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A FACILE NITRATION FOR THE SYNTHESIS OF API INTERMEDIATES USING NOVEL NANO CATALYSTS

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Abstract:
Novel nanocatalyst, copper zirconium oxide and ferric cerium oxide are synthesized with different weight percentage by Sol-Gel technique. These catalysts were used for the preparation of aromatic nitro compounds using 60-70% aqueous nitric acid at mild nitration reaction condition in good yield. This is the first report on aromatic nitration by Cu/Zr and Fe/Ce catalysts. Considering the reaction conditions, this is a highly efficient and green approach for aromatic nitration reaction.

Keywords: Nano Particles, Sol-Gel Techniques, Nitration Reaction

Introduction:

Cu/Zr/Si oxide catalyst is important for research due to its non-toxicity and eco-friendly nature. They are super statistic, crystalline, tough and non-corrosive. Importantly, Cu/Zr/Si oxide catalysts are thermodynamically stable at 900°C.[1]These catalysts are generally used for methods like photo catalytic application and water purification techniques. [2]

Establishing the safe chemical processes for manufacturing of active pharmaceutical ingredients and their intermediates in the pharmaceutical/chemical industry is increasingly becoming important and challenging.[3] Identification of critical process parameters by assessing the hazardous factors associated with material, reaction and operation that bring safety to the product and personnel involved in the production is very critical and important to grow and sustain in the business.[4]Accidents can be avoided by understanding the heat of reaction, kinetics, decomposition pattern of product mixtures, addition pattern of reagents and reactants, mischarging of reactants and catalysts, agitation problems, and proper temperature

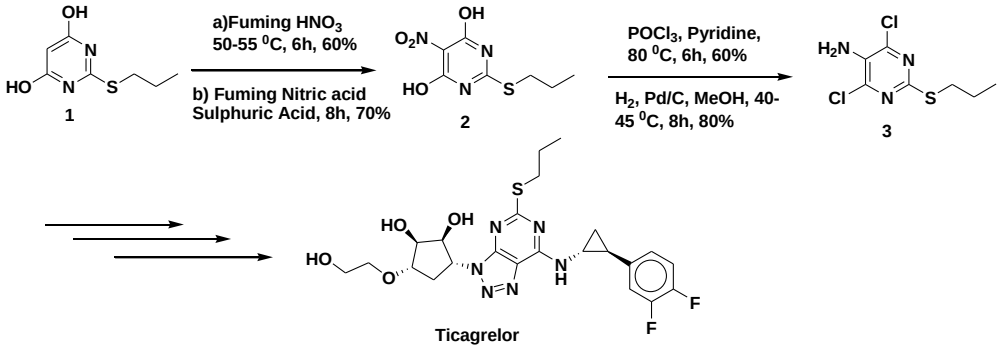
control. Our invention has disclosed process for preparation of catalysts like Cu/Zr and Fe/Ce.[5]These catalysts were previously used for the coupling reaction. We report here a facile and expeditious aromatic nitration method using the same catalyst. Remarkably, this type of nitration has never been investigated before.

Results and Discussion:

This is the first protocol for nitration reaction performed using Nano Catalysts for the synthesis of different API intermediates without using hazardous fuming nitric acid and sulphuric acid.[6] This reaction was performed using acetic acid and 60-70% nitric acid. The yield of the reaction is up to 80-90%.

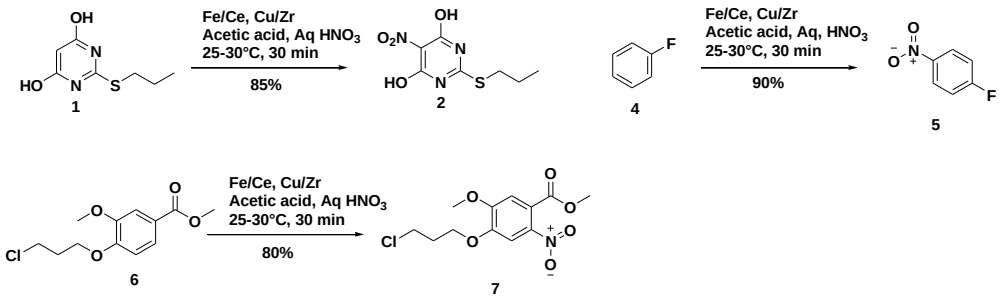
The compound 4, 6-dichloro-2-propylthiopyrimidine-5-amine (**3**) is a key intermediate for the synthesis of Ticagrelor. Ticagrelor is used for the prevention of stroke, heart attack and other events in people with acute coronary syndrome. It acts as a platelet aggregation inhibitor by antagonising the P2Y12 receptor.[7-9] The key intermediate amine **3** is synthesized from 2-(propylthio)pyrimidine-4,6-diol (**1**) in good yield (**Scheme-1**) using fuming HNO_3 and fuming H_2SO_4. Fuming HNO_3 and fuming H_2SO_4 are highly hazardous and work process is also highly complicated.[10]The reported nitration reactions yield is 60-70% and the process is exothermic and at higher scale, it is not recommended.

Scheme-1 (Reported methods)



The present work is an example of an improved process to prepare intermediate compound 5-nitro-2-(propylthio)pyrimidine-4,6-diol (**2**), 1-fluoro-4-nitrobenzene (**5**), and methyl 4-(3-chloropropoxy)-5-methoxy-2-nitrobenzoate (**7**) in excellent yield. Nitration reaction was performed using Nano catalysts such as Cu/Zr and Fe/Ce in AcOH, and aqueous HNO_3 at room temperature. This is economical and industrially safe process. The nitration reaction using nano catalysts reaction was completed within 30 minutes and isolation of the product was very simple (**Scheme 2**).

Scheme-2 (Improved methods)



Conclusions:

Nano catalysts Cu/Zr and Fe/Ce were used for aromatic nitration reaction and the products were obtained in excellent yield. This process is green, economical and industrially safe for the synthesis of several API intermediates.

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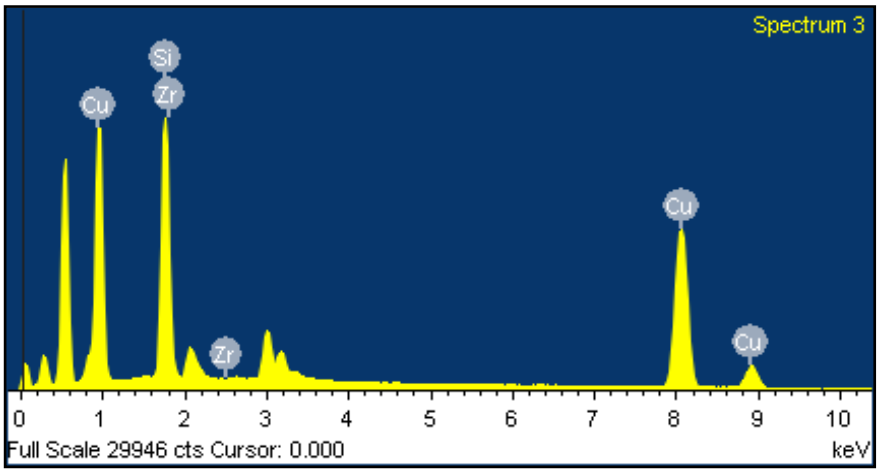
References:

1. Characterization of Zirconium−Silicon Binary Oxide Catalysts Prepared by the Sol−Gel Method, Sang-Chul, Moon, M. Fujino, H. Yamashuta, and M. Anpo, *The Journal of Physical Chemistry B*, **101**(3), 369–373 (1997).
2. Adsorption of Cu(II) and Zn(II) onto ZrO_2–SiO_2 composite: Characteristics, mechanism and application in wastewater treatment, S. Drużyński, K. Mazurek, U. Kiełkowska, F. Ciesielczyk, T. Jesionowski, *Desalination and Water Treatment*, **320**, 100657 (2024).
3. Process safety evaluation of the nitration synthesis process of Pendimethalin, Y. Liu, Z. Zhu, L.Ni, H. Yao, J. Jiang, Z. Chen, *Process Safety and Environmental Protection*, **182**, 176-187 (2024).
4. An efficient and safe process for the preparation of ticagrelor, a platelet aggregation inhibitor via resin-NO_2 catalyzed formation of triazole ring, G. B. Shinde, P. K. Mahale, S. A. Padaki, N. C. Niphade, R. B. Toche, and V. T. Mathad, *SpringerPlus* **4**, 493 (2015).
5. Synthesis and biological evaluation of ticagrelor derivatives as novel antiplatelet agents, H. Zhang, J. Liu, L. Zhang, L. Kong, H. Yao, and H. Sun, *Bioorganic & Medicinal Chemistry Letters*, **22** (11), 3598-3602 (2012).
6. Synthesis of Gefitinib from Methyl 3-Hydroxy-4-methoxy-benzoate Li, M. D.; Zheng, Y. G.; Ji, M., *Molecules*, **10**, 12(9), 2160 (2007).
7. Processes for the preparation of omeprazole and intermediates, A. E. Bandstorm, and B. R. Lamm, US 462008A.
8. Preparation Method of Cabuzantinib intermediates, G. G. Zhang, C. Zhang, J. L. Pugen, and Y. Hengli, CN109988108B.
9. As a Key Component in the, Preparation of Pazopanib, T.T.C. Bui, H.L. Luu, T.T. Luong, T.N. Nguyen, N.S.H. Dao, V.G. Nguyen, D.L. Nguyen, N.T. Trinh, V.H. Nguyen, *Chemistry*, **6** (5), 1089–1098, (2024).

10. Process preparation of Varenicline Intermediates, V.K. Kansal, S. Ahmad, A. Gupta, WO2009155403A2.
11. K.A. Jacobson and M. J. Boeynames, *drug discovery*, 570-578, (2010).
12. B. Springthorpe, A. Bailey, P. Barton, T.N. Birkinshaw, R.V. Bonnert, R.C. Brown, and D. Chapman, *Bioorganic and Medical Chemistry Letters*, **17** (21) 6013-6018, (2007).
13. **Synthesis of 5-Nitro-2-(propylthio) pyrimidine-4, 6-diol (Compound-2):** To a solution of acetic acid (500 mL) was added aqueous nitric acid (60 to 70%) (83.89 g, 1.33 mol) and stirred for 10–15 min followed by addition of nanocatalyst 10 g (10 %w/w). To this reaction mixture, 2 (propylthio)pyrimidine 4,6 diol (100.0 g; 0.54 mol) was added in five equal lot wise at 30°C to the above nitrating mixture and maintained temperature at 25°C to 30 °C. After 30 minutes, TLC showed completion of reaction. The reaction mass was diluted with water (500 mL) and stirred for 45–60 min and extracted with dichloromethane (3X300 mL). The organic layer was separated and concentrated under reduced pressure to get 90g of white crystalline solid in 80% yield. The purity was 96.3% as shown by HPLC; The compound showed IR (KBr) at 734-774, 1209, 1336-1393, 1557-1617, 2826-2977, and 3430-3436 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 0.90 (*t*, 1H), 1.40 (*m*, 2H), 3.2 (*t*, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 164.27, 158.88, 117.46, 31.97, 22.04, 13.03. ESI-Mass: For C7H9N3O4S (M+H)/z: 232.3.
14. **Synthesis of 4-Fluro Nitrobenzene (Compound-5):** To a solution of acetic acid (500 mL) was added aqueous nitric acid (60 to 70%) (291 g, 2.07 mol) and stirred for 10–15 min followed by addition of nanocatalyst 10 g (10 % w/w). To this reaction mixture, Flurobenzene (100.0 g; 1.04 mol) was added and stirred at 25°C to 30 °C. After 30 minutes, TLC showed completion of reaction. The reaction mass was diluted with water (3X500 mL) and stirred for 45–60 min and extracted with dichloromethane (3X500 mL). The organic layer was separated and concentrated under reduced pressure to get crude oily compound. The pure product was isolated by high vacuum distillation (yellow oil), solidifies upon standing overnight at 70-72°C, 8-9 mm/hg to obtain 116 g of 4-Fluro Nitrobenzene in 79-80% yield. The GC purity 99.5%; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 7.5 (*t*, 2H), 8.5 (*m*, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 116.69, 116.92, 126.53, 126.53; ESIMass: For $C6H4FNO_2$ (M+H)/z: 142.3.
15. **Synthesis of Methyl 4-(3-chloropropoxy)-5-methoxy-2-nitrobenzoate (Compound-7):** To a solution of acetic acid (400 mL) was added aqueous nitric acid (60 to 70%) (108 g, 0.77 mol) and stirred for 10–15 min followed by addition of nanocatalyst 10 gm. (10%w/w). To this reaction mixture, methyl 4-(3-chloropropoxy)-3-methoxybenzoate (100.0 g; 0.38 mol) was added and stirred at 25°C to 30 °C. After 30 minutes, TLC showed completion of reaction. The reaction mass was diluted with water (3X500 mL) and stirred for 45–60 min and extracted with dichloromethane (3X500 mL). The organic layer was separated and concentrated under reduced pressure to get crude compound. The crude compound was stirred for 2h in *n*-hexane to form precipitation at 25-30°C and after filtration, 100g of solid product, Compound-7 isolated in 85 % yield. HPLC purity 98.6%; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 2.20 (*m*, 2H), 3.70 (*t*, 2H), 3.82 (*s*, 3H), 3.90(*s*, 3H), 4.20 (*t*, 2H), 7.20 (*s*, 2H), 7.60 (*s*, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 108.3, 111.3, 120.6, 140.7, 149.24, 152.39, and 156.34. ESI Mass: For $C12H14ClNO_6$ (M+H)/z: 304.6
16. **Synthesis of Mixed oxides Nanomaterial by Sol-gel method: S**ol-gel method has been employed to synthesize the Cu/Zr/Si oxide catalyst in which Copper acetate and zirconyl nitrate have been used as a copper and zirconia, respectively. The synthesis technique will have a significant effect on the gel structure during the sol-gel system,

leading to changes in textural and catalytic performance of produced catalysts. Copper ZrO_2 supported on SiO_2(CZ) catalyst was prepared with varying molar ratio copper oxide and ZrO2 concentration (1:1, 1:2 and 2:1) in a typical procedure. The 1:1 CZ catalyst was synthesized by dissolving equimolar quantity of Cu (II) and Zr (II) in 40 mL distilled water in Sonicate for 30 min with addition of appropriate amount of Tetraethyl orthosilicate. This copper acetate solution was added drop wise to the zirconyl nitrate with constant stirring followed by the addition of tetraethyl orthosilicate. The resultant transparent bluish gel was obtained, further air dried and then heated in oven at 100ºC for 10 h. Dried catalyst was calcined at 500 ºC for 4 h. Similarly, catalysts with 1:2 and 2:1 were prepared. The below EDX spectrum (Fig 1) shows detection of metals. The Fig 1 shows elements present in our catalyst which are mentioned here on graph, the chemical composition of resulting Cu/Zr/Si Nano material has been analyzed by EDX and this pattern Si, O, Cu and Zr Peaks were clearly seen which confirmed by the composition of Nano material.



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