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# Gadolinium oxide($Gd_2O_3$) as an Effective Catalyst for Synthesis of 5-methyl-7-aryl-4,7-dihydrotetraazolo[1,5-a]pyrimidine-6-carboxylic esters

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**ABSTRACT: Various substituted dihydrotetrazolo[1,5-a] pyrimidine derivatives have been synthesized by reacting the mixture of aromatic aldehydes, ethyl acetoacetate, and 5-amino tetrazole in one pot by using gadolinium oxide($Gd_2O_3$) as catalyst. Structures were confirmed by using IR and NMR techniques.**

**Keywords:** Dihydropyrimidine; aldehydes; ethylaceto acetate 5-amino tetrazole; Biginelli reaction.

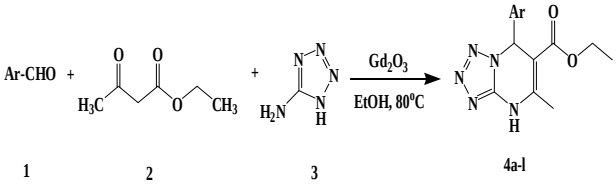
**INTRODUCTION:** In recent years dihydropyrimidines and its derivatives showed significant applications due to their pharmacological and therauptic properties[1,2].Compounds containing dihydropyrimidinecore unit shows biological activities such as antitubercular agent[3]anti-inflammatory agents,antiviral,antibacterial[4,5], antimalarial[6], antihypertensive agents[7], cytotoxic[8], calcium-channel antagonists[9] etc.

Dihydrotetrazolo[1,5-a]-pyrimidine derivatives have been reported to possess various biological activities such as fungicidal[10], antimicrobial[11], central nervous system stimulating,farnesyltransferase inhibitory, KATP channel opening[12] etc. Due to its wide application synthesis of dihydrotetraazolo[1,5-a]-pyrimidine have been of prime important. Dihydrotetrazolopyrimidine derivatives were synthesized by Biginelli type of reactions by using mineral acids[13], sulphamic acid[14], strontium chloride hexahydrate[15], iodine[16] etc. But these methods have limitations such as prolonged reaction time,low yields and use of hazardous and expensive catalysts.
In recent years numerous inorganic oxides such metal oxides have been reported to synthesis of various organic compounds and derivatives[17]. They have been found to have better catalytic activities than the conventional type of catalyst and have wide applications in synthesis due to shorter reaction time such as in Bigenelli type reactions.

Hence we have developed new methodology to synthesize DHPM by using Gadolinium oxide($Gd_2O_3$) as catalyst. This method is very effective as it increases the yield by decreasing reaction time.

## MATERIALS AND METHODS:

**Experimental Section:** All the reagents used are of research grade, purchased from SD-fine,Merck and Spectrochem. Melting points were recorded in open capillary method and are corrected. The melting points were compared with literature ones. Synthesized products were characterized by IR and $^1$H NMR. Infrared(IR) was recorded on Shimadzu FTIR spectrometer and $^1$H NMR spectra was recorded on Bruker Advance II 400 NMR Spectrometer(400 MHz) using DMSO-$d_6$ as solvent.




**[Scheme I]**

**General procedure for synthesis of Gadolinium oxide ($Gd_2O_3$):** Gadolinium oxide was synthesized by sol gel method by dissolving gadolinium nitrate(0.1 mmol) and sodium hydroxide(0.1 mmol) in 50 ml water. To this solution ethyl cellulose(0.1mmol) was added with constant stirring. Then resultant solution was heated in hot air oven at 120$^o$C for 24 hours. After cooling reaction mixture was filtered and washed with water and dried. The dried solidobtained was calcined in muffle furnace at 700$^o$C for 2 hours resulting in fine

particle sized catalyst. The catalyst was characterized by IR, XRD and SEM methods.

**General procedure for synthesis5-methyl-7-aryl-4,7-dihydrotetraazolo [1,5-a] pyrimidine-6- carboxylic esters(4a-l):** To a stirred mixture of aromatic aldehyde(1mmol), 5-amino Tetrazole(1mmol) and ethyl acetoacetate(1mmol) in 10 ml ethanol gadolinium oxide($Gd_2O_3$)(15mol%) was added. The reaction mixture was refluxed at 85$^oC$ for 4 hours. The completion of reaction was monitored by TLC. The reaction mixture was filtered at hot condition to remove the catalyst. Thereafter catalyst washed with ethanol and can be reused. Then solid precipitate obtained by cooling reaction mixture to 20$^oC$, solid precipitate filtered and washed with cold ethanol and recrystalised by ethanol(90%) to give pure product. The synthesized product was charcterised and confirmed by IR,$^1$H NMR,$^{13}$C NMR.

**Ethyl 4,7-dihydro-5-methyl-7-phenyltetrazolo[1,5-a] pyrimidine-6-carboxylate(4a):**

IR (KBr,υmax ($cm^{-1}$)): 3175, 3094, 2947, 1705, 1573, 1454, 1381, 1273, 1222,1141, 1192, 941, 837, 752, 698, 570;$^1$H NMR (DMSO-d6,400 MHz,δ ppm): 1.09(t,3H,$OCH_2CH_3$), 2.55(S,3H,5-methyl-H), 3.99(q,2H,$OCH_2CH_3$), 6.64(s,1H,CH), 7.28(s,1H,ArH), 7.30 (s,1H,ArH),7.32 (s,1H,ArH),7.34 (s,1H,ArH),7.36 (s,1H,ArH),11.26 (s,1H,CH);$^{13}$C NMR (DMSO-d6,100 MHz,δ ppm): 13.85, 18.54, 51.08, 58.77, 59.74, 78.43, 79.09, 97.69, 126.98, 128.68, 140.77, 146.69,148.56,164.60

**Ethyl7-(4-fluorophenyl)-4,7-dihydro-5-methyl tetrazolo[1,5-a] pyrimidine-6- carboxylate(4b):**

IR (KBr,υmax ($cm^{-1}$)): 3167, 3055, 2947, 1697, 1574, 1504, 1293, 1127, 1103, 1018, 840, 802, 696, 578 ;$^1$H NMR (DMSO-d6,400 MHz,δ ppm): 1.07 (t,3H,$OCH_2CH_3$), 2.53(S,3H,5-methyl-H), 4.00 (q,2H,$OCH_2CH_3$), 6.67 (s,1H,CH), 7.12 (s,1H,ArH), 7.14 (s,1H,ArH),7.36 (s,1H,ArH),7.38 (s,1H,ArH),11.30 (s,1H,CH);$^{13}$C NMR (DMSO-d6,100 MHz,δ ppm):13.88, 18.54, 58.17, 59.78, 78.48, 97.59, 115.37, 129.27, 137.04, 146.88, 148.40, 160.86, 163.30, 164.55.

**Ethyl7-(4-chlorophenyl)-4,7-dihydro-5-methyl tetrazolo[1,5-a] pyrimidine-6- carboxylate(4d):**

IR (KBr,υmax ($cm^{-1}$)): 3178, 3055, 2951, 1701, 1574, 1485, 1377, 1281, 1223, 1092, 1011, 837, 768, 570.;$^1$H NMR (DMSO-d6,400 MHz,δ ppm): 1.10 (t,3H,$OCH_2CH_3$), 2.50 (S,3H,5-methyl-H), 4.02 (q,2H,$OCH_2CH_3$), 6.64 (s,1H,CH), 7.32 (s,1H,ArH), 7.34 (s,1H,ArH),7.35 (s,1H,ArH),7.37 (s,1H,ArH),11.28 (s,1H,CH);$^{13}$C NMR (DMSO-d6,100 MHz,δ ppm): 13.83, 18.53, 58.18, 59.77, 78.24, 78.90,97.27, 128..57, 133.56,139.41, 147.01, 148.34, 164.43

**Ethyl 4,7-dihydro-7-(4-nitrophenyl)-5-methyltetrazolo[1,5-a] pyrimidine-6- carboxylate (4h):**

IR (KBr,υmax ($cm^{-1}$)): 3240, 3179, 3055, 2955, 1713, 1655, 1578, 1408, 1342, 1265, 1215, 1099, 1065, 825, 717, 567.;$^1$H NMR (DMSO-d6,400 MHz,δ ppm): 1.09 (t,3H,$OCH_2CH_3$), 2.54(S,3H,5-methyl-H), 4.01 (q,2H,$OCH_2CH_3$), 6.85 (s,1H,CH), 7.62 (s,1H,ArH), 7.63 (s,1H,ArH),7.75 (s,1H,ArH),7.76 (s,1H,ArH),11.41 (s,1H,CH);$^{13}$C NMR (DMSO-d6,100 MHz,δ ppm): 13.91, 18.50, 55.06, 58.36, 59.73, 78.84, 98.03, 113.83, 128.35, 132.93, 146.34, 148.44,159.34,164.69.

**RESULTS AND DISCUSSION:** Initially one pot and three component reaction of aromatic aldehyde, 5-amino tetrazole and ethyl acetoacetate (1:1:1) was considered a standard model reaction. During investigation variety of catalysts are screened for model reaction(Table 1). For this regard different catalysts such as HCl, $H_2SO_4$, $CrCl_3$, $I_2$, Sulphamic acid and $Gd_2O_3$ were used. From these primary studies, it is observed that $Gd_2O_3$ shows shorter reaction time with better yield than other catalysts. Therefore $Gd_2O_3$ was found to be better and effective catalyst for this one pot three component reaction.

To find out the concentration of catalyst required for model reaction, procedure was optimized by using different molar concentration. For this catalyst was loaded at different molar concentrations as shown in table-2. Table-2 shows that 15mol% of gadolinium oxide($Gd_2O_3$) shows better yield at shorter time than other catalyst.

A wide range of substituted aromatic aldehydes were used at similar reaction conditions to get different DHPM derivatives(4a-l). The resultant compounds were obtained in good yields in the shorter time(table-3). All the synthesized compounds were characterized on the basis of analytical data.

**Table 1: Effect of different Catalyst on synthesis of4a.**

| Entry | Catalyst | Temp $^oC$ | Time (h) | Yield( %) |
|---|---|---|---|---|
| 1 | HCl | 85 | 7 | 55 |
| 2 | $H_2SO_4$ | 85 | 7 | 54 |
| 3 | Sulphamic acid | 85 | 7 | 85 |
| 4 | $CrCl_3$ | 85 | 9 | 55 |
| 5 | Iodine | 85 | 5 | 72 |
| 6 | Gadolinium oxide | 85 | 4 | 86 |

**Table 2: Effect of catalyst loading on the one pot, three component synthesis of 4a.**

| Entry | $Gd_2O_3$ (%) | Temp ($^oC$) | Time (h) | Yield (%) |
|---|---|---|---|---|
| 1 | 0 | 85 | 8.0 | 52 |
| 2 | 5 | 85 | 7.5 | 60 |
| 3 | 10 | 85 | 6.0 | 72 |
| 4 | 15 | 85 | 4.0 | 86 |
| 5 | 20 | 85 | 4.0 | 86 |

**Table 3: Gadlinium oxide catalyzed synthesis of compound 4.**

| Entry | Compound No. | Ar | Time (h) | Yield (%) | M.P. ($^oC$) |
|---|---|---|---|---|---|
| 1 | 4a | $C_6H_5$ | 4.0 | 86 | 204-205 |
| 2 | 4b | 4-$FC_6H_4$ | 4.1 | 88 | 202-204 |
| 3 | 4c | 2-$ClC_6H_4$ | 4.5 | 84 | 187-188 |
| 4 | 4d | 4-$ClC_6H_4$ | 4.3 | 86 | 184-186 |
| 5 | 4e | 2-$NO_2C_6H_4$ | 4.7 | 82 | 195-197 |
| 6 | 4f | 4-$NO_2C_6H_4$ | 4.5 | 83 | 206-208 |
| 7 | 4g | 4-$N(CH_3)_2C_6H_4$ | 4.8 | 80 | 182-184 |
| 8 | 4h | 4-$(OCH_3)$ $C_6H_4$ | 4.3 | 84 | 218-220 |
| 9 | 4i | 3,4-$(OCH_3)_2$ $C_6H_3$ | 4.4 | 85 | 210-212 |
| 10 | 4j | 3,4,5-$(OCH_3)_3$ $C_6H_2$ | 4.4 | 87 | 199-201 |
| 11 | 4k | 3-Pyridine | 4.5 | 82 | 206-208 |
| 12 | 4l | 2-Thiophene | 4.2 | 80 | 225-227 |

**CONCLUSION:** In this repoted method, we have developed an efficient, ecofrienly and economic catalyst for the synthesis of 5-methyl-7-aryl-4,7-dihydrotetraazolo [1,5-a] pyrimidine-6- carboxylic esters(4a-l) with easily available reagents and high yield and can be reused several times.

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