Heterocyclic Letters
Vol. 9| No.3|327-332|May-July|2019
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

ONE POT SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL FUSED THIADIAZOLO-PYRIMIDINE DERIVATIVES

VIJAY V. DABHOLKAR* and DINESH UDAWANT[#], RAHUL JAISWAR

Organic Research Laboratory, Department of Chemistry,
**K.C. College, Churchgate, Mumbai-400 020,*
[#]Guru Nanak College, G.T.B Nagar, Mumbai - 400037, INDIA.
E-mail: vijaydabholkar@gmail.com
dins1323@gmail.com

Abstract:
One pot synthesis of 5-amino-7-(substituted-phenyl)-2-(substituted-bezyl)-5-H-[1,3,4]-thiadiazolo [3,2-a]pyrimidine-6-carbonitrile **(6)** was achieved by the reaction of 2-amino-5-(substituted)-benzyl-1,3,4-thiadiazole **(3)**, aromatic aldehyde **(4)** and malononitrile **(5)**. The contents were refluxed in presence of triethylamine as a catalyst and ethanol as a solvent. The structures of the compounds have been confirmed by IR and NMR. Representative compounds were screened for their anti-microbial activity against gram-negative bacteria, *E coli* and *P.aeruginosa*and gram-positive bacteria, *S aureus*, and *C diphtheriae*using disc diffusion method. Some of these compounds have been found to exhibit excellent antibacterial activity.

Keywords : 1,3,4-Thiadiazole, Pyrimidine, Malononitrile.

Introduction:

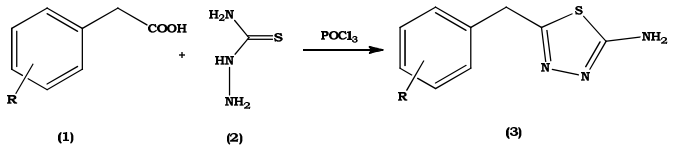
Recently, the chemistry of 1,3,4-thiadiazole derivatives is highlighted due to their wide spectrum of biological activities including antimicrobial[1-3], anti-inflammatory[4,5], antioxidant[6,7], anti-tumour[8], anti-cancer[9] and have other pharmacological activities [10,11]. Moreover, this ring system is valuable building block for the synthesis of other fused heterocyclic systems. One such system is thiadiazolo [3,2-a]pyrimidine derivatives resulting from the annulations of a pyrimidine ring on thiadiazole as potential bioactive molecules. These fused heterocyclic derivatives have generated great interest in recent years due to their wide range of biological and pharmacological activities including antibacterial[12], antitumor [13,14], fungicidal[15], neuraminidase inhibitors[16] etc.

In view of the versatile biological activities and the benefits of thiadiazolo [3,2-a]pyrimidine derivatives and as a continuation of the efforts to synthesis isolated and fused heterocyclic compounds, herein is reported a facile and convenient route of synthesis of 5-amino-7-(substituted-phenyl)-2-(substituted-bezyl)-5-H-[1,3,4]-thiadiazolo [3,2-a]pyrimidine-6-carbonitrile **(6)**.

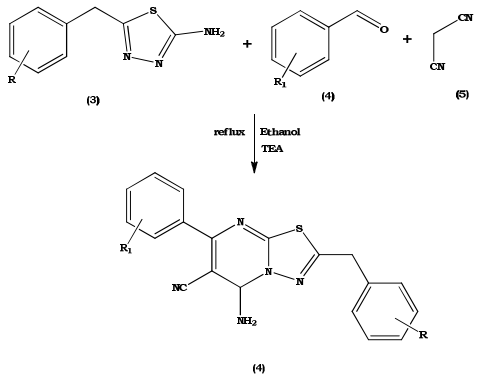
Results and discussion

5-amino-7-(substituted-phenyl)-2-(substituted-bezyl)-5-H-[1,3,4]-thiadiazolo [3,2-a]pyrimidine-6-carbonitrile **(6)** was achieved by the reaction of 2-amino-5-(substituted)-benzyl-1,3,4-thiadiazole **(3)**, aromatic aldehyde **(4)** and malononitrile **(5)**. The content was refluxed in presence of triethylamine as a catalyst and ethanol as a solvent**(Scheme II)** .The structures of the compounds have been confirmed by IR and NMR. Representative compounds were screened for their anti-microbial activity against gram-negative bacteria, *E coli* and *P.aeruginosa*and gram-positive bacteria, *S aureus*, and *C diphtheriae*using disc diffusion method. Some of these compounds have been found to exhibit excellent antibacterial activity.

Scheme I:



Scheme II:



The spectral analysis of representative compounds will be as follows:

*2-amino-5-(methoxy)-benzyl-1,3,4-thiadiazole **(3a)***

Yield: 78%; m.p.=191-195°C;

Anal.Calcd for $C_{10}H_{11}N_30S$: C, 54.28; H, 5.01; N, 18.99%.Found: C,54.17; H,4.97,N,18.76%.

IR (cm^{-1}):3205(NH_2), 1496 (C=N)

^{1}H NMR (DMSO-d_6, δ /ppm):3.48(s, 2H, CH_2), 3.86(s, 3H, OCH_3), 6.65 – 6.80 (m, 4H, ArH), 8.4(s, 2H, NH_2).

^{13}C NMR (DMSO-d_6,δ /ppm):41.5 (CH_2), 60.35 (OCH_3), 118.96- 137.89 (C=C &Ar C), 153.43 (C-OCH_3), 172.1 & 173.2 (2 x S-C=N).

*2-amino-5-(2-methyl)-benzyl-1,3,4-thiadiazole **(3b)***

Yield: 71%; m.p.=210-213°C;

Anal.Calcd for $C_{10}H_{11}N_3S$: C,58.51;H,5.40; N,20.47%. Found: C,58.42; H,5.36,N,20.38%.

IR (cm^{-1}):3316(NH_2), 1598 & 1522 (C=N).

^{1}H NMR (DMSO-d_6, δ /ppm):2.65 (s, 3H, CH_3), 3.51(s, 2H, CH_2), 6.69 – 6.96(m, 4H, ArH), 8.32(s, 2H, NH_2).

^{13}C NMR (DMSO-d_6,δ /ppm):23.2 (CH_3), 39.6(CH_2), 124.9- 141.65 (C=C &Ar-C), 169.1 & 170.2 (2 x S-C=N).

5-amino-7-(4-methoxy-phenyl)-2-(4-methoxy-bezyl)-5-H-[1,3,4]-thiadiazolo [3,2-a]pyrimidine-6-carbonitrile (6a)

Yield: 69%; m.p.=185-189°C;

Anal.Calcd for $C_{21}H_{19}N_5O_2S$: C,62.21; H,4.72; N,17.27%.Found: C,62.12; H,4.56,N,17.13%.

IR (cm^{-1}): 3374(NH_2), 2189 (CN), 1594 (C=N).

^{1}H NMR(DMSO-d_6, δ /ppm): 3.31(s,2H,CH_2), 3.82 (s,3H,OCH_3), 3.91(s, 3H,OCH_3), 4.54 (s, 1H, CH), 5.21 (s, 2H,NH_2), 6.87-7.62 (m,8H,Ar- H)

^{13}C NMR (DMSO-d_6,δ /ppm): 39.15 (CH_2), 59.13(OCH_3), 57.17(OCH_3), 69.5(C-NH_2), 97.5(C-CN),115.3(CN), 121.26-138.89 (C=C &Ar C),146.3(S-C=N) ,158.3 (C=N), 162.21 (N=C-S).

5-amino-7-(4-methoxyphenyl)-2-(2-methylbenzyl)-5H-[1,3,4]thiadiazolo [3,2-a]pyrimidine-6-carbonitrile (6b)

Yield: 71%; m.p.=201-205°C;

Anal.Calcd for $C_{21}H_{19}N_5OS$: C,64.76; H,4.92; N,17.98%. Found: C,64.17; H,4.81,N,17.76%.

IR (cm^{-1}): 3289(NH_2), 2145 (CN), 1491 (C=N).

^{1}H NMR (DMSO-d_6, δ /ppm): 2.39 (s, 3H, CH_3), 3.29 (s, 2H, CH_2), 3.89 (s, 3H, OCH_3), 4.51 (s, 1H, CH), 5.25 (s, 2H, NH_2), 6.94 – 7.40 (m, 8H, ArH),

^{13}C NMR (DMSO-d_6,δ /ppm): 19.9(CH_3),38.2 (CH_3),59.3(OCH_3),70.3(C-NH_2),98.2(C-N),115.3(CN) 124.5- 137.89 (C=C &Ar C), 149.2(S-C=N),157.3 (C=N), 161.3 (N=C-S).

5-amino-7-(4-chlorophenyl)-2-(2-methylbenzyl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-6-carbonitrile (6g)

Yield: 61%; m.p.=203-208°C;

Anal.Calcd for $C_{20}H_{16}N_5SCl$, C,60.98; H,4.09; N,17.78%. Found: C,60.91; H,4.01,N,17.66%.

IR (cm^{-1}): 3463(NH_2), 2193 (CN), 1576 (C=N).

^{1}H NMR (DMSO-d_6, δ /ppm): 2.25 (s, 3H, CH_3), 3.21 (s, 2H, CH_2), 4.59 (s, 1H, CH), 5.31 (s, 2H, NH_2), 6.91 – 8.14 (m, 8H, ArH).

^{13}C NMR (DMSO-d_6,δ /ppm): 20.35 (CH_3), 40.93 (CH_2), 70.9 (C-NH_2), 98.14 (C-CN), 117.2 (CN), 126.73- 139.89 (C=C &Ar C), 147.33 (S-C=N), 157.23 (CN), 162.3 (N=C-S).

5-amino-2-(4-chlorobenzyl)-7-(4-chlorophenyl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-6-carbonitrile(6h)

Yield: 74%; m.p.=215-219°C;

Anal.Calcd for $C_{19}H_{13}N_5SCl_2$: C,55.08; H,3.16; N,16.90%. Found: C,54.87; H,3.08, N,16.76%.

IR (cm^{-1}): 3363(NH_2), 2145 (CN), 1568 (C=N).

^{1}H NMR (DMSO-d_6, δ /ppm): 3.25 (s, 2H, CH_2), 4.61 (s, 1H, CH), 5.29 (s, 2H, NH_2), 7.12 – 7.65 (m, 8H, ArH).

^{13}C NMR (DMSO-d_6,δ /ppm): 39.51 (CH_2), 69.58 (C-NH_2), 98.72 (C-CN), 116.23 (CN), 126.72- 141.23 (C=C &Ar C), 149.23 (S-CN),158.32 (C=N), 163.23 (N=C-S).

5-amino-2-(4-methoxybenzyl)-7-phenyl-5H-[1,3,4] thiadiazolo [3,2-a]pyrimidine-6-carbonitrile(6k)

Yield: 66%; m.p.=210-215°C;

Anal.Calcd for $C_{20}H_{17}N_5OS$: C,63.98; H,4.56; N,18.65%. Found: C,63.87; H,4.42,N,18.58%.

IR (cm^{-1}): 3253(NH_2), 2386 (CN), 1597 (C=N).

^{1}H NMR (DMSO-d_6, δ /ppm): 3.19 (s, 2H, CH_2), 3.91 (s, 3H, OCH_3), 4.55 (s, 1H, CH), 5.19 (s, 2H, NH_2), 6.87 – 7.62 (m, 9H, ArH).
^{13}C NMR (DMSO-d_6,δ /ppm): 40.21 (CH_2), 60.12 (OCH_3), 70.28 (C-NH_2), 99.25 (C-CN), 116.1 (CN), 119.21- 138.39 (C=C &Ar C), 148.2 (S-CN),159.32 (C=N), 162.47 (N=C=S).

5-amino-2-(4-chlorobenzyl)-7-phenyl-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-6-carbonitrile(6m)
Yield: 68%; m.p.=193-198°C;
Anal.Calcd for $C_{19}H_{14}N_5SCl$: C,60.07; H,3.71; N,18.44%. Found: C,59.89; H,3.59,N,18.31%.
IR (cm^{-1}): 3336(NH_2), 2200 (CN), 1601 (C=N).
^{1}H NMR (DMSO-d_6, δ /ppm): 3.19 (s, 2H, CH_2), 4.53 (s, 1H, CH), 5.21 (s, 2H, NH_2), 7.03– 7.82 (m, 9H, ArH).
^{13}C NMR (DMSO-d_6,δ /ppm): 39.21 (CH_2), 69.28 (C-NH_2), 97.23 (C-CN), 114.53 (CN), 126.52- 138.32 (C=C &Ar C), 148.21 (S-C=N), 160.23 (C-C=N), 161.24 (N=C-S)

Experimental
Melting points of all synthesized compounds were determined in open capillary tubes on an electro thermalapparatus and are uncorrected. The progress of reaction was monitored by thin layer chromatographyon silica gel coated aluminum plates (Merck) as adsorbent and UV light as visualizing agent. ^{1}H NMR and ^{13}C NMRspectra were recorded on Varian 500 MHz NMR spectrophotometer using CDCl3/DMSO-d6 as solvent and TMS as an internal standard (chemical shifts in δ ppm). C, H, N estimation was recorded on Carlo Erba1108 (CHN) Elemental Analyzer.

Synthesis of 2-amino-5-(substituted)-benzyl-1,3,4-thiadiazole (3):
General Procedure.
An equimolar mixture of phenyl acetic acid **(1)** (0.01 mol) and Thiosemicarbazide **(2)** (0.01 mol,) in phosphorous oxychloride (10 ml) was refluxed for about 1 hr. The progress of reaction was monitored on TLC. Upon completion, the reaction mixture was quenched onto crushed ice. The resultant solution was further refluxed for 4hrs and filtered. The filtrate was neutralized with dilute KOH solution, to maintained pH 8-10, thus the product was precipitated out, was filtered, washed with water and purified by recrystallization from ethanolic water to yield **(3)**.
The physical characterization of synthesized compounds **(3a-e)** was given in **Table I**.
Table-I
Physical data of 2-amino-5-(substituted)-benzyl-1,3,4-thiadiazole (3)

Compounds	**R**	**m.p. (°C)**	**Yield (%)**
3a	4-OCH_3	191-95	78
3b	2-CH_3	210-13	71
3c	4-Cl	220-23	85
3d	2,4-dichloro	245-47	72
3e	H	214-17	69

Synthesis of 5-amino-7-(substituted-phenyl)-2-(substituted-bezyl)-5-H-[1,3,4]-thiadiazolo [3,2-a]pyrimidine-6-carbonitrile (6):
General Procedure.
An equimolar mixture of 2-amino-5-(substituted)-benzyl-1,3,4-thiadiazole **(3)** (0.01 mol, 1.66 gms), aromatic aldehyde **(4)** (0.01 mol, 1.36 gms) and malononitrile **(5)** (0.01 mol, 0.91 gms)

in ethanol (10 ml) as a solvent and triethylamine as a catalyst, was refluxed for about 10-12 hrs. The progress of reaction was monitored on TLC. Upon completion, the reaction mixture was cooled to room temperature. The product was precipitated out was filtered, washed with water and purified by recrystallization from ethanolic water to yield **(6)**.

The physical characterization of synthesized compound**(6a-o)** was given in **Table II**.

Table-II

Physical data of 5-amino-7-(substituted-phenyl)-2-(substituted-bezyl)-5-H-[1,3,4]-thiadiazolo [3,2-a]pyrimidine-6-carbonitrile (6)

Compounds	R	R1	m.p. (°C)	Yield (%)
6a	4-OCH_3	4-OCH_3	185-189	69
6b	2-CH_3	4-OCH_3	201-205	71
6c	4-Cl	4-OCH_3	218-223	68
6d	2,4-dichloro	4-OCH_3	220-225	63
6e	H	4-OCH_3	211-217	72
6f	4-OCH_3	4-Cl	190-195	64
6g	2-CH_3	4-Cl	203-208	61
6h	4-Cl	4-Cl	215-219	74
6i	2,4-dichloro	4-Cl	191-197	65
6j	H	4-Cl	204-209	59
6k	4-OCH_3	H	210-215	66
6l	2-CH_3	H	202-208	73
6m	4-Cl	H	193-298	68
6n	2,4-dichloro	H	189-294	62
6o	H	H	221-227	70

Antimicrobial and antifungal activities

All the newly synthesized compounds were evaluated for their antibacterial activity against gram-negativebacteria, E coli and P aeruginosa and gram-positive bacteria, S aureus, and C diphtheriae using discdiffusion method[17, 18]. The zone of inhibition was measured in mm and the activity was compared withstandard drug. The antimicrobial data was given in **Table II**.

TABLE III:Antibacterial Activity of compound 6

Antibacterial Activity of compound 6				
Comp.	**Zone of inhibition (in mm)**			
	Gram Positive		**Gram negative**	
	S.aureus	**C.diphtheria**	**P.aeruginosa**	**E.coli**
6a	21	22	20	23
6b	23	24	21	26
6d	18	20	19	20
6h	22	23	23	19
6i	20	19	26	21
6j	14	17	22	17

6l	12	14	21	24
6o	23	24	20	22
Amphicilintrihydrate	26	28	24	21
DMSO	0	0	0	0

* Diameter of the disc was 6mm;
Concentration of the compounds taken was about 100 µg/mL.

Acknowledgements.
The authors are thankful to the Management ofK. C. College and Guru Nanak College, Mumbai, India, for the constant encouragement and providing the necessary facilities. The authors are also thankful to The Director, TIFR Mumbai for the spectral data.

References:

1. M. Abdul Rahiman, G.H. Suryateja, *J. Applicable. Chem,* **2015**, 4 (5), 1469-1476.
2. X. Liu, Y. Shi, Y. Ma, *Eur. J. Med. Chem,* **2009**, 44, 2782–2786.
3. Thoraya A. Farghaly, Magda A. Abdallah, *Molecules,* **2012**, 17, 14625-14636.
4. Sergey V. Ryabukhin, Andrey S. Plaskon, *Tetrahedron letters*, **2010**, 51, 4229-5232.
5. Hai-Ming Guo, WU Yan-Yan, *„J Org Chem,* **2010**, 75: 3863-3866.
6. D. Cressier, C. Prouillac, *Bioorg Med Chem,* **2009,** 17, 5275–5284.
7. D. Sunil, A.M. Isloor, P. Shetty, *Arabian J. Chem,* **2010**, 3, 211-217.
8. D.A. Ibrahim, *Eup. J. Med. Chem,* **2009**, 44, 2776-2781.
9. Doaa E. Abdel Rahman, Khaled O. Mohamed, *Der PharmaChemica*, **2014**, 6(1), 323-335.
10. V. Mathew, J. Keshavayya, *Eur. J. Med. Chem,* **2007**, 42, 823-840.
11. J. Ramprasad, N. Nayak, *Eur. J. Med. Chem,* **2015**, 95, 49-63.
12. A.K. Gadad, C.S. Mahajanshetti, *Eur. J. Med. Chem,* **2000**, 35, 853–857.
13. N.S. El-Sayed, E.R. El-Bendary, *Eur. J. Med. Chem,* **2011**, 46, 3714–3720.
14. R. Lin, S.G. Johnson, P.J. Connolly, *Bioorg. Med. Chem. Lett,* **2009**, 19, 2333–2337.
15. S.S. Shukurov, M.A. Kukaniev,*Russ. Chem. Bull,* **1993**, 11, 1871–1874.
16. C.W. Sun, X.D. Zhang, H. Huang, P. Zhou, *Bioorg. Med. Chem. Lett,* **2006**, 14, 8574–8581.
17. Cruickshank R, Duguid J P, Marmion B P, *Medicinal Microbiology* ,12th edn, **Vol 11**, (1975) (Churchill Livingstone, London).
18. Arthington-Skaggs B A, Motley M, Morrison C J, *J Clin Microbiology*, **38,** 2254 (2000).

Received on July 7, 2019.