Bull. Chem. Soc. Ethiop. **2018**, 32(1), 133-138.
DOI: https://dx.doi.org/10.4314/bcse.v32i1.12

ISSN 1011-3924
Printed in Ethiopia

MULTI COMPONENT ONE POT SYNTHESIS AND CHARACTERIZATION OF DERIVATIVES OF 2-AMINO-7,7-DIMETHYL-5-OXO-4-PHENYL-5,6,7,8-TETRAHYDRO-4H-CHROMENE-3-CARBONITRILE AND STUDY OF ANTI-MICROBIAL ACTIVITY

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(Received June 7, 2017; Revised January 21, 2018; Accepted January 23, 2018)

ABSTRACT. An efficient and convenient procedure has been described for one-pot multi-component synthesis of tetrahydrobenzo[b]pyrans known as 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile which can be obtained from the reaction of substituted aromatic aldehydes, dimedone, malonitrile, in the presence of base such as potassium tertiary butoxide and THF in methanol as solvent at RT condition. All the compounds were examined by advanced spectroscopic data (^{1}H NMR, ^{13}C NMR and LCMS) and the structural determination was evaluated by elemental analysis. In addition to this, all the newly synthesized compounds were examined for their antibacterial activities and antifungal activity by disc diffusion method against the organism of *Aspergillus niger* and *Candida ablicans* L.

KEY WORDS: Aromatic aldehydes, Dimedone, Malonitrile, Potasium tertiary butoxide, 2-Amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile, Anti-microbial activity

INTRODUCTION

Multi-component reactions (MCRs) are known as efficient method for synthesis of various products in synthetic organic and medical chemistry. They have attracted more important in industrial and academic interests. Moreover, these reactions appear as useful sources for approaching small drug-like molecules with several levels of structural diversity. In such processes, three or more compounds undergo consecutive reactions in a single event to form new products, which contain the essential parts of all the starting materials. Benzopyrans are an important class of oygen-containing heterocyclic compounds in which benzene ring is fused to pyran ring and these 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile is called benzopyrans. These compounds are also called as hromenes. Chromenes are widely distributed in many natural products such as alkaloids, to copherels, flavonoids and anthocyanins [1]. A large number of chromeneheterocycles have been isolated from natural sources exhibiting siginificant pharamacetical potential. Conrauinone A is a naturally occurring chromene which has been isolated from the bark of the tree *M. conrauri* and potentially use for the treatment of intestinal parasites [2]. 2-Amino-4-(3-bromo-4,5-dimethoxy phenyl)-7-(dimethyl amino)-4H-chromene-3-carbonitrile and 2-amino-7-(dimethylamino)-4-(7-methoxy-1,3-benzodionol-5-yl)-4H-chromene-3-carbonitrile belongs to a novel class of microtubule inhibitors and the substitution of 4- aryl group increase the anticancer activity of the compound [3]. Benzopyrans are widely employed as potential biodegradable agrochemicals [4] photoactive materials [5], cosmetics and pigments [6]. Benzo[b]pyrans have a broad spectrum of biological

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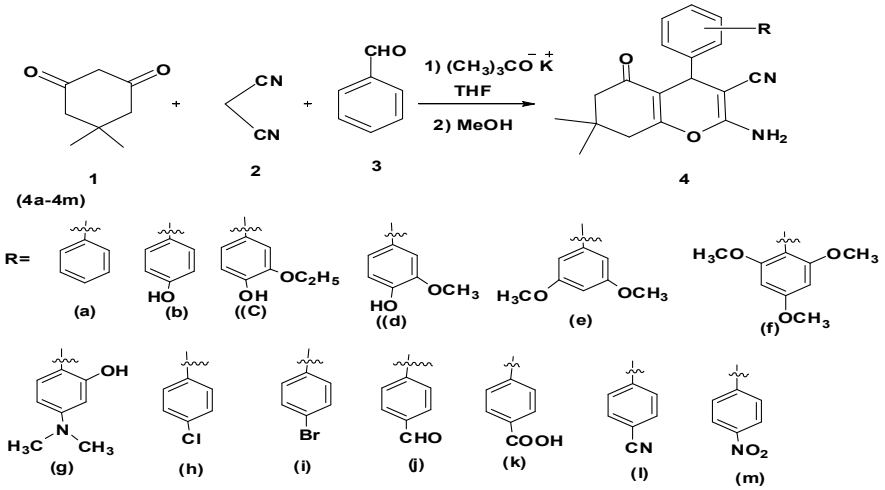
properties and it is well known structural scaffold of several natural products and artificial drugs [7]. These are used for antibacterial and anti-fungal activity [8], anticancer activity [9], insecticidal activity [10], antimicrobial [11] and anti-inflammatory agent [12], antioxidant [13], anti-anaphylactic and diuretic agent.

EXPERIMENTAL

All the chemicals and synthetic grade reagents were procured from Sigma Aldrich India and Merck chemicals. They were used without further purification. The progress of the reaction was monitored by thin layer chromatography (ethylacetate:n-hexane). The melting point of the all the newly synthesized compounds were determined open at one end capillary tube and were uncorrected using an Electrochemical Mk3 apparatus. ^{1}H NMR and ^{13}C NMR spectrum were recorded on 400MHz Brucker spectrometer in $CDCl_3$ as a solvent and chemical shift values are recorded in units δ (ppm) relative to tetramethylsilanes (Me_4Si) as an internal standard. Molecular mass of the synthesized compound were determined by LCMS. The solid product can be separated by column chromatography using silica gel.

General procedure for synthesis

A mixture of aromatic aldehydes (1.2 mmol), malonitrile (1 mmol), dimedone (1 mmol) are introduced in 100 mL of round bottom flask, methanol was added gradually until the mixture was dissolved. A catalytic amount of potassium tertiary buyoxide and THF added to the above miture. The reaction mixture was carried out on the magnetic stirrer under RT condition. The progress of the reaction was monitored by TLC in ethylacetate:n-hexane (3:7). After completion of the reaction, the mixture was cooled to room temperature and poured on 10 mL ice cold water. The crude was filtered and washed with ethylacetate and a saturated solution of anhydrous sodium bicarbonate several times. The solid product can be separated by column chromatography (ethylacetate:n-hexane, 3:7) (Scheme 1).



Scheme 1. Scheme of synthesis.

2-Amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile ***(4a)***. White solid; yield 86%; m.p. 228-230 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm: 7.36-7.21 (m,

5H, Ar-H), 6.61 (s, 2H, NH_2), 4.13 (s, 1H, CH), 2.32 (s, 2H, CH_2), 2.12-1.82 (m, 2H), 1.05 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ in ppm: 193.4, 158.1, 153.8, 143.6, 128.7, 126.2, 124.3, 118.7, 113.6, 57.2, 49.8, 39.5, 36.9, 31.4, 26.8. LCMS (m/z): 293.85. Molecular formula: $C_{18}H_{18}N_2O_2$. Elemental analysis: caliculated: C-73.65, H-6.16, N-9.52, O-10.87. Obtained: C-73.69, H-6.15, N-9.51, O-10.85.

*2-Amino-4-(4-hydroxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbo nitrile (**4b**)*. White solid; yield 92%; m.p. 205-206 °C. ^1H NMR (400 MHz, $CDCl_3$) δ in ppm: 9.32 (s, 1H, -OH), 7.05-6.65 (m, 4H, Ar-H), 6.59 (s, 2H, NH_2), 4.12 (s, 1H, CH), 2.25 (s, 1H, CH_2), 2.19-1.92 (m, 2H, CH_2), 1.01 (s, 3H, CH_2), 0.95 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ in ppm: 195.1, 157.5, 1552, 153.8, 135.4, 130.8, 118.7, 116.0, 112.8, 56.5, 50.2, 38.4, 37.3, 30.9, 27.1. LCMS (m/z): 310.09. Molecular formula: $C_{18}H_{18}N_2O_3$. Elemental analysis: calculated: C-69.66, H-5.84, N-9.03, 015.47. Obtained: C-69.69, H-5.83, N-9.02, O-15.46.

*2-Amino-4-(3-ethoxy-4-hydroxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**4c**)*. White solid; yield 92%; m.p. 229 °C. ^1H NMR (400 MHz, $CDCl_3$) δ in ppm: 9.52 (s, 1H, -OH), 6.87-6.64 (m, 3H, Ar-H), 6.51 (s, 2H, NH_2), 4.21 (s, 1H, CH), 4.17-1.08 (s, 2H-, CH_2), 1.29 (t, J = 7.6 Hz, 3H), 2.20 (s, 2H, CH_3), 2.03 (d, J = 8.0 Hz, 2H), 1.04 (s, 3H, CH_3), 1.01 (s, 3H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ in ppm: 194.7, 157.8, 153.9, 146.6, 143.8, 134.6, 121.5, 118.7, 114.8, 113.2, 112.6, 63.7, 57.6, 49.7, 38.4, 37.0, 31.4, 26.2, 14.2. LCMS (m/z): 354.53. Molecular formula: $C_{20}H_{22}N_2O_4$. Elemental analysis: calculated: C-67.78, H-6.26, N-7.90, O-18.06. Obtained: C-67.82, H-6.25, N-7.89, O-18.04.

*2-Amino-4-(4-hydroxy-3-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-Tetrahydro-4H-chromene-3-carbonitrile (**4d**)*. White solid solid; yield 90%; m.p. 231 °C. ^1H NMR (400 MHz, $CDCl_3$) δ in ppm: 9.49 (s, 1H, OH), 6.87-6.67 (m, 3H, Ar-H), 6.54 (s, 2H, NH_2), 4.18 (s, 1H, CH), 3.67 (s, 3H, OCH_3), 2.26 (s, 2H, CH_2), 2.22 (d, J = 8.0 Hz, 2H), 1.85-1.81 (m, 2H, CH_2), 1.06 (s, 3H, CH_3), 0.97(s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ in ppm: 165.2, 163.5, 155.9, 131.8, 128.6, 122.2, 118.9, 114.7, 110.9, 55.45 (OMe). LCMS (m/z):339.79. Molecular formula: $C_{19}H_{20}N_2O_4$. Elemental analysis: calculated: C-71.70, H-5.21, N-16.72, O-6.37. Obtained: C-71.75, H-5.20, N-16.70, O-6.35

*2-Amino-4-(3,5-dimethoxy phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chrome-3-carbonitrile (**4e**)*. White solid; yield 88%; m.p. 171 °C. ^1H NMR (400 MHz, $CDCl_3$) δ in ppm: 6.71 (s, 2H, NH_2), 6.12 (s, 1H, Ar-H), 6.07 (s, 1H, Ar-H), 4.18 (s, 1H, CH), 3.75 (s, 9H, OCH_3), 2.33 (s, 2H, CH_2), 1.78 (s, 2H, CH_2), 1.06 (s, 3H, CH_3), 0.88 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ in ppm: 195.7, 160.6, 158.4, 153.7, 143.6, 118.3, 114.4, 104.7, 95.68, 57.5, 54.7, 50.4, 39.15, 37.4, 31.8, 26.96. LCMS (m/z): 354.39. Molecular formula: $C_{20}H_{22}N_2O_4$. Elemental analysis: calculated: C-67.78, H-6.26, N-7.89, O-18.06. Obtained: C- 67.82, H-6.25, N-7.89, O-18.04.

*2-Amino-4-(2,4,6-trimethoxy phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**4f**)*. White solid; yield 92%; m.p. 235 °C. ^1H NMR (400 MHz, $CDCl_3$) δ in ppm: 6.71 (s, 2H, NH_2), 6.07 (s, 1H, Ar-H), 4.18 (s, 1H, CH), 3.75 (s, 9H, OCH_3), 2.33 (s, 2H, CH_2), 1.78 (s, 2H, CH_2), 1.06 (s, 3H, CH_3), 0.88 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ in ppm: 193.9, 160.7, 159.1, 157.7, 153.3, 118.2, 113.1, 100.9, 92.9, 57.3, 54.8, 50.6, 36.7, 31.4, 24.4, 26.7. LCMS (m/z): 384.28. Molecular formula: $C_{21}H_{24}N_2O_5$. Elemental analysis: calculated: C-65.61, H-6.29, N-7.29, O-20.81. Obtained: 65.69, H-6.28, N-7.29, O-20.79.

*2-Amino-4-(4-(dimethyl amino)-2-hydroxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**4g**)*. Pale red solid; yield 89%; m.p. 235 °C. ^1H NMR (400 MHz, $CDCl_3$) δ in ppm: 9.42 (s, 1H, -OH), 6.89 (d, J = 7.6 Hz, 1H, Ar-H), 6.71 (s, 2H, NH_2), 6.22 (d, J

= 8.4 Hz, 1H, Ar-H), 6.14 (s, 1H, Ar-H), 4.23 (s, 1H, CH), 2.25 (s, 2H, CH_2), 2.13-1.92 (m, 2H, CH_2), 1.06 (s, 3H, CH_3), 1.02 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ in ppm: 194.3, 157.4, 156.3, 153.7, 147.2, 130.4, 118.7, 110.7, 1057, 57.25, 36.62, 40.4, 32.2, 30.7, 27.4. LCMS (m/z): 354.28. Molecular formula: $C_{20}H_{23}N_3O_3$. Elemental analysis: calculated: C-67.97, H-6.56, N-11.89, O-13.58. Obtained: C-68.02, H-6.55, N-11.87, O-13.57.

2-Amino-4-(4-bromophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahyro-4H-chromene-3-carbonitrile ***(4h)***. Pale red solid; yield 93%; m.p. 208 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm: 7.84 (d, J = 8.0 Hz, 1H, Ar-H), 7.54 (d, J = 7.6 Hz, 1H, Ar-H), 7.14 (d, J = 8.4 Hz, 1H, Ar-H), 7.05 (s, 1H, Ar-H), 6.71 (s, 2H, NH_2), 4.17 (s, 1H, CH), 2.31 (s, 2H, CH_2), 1.72 (s, 2H, CH_2), 1.08(s, 3H, CH_3), 0.92 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ in ppm: 197.2, 157.7, 154.2, 143.2, 130.1, 129.4, 120.4, 118.8, 112.7, 58.6, 50.8, 39.3, 37.9, 31.5, 27.1. LCMS (m/z): 373.12. Molecular formula: $C_{18}H_{17}BrN_2O_2$. Elemental analysis: calculated: C-57.92, H-4.59, Br-21.41, N-7.51, O-8.57. Obtained: 57.96, H-4.58, Br-21.40, N-7.50, O-8.56.

2-Amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbo-nitrile ***(4i)***. White solid; yield 93%; m.p. 206 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm: 7.35-7.14 (m, 4H, Ar-H), 6.57 (s, 2H, NH_2), 4.23 (s, 1H, CH), 2.26 (s, 2H, CH_2), 2.19 (d, J = 8.0 Hz, 2H), 2.08 (s, 2H, CH_2), 1.07 (s, 3H, CH_3), 1.02 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ in ppm: 196.2, 157.36, 153.84, 140.7, 130.5, 129.1, 127.6, 118.7, 114.0, 56.4, 50.3, 38.6, 31.1, 26.9. LCMS (m/z): 328.51. Molecular formula: $C_{18}H_{17}ClN_2O_2$. Elemental analysis: calculated: C-65.77, H-5.20, Cl-10.78, N-8.52, O-9.72. Obtained: C-65.82, H-5.20, Cl-10.76, N 8.51,O-9.71.

2-Amino-4-(4-formylphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile ***(4J)***. Pale yellow solid; yield 89%; m.p. 238 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm: 9.92 (s, 1H, -CHO), 7.75-7.43 (m, 4H, Ar-H), 6.53 (s, 2H, NH_2), 4.18 (s, 1H, CH), 2.26 (s, 2H, CH_2), 2.19-2.02 (m, 2H, CH_2), 1.72 (d, J = 7.6 Hz, 2H), 0.99 (s, 3H, CH_3), 0.92 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ in ppm: 195.6, 168.3, 157.6, 154.2, 147.6, 132.5, 128.8, 127.6, 118.9, 113.6, 57.450.5, 38.7, 37.6, 31.9, 27.7. LCMS (m/z):321.87. Molecular formula: $C_{19}H_{18}N_2O_3$. Elemental analysis: calculated: C-70.79, H-5.63, N-8.69, O-14.89. Obtained: C-70.83, H-5.62, N-8.68, O-14.87.

4-(2-Amino-3-cyano-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-4-yl)benzoic acid ***(4k)***. White solid; yield 88%; m.p. 235 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm: 12.37 (s, 1H, -COOH), 8.21 (d, J = 8.4 Hz, 1H, Ar-H), 8.07 (d, J = 7.6 Hz, 1H, Ar-H), 7.52 (d, J = 7.4 Hz, 1H, Ar-H), 7.38 (s, 1H, Ar-H), 6.69 (s, 2H, NH_2), 4.26 (s, 1H, CH), 2.24 (s, 2H, CH_2), 2.13-1.83 (m, 2H, CH_2), 1.08 (s, 3H, CH_3), 1.04 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ in ppm: 197.3, 164.5, 157.2, 153.4, 148.6, 127.1, 126.7, 125.9, 119.2, 112.6, 57.7, 49.8, 39.2, 36.7, 32.6, 26.9. LCMS (m/z):338.49. Molecular formula: $C_{19}H_{18}N_2O_4$. Elemental analysis: calculated: C-67.44, H-5.36, N-8.28, O-18.92. Obtained: C-67.49, H-5.35, N-8.27, O-18.90.

2-Amino-4-(4-cyanophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile ***(4l)***. White solid; yield 89%; m.p. 249 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm: 7.68-7.51 (m, 4H, Ar-H), 6.71 (s, 2H, NH_2), 4.23 (s, 1H, CH), 2.26 (s, 2H, CH_2), 2.19 (d, J = 8.0 Hz, 2H), 2.08 (s, 2H, CH_2), 1.07 (s, 3H, CH_3), 1.02 (s, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ in ppm: 195.9, 158.2, 154.6, 147.2, 131.7, 127.8, 118.9, 118.0, 112.7, 109.8, 58.2, 50.7, 38.2, 37.4, 31.7, 27.6. LCMS (m/z):319.41.Molecular formula: $C_{19}H_{17}N_3O_2$. Elemental analysis: calculated: C-71.46, H-5.36, N-13.14, O-10.02. Obtained: C-71.49, H-5.36, N-13.14, O-10.01.

2-Amino-7,7dimethyl-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile ***(4m)***. Yellow solid; yield 86%; m.p. 250 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm: 8.16 (d, J =

7.6 Hz, 1H, Ar-H), 8.09 (d, J = 8.0 Hz, 1H, Ar-H), 7.61 (d, J = 7.6 Hz, 1H, Ar-H), 7.42 (s, 1H, Ar-H), 6.75 (s, 2H, NH_2), 4.20 (s, 1H, CH), 2.22 (s, 2H, CH_2), 2.05 (d, J = 8.0 Hz, 2H, 2.01 (s, 2H, CH_2), 1.03 (s, 3H, CH_3), 0.97 (s, 3H, CH_3). ^{13}CNMR (100 MHz, $CDCl_3$) δ in ppm: 197.7, 158.4, 153.8, 149.2, 143.7, 125.5, 123.5, 118.6, 112.8, 57.3, 50.6, 38.7, 37.4, 30.5, 26.5. LCMS (m/z): 341.29. Molecular formula: $C_{18}H_{17}N_3O_4$. Elemental analysis: calculated: C-63.71, H-5.05, N-12.38, O-18.86. Obtained: C-63.76, H-5.04, N-12.36, O-18.84.

Anti bacterial activity

The anti bacterial activities of newly synthesized compounds are examined against 5 pathogenic bacteria strains. The gram negative bacteria screened were *Escerichia coli* and *Pseudomonas aeruginosa*. The gram positive bacteria screened were *S. ureas* and *B. substills*. The target compounds were used at the concentration of 250 µg/mL and 500 µg/mL using DMSO as a solvent the amoxylin 10 µg/mL disc were used as a standard. The rest of the compounds were found to be moderate active against the tested micro organism.

Anti fungal activity

Anti fungal activity of new synthesized compounds were examined by disc diffusion method against the organism of *Aspergillus niger* and *Candida ablicans* L. Compared were treated at the concentrations of 500 µg/mL and 1000 µg/mL using DMSO as a solvent. The standard drug was used as ketoconazol 50 µg/mL against both organisms.

Table 1. Antimicrobial activity screening activity synthesized scaffold.

Compound code	*Zone of inhibition in (mm)					
	Bacteria				Fungi	
	S. aureus	*E. coli*	*S. typhi*	*B. substills*	*A. niger*	*C. albicans*
5a	10	10	06	04	09	07
5b	19	18	11	20	07	08
5c	21	18	10	19	06	08
5d	18	20	09	20	17	21
5e	16	10	11	13	09	07
5f	21	18	12	19	11	09
5g	22	17	12	20	05	08
5h	21	18	13	12	16	15
5i	21	22	12	21	16	17
5j	16	15	13	13	14	12
5k	15	16	12	14	15	11
5l	12	14	07	10	12	10
5m	10	08	08	10	10	09
Amoxycilline	25	25	22	22	NA	NA
Ketoconazole	NA	NA	NA	NA	20	20
DMSO	--	--	--	--	--	--

RESULTS AND DISCUSSION

All newly titled synthesized compounds can be synthesized under reflux condition. These target compounds can be obtained, we used to mixture of potassium tertiary butoxide and THF in protic solvent. This catalyst can be used to improve the reaction conditions and reaction is completed maximum 2 hours. The rate of reaction was increased by using this catalyst. We used various substituted aryl aldehydes such as electron donating group of aldehydes and electron withdrawing group of aldehydes and halogen containing aldehydes. All the synthesized compounds were examined anti bacterial activity as well as antifungal. The electron

withdrawing group of compounds (**5o**) did not show any activities. Other hand electron withdrawing group of compounds exhibited poor activity compared with electron donating groups. All halogen compounds exhibit excellent activity. The compound which possess electron donating group shows moderate activity as shown in Table 1.

CONCLUSION

The reaction condition carried at RT for all the newly synthesised compounds. The yield of the titled compounds obtained from 86-93%.The compound possesses electron donating group gives maximum yeild than that of the compound possesses electron withdrawing group. The rate of reaction developed by using the reagent as well as protic solvent. All the compounds tested by anti microbial activity against gram positive, gram negitive and fungal. The compound having halogens showed excelent active potential. Other wise the compounds having electron donating group which showed better active potential than that of the electron with drwing group.

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