O₂S Calculated: (%) C 43.85, H 2.34, N 32.54, O 10.62, S 10.64 Found (%) : C 43.78, H 2.30, N 32.45, O 10.55, S 10.47.

2) 3- Amino – 4 – imino – 8 – nitro – 2 – phenyl - pyrazolo[3,4-*e*]pyrimido[2,3-*b*][1,3]benzothiazole(b): Yield: 58 %, M.P : 284 °C, IR:(KBr/cm⁻¹) : 3430 (=NH), 3388 cm⁻¹(-NH), 3314(-NH₂), 1542 & 1388 (-NO₂, asymmetric and symmetric stretching), ¹H-NMR: (DMSO) : δ 4.2 (s 2H NH₂), δ 8.4 to δ 9.2 (m 8H Ar-H) and δ 9.5 (s 1H =NH) EI-MS : (m/z:RA%) : 378 (M+1, 15%), Elemental analysis : C₁₇H₁₁N₇O₂S Calculated: (%) C 54.11, H 2.94, N 25.98, O 8.48, S 8.50 Found (%) : C 54.05, H 2.90, N 25.92, O 8.41, S 8.44

3) 3-Amino-4-imino-8-nitro-2-(4'-nitrophenyl) pyrazolo [3,4-*e*] pyrimido [2,3-*b*] [1,3] benzothiazole (c)

Yield: 60 %, M.P : 271 °C, IR:(KBr/cm⁻¹) : 3435 (=NH), 3265 (-NH₂), 1525 & 1345 (-NO₂, asymmetric and symmetric stretching), EI-MS: (m/z:RA%) : 422 (M⁺, 30%), Elemental analysis : C₁₇H₁₀N₈O₄S Calculated: (%) C 48.34, H 2.39, N 26.53, O 15.15, S 7.59 Found (%) : C 48.30, H 2.32, N 26.51, O 15.12, S 7.56.

4) 3-Amino -4-imino -8-nitro-2- (2',4'-dinitrophenyl) pyrazolo [3,4-*e*] pyrimido [2,3-*b*] [1,3] benzothiazole (d)

Yield: 65 %, M.P : 282 °C, IR:(KBr/cm⁻¹) : 3430 (=NH), 3255 (-NH₂), 1552 & 1350 (-NO₂, asymmetric and symmetric stretching), EI-MS: (m/z:RA%) : 469 (M⁺, 20%), Elemental

analysis : C₁₇H₉N₉O₆S Calculated: (%) C 43.69, H 1.94, N 26.97, O 20.54, S 6.86 Found (%) : C 43.65, H 1.90, N 26.93, O 20.51, S 6.82.

5) 3-Amino-4-imino -8-nitro-2-(2'-benzothiazolyl) pyrazolo [3,4-*e*] pyrimido [2,3-*b*] [1,3] benzothiazole (e)

Yield: 70 %, M.P : 264 °C, IR:(KBr/cm⁻¹) : 3451 (=NH), 3267 (-NH₂), 1543 & 1337 (-NO₂, asymmetric and symmetric stretching), EI-MS: (m/z:RA%) : 435 (M+1, 45%), Elemental analysis : C₁₈H₁₀N₈O₂S₂, Calculated: (%) C 49.76, H 2.32, N 25.79, O 7.37, S 14.76 Found (%) : C 49.72, H 2.30, N 25.75, O 7.31, S 14.73

6) 3-Amino-4-imino-8-nitro-2-(6'-nitro-2'-benzothiazolyl) pyrazolo [3,4-*e*] pyrimido [2,3-*b*] [1,3] benzothiazole (f)

Yield: 53 %, M.P : 272 °C, IR:(KBr/cm⁻¹) : 3460 (=NH), 3250 (-NH₂), 1550 & 1344 (-NO₂, asymmetric and symmetric stretching). EI-MS: (m/z:RA%) : 479 (M⁺, 35%), Elemental analysis : C₁₈H₉N₉O₄S₂, Calculated: (%) C 45.09, H 1.89, N 26.29, O 13.35, S 13.38 Found (%) : C 45.02, H 1.85, N 26.25, O 13.30, S 13.33

7) 3-Amino-4-imino-8-nitro-2-(6'-methyl-2'-benzothiazolyl) pyrazolo [3,4-*e*] pyrimido [2,3-*b*] [1,3] benzothiazole (g)

Yield: 62 %, M.P : 261 °C, IR:(KBr/cm⁻¹) : 3467 (=NH), 3255 (-NH₂), 1554 & 1361 (-NO₂, asymmetric and symmetric stretching), EI-MS: (m/z:RA%) : 449 (M+1, 40%), Elemental analysis : C₁₉H₁₂N₈O₂S₂, Calculated: (%) C 50.88, H 2.70, N 24.99, O 7.13, S 14.30 Found (%) : C 50.83, H 2.65, N 24.95, O 7.10, S 14.26.

RESULTS AND DISCUSSION

Multicomponent reactions which are one pot reactions constitute an especially attractive recent synthetic strategy since they provide easy and rapid access to large number of organic compounds with diverse substitution pattern. In present work, we report multicomponent synthesis of novel fused heterocyclic compound, 3-amino-4-imino-8-nitro-2H-pyrazolo[3,4-*e*]pyrimido[2,3-*b*][1,3] benzothiazole and its 2-substituted derivatives (a to g).

Accordingly, a mixture of 3-amino-4-imino-8-nitropyrazolo [3,4-*e*] pyrimido [2,3-*b*] [1,3] benzothiazole by refluxing 2-Amino-6-nitro benzothiazole, bis methylthio methylene malononitrile independently with hydrazine hydrate, phenyl hydrazine/ 4-nitro phenyl hydrazine /2,4-dinitro phenyl hydrazine /2-hydrazino benzothiazole /6-nitro-2-hydrazino

benzothiazole /6-methyl-2-hydrazino benzothiazole in the presence of dimethyl formamide and catalytic amount of potassium carbonate to isolate respective 2-substituted derivatives.

CONCLUSION

In conclusion a facile multicomponent and one pot synthesis has been developed for the title compounds using readily available starting materials.

ACKNOWLEDGEMENTS

The authors are thankful to the Director, Indian Institute of Chemical Technology, Hyderabad and the principle Yeshwant College Nanded for providing spectra.

REFERENCES

1. Nair M. D., George Thomas, Chem. Abstr. 1968; 70: 47489b.
2. Covington R. R., Temple D. L., Jr. Yevich, Joseph P., Ger. Offen. 1979, 2918085, Chem. Abstr., 1980; 92: 163993q.
3. Alaimo R.J., J. Het. Chem, 1973; 10(5): 769-72.
4. Jimonet P, Audiau F, Barreau M, et al., J Med Chem., 1999; 42: 2828.
5. Bradshaw T.D., Shi D.F., Schultz R.J., et al. Br J. Cancer. 1998; 78: 421-429.
6. Hutchinson I, Chua M, Browne HI, et al. J Med Chem. 2001; 44: 1446.
7. Garin J., Guillen C., Melendez E., Merchan F.L., Orduna J., Tejero T., Heterocycle, 1987; 26(9): 2371-2379.
8. Baheti K.G., Kuberkar S.V., J. Het. Chem., 2003; 40: 547 (USA).
9. P. Ravi Prasad, Sanjay D. Shinde, Gangadhar S. Waghmare, V. Lakshma Naik, K. Bhuvaneshwari and Kuberkar S. V., J. Chem. Pharm. Res., 2011; 3(5): 20-27.
10. Deshmukh V.K., Kuberkar S.V. International Journal of Chem Tech Research, 2011; 3(1): 136-142.
11. Kamal F.M. Atta , Omaina O.M. Farahat, Somaya M. Ghobashy and Mohamed G. Marei Molecules 2011; 16: 10387-10408.
12. Wageeh S. El-Hamouly, Kamelia M. Amin, Samy A. El-Assaly AND Eman A. Abd E Meguid , Der Pharma Chemica, 2011; 3(6): 282-292.
13. Saman Damavandi, Reza Sandaroos, Chem Sci Trans, 2012; 1(1): 117-120.