J. Mater. Environ. Sci. 5 (5) (2014) 1653-1657
ISSN : 2028-2508
CODEN: JMESCN

Triethylamine: an efficient N-base catalyst for synthesis of annulated uracil derivatives in aqueous ethanol

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Received 2 Apr 2014, Revised, Revised 3 July 2014, Accepted 3 July 2014
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Abstract
The one-pot three-component reaction for the synthesis of pyrano[2,3-d]pyrimidine derivatives has been reported via initial Knoevenagel, subsequent addition and final heterocyclization of substituted aromatic aldehydes, ethylcyanoacetate and barbituric acid in aqueous ethanol solvent using triethyamine as N- base catalyst under reflux condition. The results showed that a series of aromatic aldehydes were effectively used to prepare the targeted pyrano[2,3-d]pyrimidine derivatives with good to excellent yields (**69-94%**) and there is no major effect on the yield of product by electron donating/withdrawing substituents. Environment friendly procedure, excellent yields, inexpensive and readily available catalyst are the advantages of this procedure. All synthesized compounds were characterized by IR, ^{1}HNMR and ^{13}CNMR spectral data.

Keywords: Annulated uracils, Ethylcyanoacetate, barbituric acid, aromatic aldehydes, triethylamine.

1. Introduction
Biologically active six membered annulated pyrano[2,3-d]pyrimidine heterocycles compound consisting uracil moieties clubbed in to one molecule and the resultant derivative enhances its pharmaceutical activity such as antitumour [1], cardiotonic [2] antifungal [3] antihypertensive [4] antimalarial, antagonist and antimetabolite [5] activities. Annulated pyrano[2,3-d]pyramidine consists of uracil ring is unsaturated **N** and **O** type heterocyclic as a fusion of pyran and pyrimidine rings, involves one oxygen atom at **8** and two nitrogen atoms at **1** and **3** positions respectively. The biologically active uracil based heterocyclic compounds are synthesized by diverse procedures based on Knoevenagel condensation, Michael addition followed by cyclodehydration strategy and ultimately heterocyclization [5]. Multicomponent reactions (MCRs) are special consequence in organic and medicinal chemistry having significant advantages over conventional type syntheses [6]. MCRs in heterocyclic scaffolds are particularly useful for the creation of diverse chemical libraries of 'drug-like' molecules for biological screening, since the combination of three or more small molecular weight building blocks in a single operation leads to high combinatorial efficacy.
The development of environmentally benign and clean synthetic procedures based on water is the prevalent goal in organic synthesis. Water plays an essential role as a medium for organic reactions [7, 8]. The organic reactions in aqueous media have attracted much attention in organic synthesis, not only because water is one of the most abundant, cheapest and environmentally friendly solvent, but also because this green solvent is highly polar and therefore immiscible with most organic compounds. Reaction in aqueous media are environmentally safe, devoid of any carcinogenic effects, has simple work up and especially are important in industrial fields [9]. Moreover the water soluble catalyst resides and operates in the aqueous media, and separation of organic compounds is easy. Thus, it needs to develop multicomponent reactions (MCRs) in water and without the use of any harmful organic solvent. Multi-component reactions also emerged as an important tool in the situation of modern combinatorial synthesis. Moreover, high productivity, facile execution and simple reaction profile are the vital strategies in executing multicomponent reactions, which have expanded rapidly in organic chemistry

[10-14]. Herein we use Triethylamine moiety as catalyst which is N-type base was investigated in catalyzing Knoevenagel-Michael addition reaction. Triethylamine is weak base having aliphatic tertiary amine type with three alkyl groups attached to nitrogen atom imparting basic nature that is successfully used in synthesis of annulated uracil. As a weak base, triethylamine makes the Knoevenagel condensation and Michael addition reaction at room temperature with good to excellent yields .In this regard, the synthetic exploitation of nucleophilic double bond of annulated pyrano[2,3-d]pyrimidine is an important synthetic strategy. Therefore, for the preparation of these complex molecules large efforts have been directed towards the synthetic manipulation of new series of Pyrano[2,3-d] pyrimidine derivatives that occupy a distinct and unique place in medicinal chemistry.

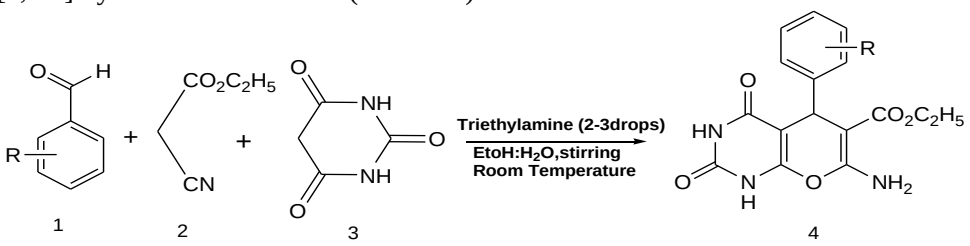
2. Experimental Section

2.1. Reagents and analysis

Melting points were determined by open capillary method and were uncorrected.^{1}H NMR spectra were obtained on a BRUKER instrument (300 MHz). IR spectra were recorded on a Perkin–Elmer 298 spectrophotometer using KBr pellet and ^{13}C-NMR (100 MHz) spectra were recorded in DMSO-*d6* as solvent with TMS as internal standard. Chemical shifts are reported in ppm. Reactions have been monitored by thin layer chromatography on 0.2-mm precoated plates of silica gel G60 F254 (Merck).

2.2. General Synthetic procedure

Aromatic aldehydes (**1**) (1mmol), Ethylcyanoacetate (**2**) (1.2mmol) barbituric acid (**3**) (1mmol) and 2- 3 drops of Triethylamine (TEA) base catalyst taken in R.B flask with 10-15 ml ethanol**:** water (1:1 ratio) solvent mixture and stirred for 43-110 minutes at room temperature. The reaction was monitored by TLC (thin layer chromatography). The solid compound was filtered, washed with cold water and recrystallization from 95% ethanol to obtain pure product Pyrano[2,3-d] Pyrimidine derivatives. (*Scheme 1*)



Scheme1: Synthesis of Pyrano[2,3-d] pyramidine derivatives.

2.3. Spectral data

*Ethyl 7-amino-5-(4-methylphenyl)-2,4-dioxo- 1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-Carboxylate (**4a**; Table 1; Entry 1):*

White solid. MP = 293 ^{0}C. IR (KBr, cm^{-1}): 3495, 3103, 2221, 1912, 1845, 1662, 1567, 1734; ^{1}H NMR (300 MHz, DMSO-d_6, δppm): δ 2.36 (s, 3H, CH_3), 2.6(s, 3H, CH_3), 4.13 (s, 1H, H-5), 5.21 (s, 2H, CH_2), 7.12 (s, 2H, H-Ar), 7.20 (s, 2H, H-Ar), 7.60 (s, 2H, NH_2), 10.89 (s, 1H, NH), 11.43 (s, 1H, NH); ^{13}C NMR (100MHz, DMSO-d_6, δppm) δ: 20.4, 88.01, 98.4, 115.9, 127.3, 128.09, 133,2, 137.4, 150.3, 155.01, 155.7, 159.3, 159.5, 16.07 ppm. EI-MS: (m/z) = 343 (M+), 328, 271, 252, 217, 112. CHN analyses ($C_{17}H_{17}N_3O_5$): calcd. C, 59.47; H, 4.99; N, 12.24%. Found C, 59.51; H, 4.87; N, 12.22%.

*Ethyl 7-amino-2,4-dioxo-5-phenyl-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carboxylate (**4b**;* Table 1; Entry 2*):*

Yellow powder. MP = 207 ^{0}C. IR (KBr, νcm^{-1}): 3381, 3168, 2289, 2202, 1664, 1708, 1560; ^{1}H NMR (300 MHz, DMSO-d_6, δppm): 3.6(s, 3H, CH_3), 4.19 (s, 1H, H-5), 4.31 (s, 2H, CH_2), 6.07 (s, 1H, H-Ar), 7.10 (s, br, 2H, NH_2), 6.51-8.13 (s, 5H-Ar), 11.12 (s, 1H, NH), 12.14 (br, s, 1H, NH); ^{13}CNMR (100MHZ, DMSO-d_6,δppm) δ: 30.02, 60.2, 69.2, 128.6, 129.8, 135.4, 152.8, 156.3 ppm. EI-MS: (m/z) = 329 (M+), 256, 243, 228, 201, 154, 78. CHN analyses ($C_{16}H_{15}N_3O_5$): calcd. C, 58.36; H, 4.59; N, 12.76%. Found C, 58.32; H, 4.57; N, 12.54%.

*Ethyl 7-amino-5-(4-methoxyphenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6- carboxylate (**4c**; Table 1; Entry 3):*
Yellow powder. MP = 293 ^{0}C. IR (KBr, *v* cm^{-1}): 3413, 3278, 2239, 2165, 1878, 1662, 1543; ^{1}H NMR (300 MHz, DMSO-d_6, δppm): 3.32 (s, 3H, OCH_3), 4.41 (s, 1H, H- 5), 3.71(s, 2H, CH_2), 2.49 (s, 3H, CH_3) 6.93 (m, 2H, H- Ar), 7.65 (m, 2H, H-Ar), 9.07 (s, 2H, NH_2), 11.09-10.03 (s, 2H, NH); ^{13}CNMR (100MHz, DMSO-d_6, δppm) δ: 33.03, 37.2, 55.8, 75.6, 114.2, 130.1, 134.3, 143.1, 150.5, 157.2, 162.4, 167.3 ppm. EI-MS: (m/z) = 339 (M+), 331, 328, 286, 270, 122. CHN analyses ($C_{17}H_{17}N_3O_6$): calcd. C, 56.83; H, 4.77; N, 11.69%. Found C, 56.89; H, 4.68; N, 11.72%.

*Ethyl 7-amino-5-(3,4-dimethoxyphenyl)-2,4- dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3- d]pyrimidine-6-carboxylate (**4d**; Table 1; Entry 4):*
Yellow solid. MP = 305 ^{0}C. IR (KBr, *v* cm^{-1}): 3495, 3303, 3123, 2987, 2164, 1662, 1576; ^{1}H NMR (300 MHz, DMSO-d_6, δppm) δ: 3.12 (s, 3H, CH_3), 3.5 (s, 2H, CH_2), 3.6 - 4.02 (s, 3H, OCH_3), 4.2 (s, 1H, H-5), 7.1 (s, 2H, NH_2), 11.1 (s, 1H, NH), 11.4 (s, 1H, NH), 8.27 (m, 2H, H-Ar), 8.47 (m, 2H, H-Ar); ^{13}C NMR (100MHz, DMSO-d_6, δppm) δ: 37.9, 56.3, 57.4, 79.7, 114.2, 135.8, 146.9, 149.4, 163.8, 150.1ppm. EI-MS: (m/z) = 389 (M+), 358, 317, 302, 216, 138. CHN analyses ($C_{18}H_{19}N_3O_7$): calcd. C, 55.53; H, 4.92; N, 10.79%. Found C, 55.546; H, 4.89; N, 10.77%.

*Ethyl 7-amino-5-(3-hydroxyphenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6- carboxylate (**4e**; Table 1; Entry 5):*
Yellow powder. MP = 270 ^{0}C. IR (KBr, *v* cm^{-1}): 3439, 3337, 3193, 3028, 2206, 1677, 1625; ^{1}H NMR (300MHz, DMSO-d_6, δppm) 3.6 (s, 3H, CH_3), 3.91 (s, 2H, CH_2), 4.10 (s, 1H, H-5), 6.56 (br, s, 2H, NH_2), 6.59 (m, 1H, H-Ar), 7.04-7.10 (m, 3H, H-Ar), 9.33 (s, 1H, OH), 11.09 (s, 1H, NH), 12.07 (s, 1H, NH); ^{13}C NMR (100MHz, DMSO-d_6, δppm) δ: 35.6, 59.9, 89.5, 114.7, 114.9, 118.8, 120.1, 130.1, 146.5, 150.4, 153.1, 158.1, 158.5, 163.3 ppm. EI-MS: (m/z) = 345 (M+), 331, 273, 261, 219, 172, 108. CHN analyses ($C_{16}H_{15}N_3O_6$): calcd. C, 55.65; H, 4.38; N, 12.17%. Found C, 55.64; H, 4.37; N, 12.11%.

*Ethyl 7-amino-5-(4-hydroxyphenyl)-2,4-dioxo- 1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6- carboxylate (**4f**; Table 1; Entry 6):*
Yellow powder. MP = 247 ^{0}C. IR (KBr, *v* cm^{-1}): 3343, 3191, 3142, 2209, 1909, 1796, 1685; ^{1}H NMR (300 MHz, DMSO-d_6, δppm): 3.69 (s, 1H, H- 5), 3.17 (s, 2H, CH_2), 2.43 (s, 3H, CH_3), 7.31 (br s, 2H, NH_2), 5.97 (m, 2H, H-Ar), 6.74 (m, 2H, H-Ar), 6.07 (s, 1H, OH),10.47 (s, 1H, NH), 11.03 (s, 1H, NH); ^{13}C NMR (100MHz, DMSO-d_6, δ, ppm) δ: 29.03, 37.2, 61.5, 75.2, 79.9, 115. 3, 134.4, 142.3, 150.4, 155.5, 160.1, 163.5 ppm. EI-MS: (m/z) = 345 (M+), 331, 261, 194, 186, 149, 112. CHN analyses ($C_{16}H_{15}N_3O_6$): calcd. C, 55.65; H, 4.38; N, 12.17%. Found C, 55.64; H, 4.37; N, 12.19%.

*Ethyl 7-amino-5-(4-chlorophenyl)-2,4-dioxo- 1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6- carboxylate (**4g**; Table 1; Entry 7):*
White solid. MP = 295 ^{0}C. IR (KBr, cm^{-1}): 3311, 3188, 3091, 2228, 1899, 1648, 1543. ^{1}H NMR (100 MHz, DMSO-d_6, δppm): 2.17(3H, s, CH_3), 4.8 (2H, s, CH_2), 5.28 (s, 1H, H-5) 4.11 (2H, s, CH_2), 2.29 (3H, s, CH_3), 7.28 (m, H-Ar), 7.38 (m, 2H, H-Ar), 7.75 (br s, 2H, NH_2), 10.99 (s, 1H, NH), 11.55 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6, δppm) δ: 88.3, 98.5, 114.8, 126.9, 128.8, 129.0, 129.9, 130.5, 135.9, 150.1, 155.4, 155.8, 159.7, 160.9 ppm. EI-MS: (m/z) = 364 (M+), 329, 291, 280, 240, 237, 127. CHN analyses ($C_{16}H_{14}ClN_3O_5$): calcd. C, 52.83; H, 3.88; N, 11.55%. Found C, 52.87; H, 3.79; N, 11.53%.

*7-amino-5-(4-bromophenyl)-2,4-dioxo-1,3,4,5- tetrahydro-2H-pyrano[2,3-d]pyrimidine-6- carboxylate (**4h**; Table 1; Entry 8):*
Yellow powder. MP = 235 ^{0}C. IR (KBr, *v* cm-1): 3340, 3370, 3189, 3080, 2220, 1684, 1567; ^{1}H NMR (300 MHz, DMSO-d_6, δppm) 3.2 (s, 3H, CH_3), 3.8 (s, 2H, CH_2), 4.26 (s, 1H, H-5), 7.17 (s, 2H, NH_2) 7.20 (m, 2H, H-Ar), 7.48 (m, H-Ar), 12.45 (s, 1H, NH), 13.66 (s, 1H, NH); ^{13}C NMR (100MHz, DMSO-d_6, δppm) δ: 35.3, 58.5, 82.8, 119.0,120.0, 129.9, 132.2, 132.7,143.0, 157.4, 160.3, 174.0 ppm. EI-MS: (m/z) = 408 (M+), 336, 281, 257, 237, 171, 115. CHN analyses ($C_{16}H_{14}BrN_3O_5$): calcd. C, 47.08; H, 3.46; N, 10.29%. Found C, 47.10; H, 3.49; N, 10.27%.

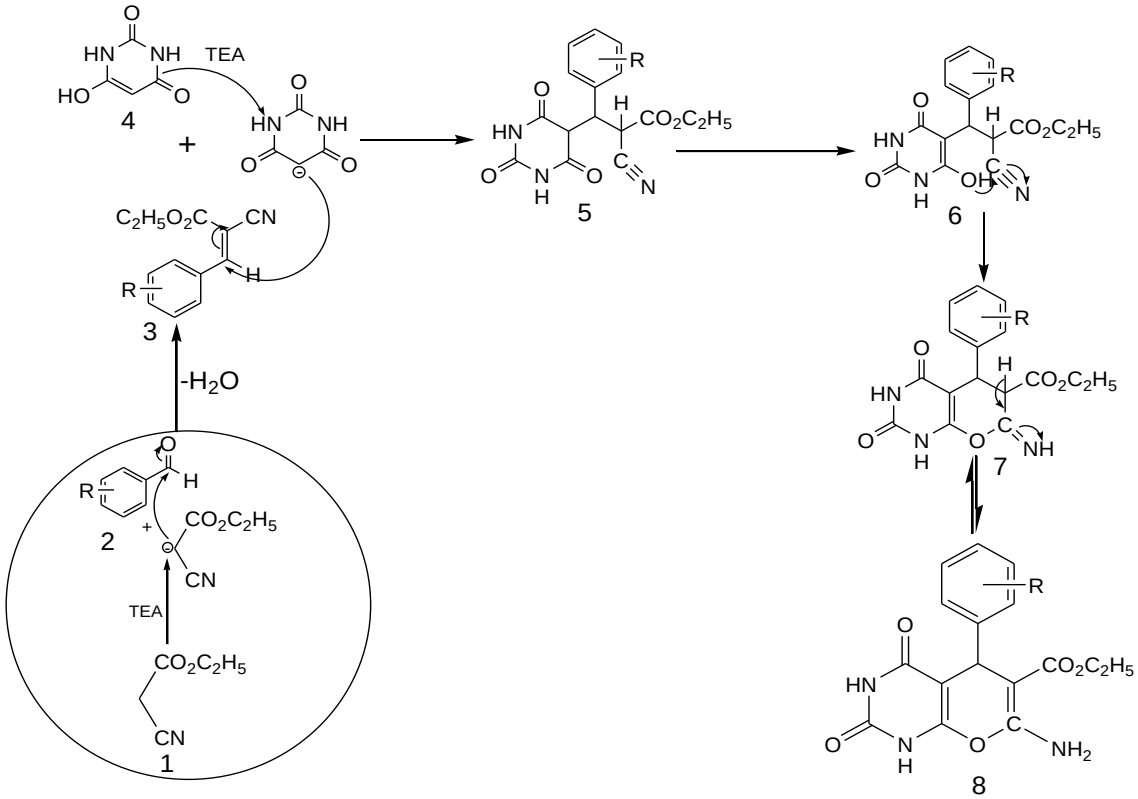
*Ethyl 7-amino-5-(3-nitrophenyl)-2,4-dioxo- 1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6- carboxylate (**4i**; Table 1; Entry 9):*
White solid. MP = 237 ^{0}C. IR (KBr, *v* cm^{-1}): 3380, 3321, 3182, 2896, 1796, 1640,1519; ^{1}H NMR (300MHz, DMSO-d_6, δppm): 3.6 (3H, s, CH3), 4.1 (s, 2H, CH2), 4.82 (s, 1H, H-5), 7.26 (s, 2H, NH_2), 7.52 (m, 2H, H-Ar), 8.14 (m, 2H, H-Ar), 11.12 (s, 1H, NH), 12.17 (s, 1H, NH); ^{13}C NMR (100MHz, DMSO-d_6, δppm) δ: 35.7, 57.5, 87.5, 119.0, 124.3, 130.7,

146.4, 149.6, 151.9, 152.7, 157.8, 162.6 ppm. EI-MS: (m/z) = 374 (M+), 302, 290, 271, 250, 137, 123. CHN analyses ($C_{16}H_{14}N_4O_7$): calcd. C, 51.34; H, 3.77; N, 14.97%. Found C, 51.37; H, 3.79; N, 14.94%.

*Ethyl7-amino-5-(4-nitrophenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6- carboxylate (**4j**; Table 1; Entry 10):*
White solid. MP = 289 ^{0}C. IR (KBr, *v* cm^{-1}): 3420, 3367, 3106, 2986, 1978, 1749, 1604; ^{1}H NMR (300MHz, DMSO-d6, δ, ppm): 3.92 (s, 1H, H-5), 7.26 (s, 2H, NH_2), 7.32 (m, 2H, H-Ar), 8.09 (m, 2H, H-Ar), 9.67 (s,1H, NH), 10.15 (s, 1H, NH), 4.12 (s, 2H, CH_2), 3.09 (s, 3H, CH_3); ^{13}CNMR (100 MHZ, DMSO-d6, δppm) δ: 14.2, 37.2, 61.7, 79.5, 121.0, 130.0, 145.4, 148.3, 150.5, 160.3, 162.3, 163.8, 167.2 ppm. EI-MS: (m/z) = 374 (M+), 329, 287, 271, 179.112. CHN analyses ($C_{16}H_{14}N_4O_7$): calcd. C, 51.34; H, 3.77; N, 14.97%. Found C, 51.37; H, 3.79; N, 14.94%.

3. Results and discussion

Herein, we use N-type Triethylamine (TEA) as base catalyst and its efficient application to the Knoevenagel-Michael addition via multicomponent mode worked out in aqueous medium at room temperature. Since, triethylamine is simple amine where the study of result of the alkyl group attached to the nitrogen atom could be done. Catalyst gets easily removed by aqueous washing due to its solubility in water, hence no need of further neutralization and work-up is accomplished by simple filtration and recrystallization by ethanol. Triethylamine is basic in character, so facilitates proton removal from active methylene compounds, there by increases reaction rate and yields of annulated pyrano [2, 3-d] pyrimidinones/uracils. Assorted products were obtained in high yield with very good purity, hence suggested that triethylamine is an effective catalyst for the formation of higher reactive iminium group which is utilized to facilitate Knoevenagel condensation between aryl aldehydes and active methylene compounds, which proceeds via intermediate, undergoes dehydration and finally heterocyclization to produced deseried annulated uracils **Scheme 2**.



Scheme 2: Plausible mechanism for the formation of pyrano[2,3-d]pyrimidine derivatives.

Result showed a series of representative aromatic aldehydes with active methylene compounds and barbituric acid to yield pyrano[2,3-d]pyrimidinones **4a-4j** as a sole products **Table 1**. Triethylamine as N-type catalyst in

synthetic routes is easy to handle, non-corrosive in environmentally benign aqueous media, cheap, nontoxic and commercial availability with an advantageous high products, selectivity and yields. These synthesised pyrano [2, 3-d] pyrimidines/uracils acts as biological agents may become excellent derivatives for globally alarming drug resistance issues in clinically used therapeutics.

Table 1: Synthesis of pyrano[2,3-d]pyrimidine derivatives

Entry	Product	R	Time (min)	Yield (%)[a]	M.P. (^{0}C)
1	4a	4-Me-C_6H_4	55	72	293
2	4b	C_6H_5	43	69	207
3	4c	4-MeO-C_6H_4	80	83	293
4	4d	3,4-MeO-C_6H_4	67	79	305
5	4e	3-OH-C_6H_4	48	92	270
6	4f	4-OH-C_6H_4	55	94	247
7	4g	4-Cl-C_6H_4	92	86	295
8	4h	3-Br-C_6H_6	110	84	235
9	4i	3-NO_2-C_6H_4	97	82	237
10	4j	4-NO_2-C_6H_4	105	83	289

[a]Isolated yields.

Conclusion

In conclusion we have developed a rapid and an efficient synthetic route for one-pot three component synthesis of annulated Pyrano [2,3-d] pyrimidine derivatives in aqueous ethanol at room temperature using triethylamine as catalyst. The present synthetic route has the advantages of operational simplicity, mild reaction conditions and good to high yield of the biological active products. Our method is simple as no extraordinary apparatus, reagents or chemicals, for work up are required, and the compound formed is filtered and purified just by simple crystallization. This synthesis is also advantageous in terms of atom economy as well as avoided from of any hazardous chemicals.

Acknowledgments-The authors are thankful to Indian institute of chemical technology, Hyderabad for providing spectral data and Head, department of chemistry, RTM Nagpur University for providing lab. Facilities.

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