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Green Synthesis Of 6-Amino 1, 4 Dihydropyrano[2,3-c]Pyrazole-5-Carbonitrile Under Aqueous Medium.

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Abstract-

An eco-friendly benign multi-component reaction in aqueous medium in the presence of SiO_2-$TiCl_4$ has been developed for the synthesis of 1,4 dihydropyrano[2,3-c]pyrazole-5-carbonitrile.The present study follows green protocol starting with aromatic aldehyde, malonitrile, ethyl acetate, hydrazine hydrate reacted under aqueous medium to produce pyranopyrazole. The presented method is mild, eco-friendly, economic, efficient, energy saving and functionality tolerant and gives the products in good to excellent yields.SiO_2-TiCl4 Catalyst works effectively without any further side product. The key advantage of catalyst is that it is isolated easily at the end of reaction without any tedious procedure; reported pyranopyrazole derivative is confirmed by spectroscopic tools.i.e NMR, Mass, IR.

Keyword- SiO_2-TiCl4, Multi-component reaction, aqueous medium etc

1.0 Introduction-

Heterocyclic chemistry is of prime importance as a sub-discipline of Organic Chemistry, as millions of heterocyclic compounds are known with more being synthesized regularly.

The challenging task in chemistry is to develop practical methods, reaction media, conditions,

and the use of materials based on the principles of green chemistry. The concept of ‘‘Green Chemistry’’ has emerged as one of the guiding principles of environmentally benign synthesis. [1].Thus, organic chemists are switching over to the maximum use of eco-friendly and sustainable in recent years, finding creative ways to reduce environmental pollution has been the goal of many organic resources [2]. In water, organic reactions arising from hydrophobic effect will have reduced activation energies and faster reactions [3]. It has been focused on reducing or eliminating the use of toxic solvents to minimize damage for the human and environmental.

Pyranopyrazole heterocycles have special importance in synthetic and medicinal chemistry.

These compounds are found in synthetic products and many natural compounds that show a

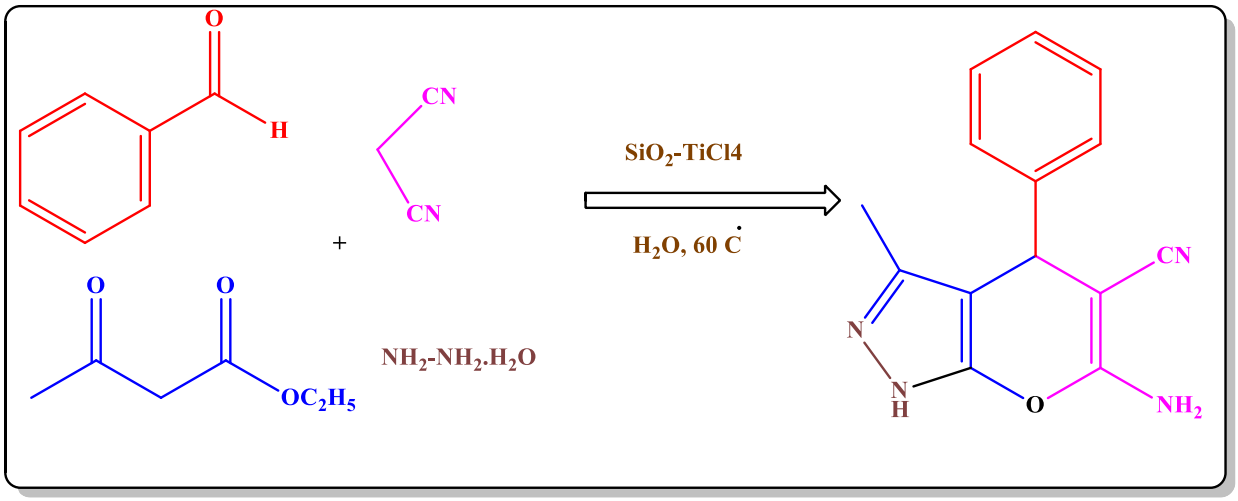
Wide range of biological activities [4]. It is also applicable to note that pyranopyrazole derivatives exhibit antihypertensive [5], anti-inflammatory [6], antimicrobial [7], anticancer [8], analgesic [9], insecticidal [10], antifungal activities [11].

Multicomponent processes have recently gained considerable economic and ecological impetus as they address fundamental principles of synthetic efficiency and reaction design. Multicomponent reactions (MCRs) have been proven to be very elegant and rapid way to access complex structures in a single synthetic operation from simple building blocks and show high atom economy and high selectivity [12-15].Therefore, choice of catalyst for green reaction is limited and has become a matter of concern for researchers nowadays. In recent times, few synthetic methods were developed for the preparation of pyranopyrazoles available in the literature [16, 17]. Amongst which the four components, one pot synthesis of pyranopyrazoles from ethyl acetate, malononitrile, aromatic aldehyde and hydrazine hydrate is a suitable methodology. Furthermore, a few procedures have described the one pot multicomponent synthesis of pyranopyrazoles based on catalysts such as 1, 4-diazabicyclo [2.2.2] octane (DABCO) [18], cinchona alkaloid [19] and many others. The procedure had certain disadvantages such as the use of toxic catalysts, monotonous workup and poor yields.

2.Experimental. All the chemicals used were purchased from Sigma Aldrich without further purification. All products are already known, and were confirmed by comparison of spectral and physical data with the existing literature. Melting points of all compounds were determined on a melting point apparatus and are found to be uncorrected. IR spectra were recorded on PerkinElmer FTIR spectrophotometer. The 1H NMR spectra were recorded on Bruker Spectrospin spectrometer (300 MHz) using TMS as an internal standard.

2.1General Procedure

To the aqueous mixture of hydrazine hydrate, (1 mmol) and ethyl acetoacetate (1 mmol), aromatic aldehyde (1 mmol), malononitrile (1 mmol) and silica-TiCl4 as catalyst were added in a catalytic amount is refluxed for 60 ^{0}C for a specific period till reaction is completed. The progress of reaction is confirmed by taking TLC periodically. After completion of the reaction the reaction mixture was filtered and obtained a solid crude product. The product was recrystallized by hot ethanol. The catalyst was recovered was simple filtration process which is dried under vacuum. The catalyst was recycled for further use.



3. Spectra of some selected compounds-

6-amino-4-(4-methoxy phenyl) 3-methyl-1, 4 dihydropyrano [2,3-c] pyrazole 5-carbonitrile.

IR (cm^{-1}) 3483, 3254, 3109, 2835, 2190, 1640, 1492; ^{1}HNMR (300MHz,$CDCl_3$) δ 1.77 (3H,s,CH_3), 3.70 (3H,s,-OCH_3), 4.53 (1H,s,CH), 6.82 (2H,s,NH_2), 6.85-6.88 (2H,d,Ar-H), 7.05-7.08 (2H,d,Ar-H), 12.09 (1H,s,NH); ^{13}C–NMR (300MHz, $CDCl_3$) δ 9.73, 35.42, 54.98, 57.59, 97.86, 113.72, 120.80, 128.48, 135.51, 136.46, 154.73, 157.90, 160.65 ppm; m/z 283 ($M^{+\cdot}$,100%)

6-amino-4-(4-methyl phenyl) 3-methyl-1, 4 dihydropyrano [2,3-c] pyrazole 5-carbonitrile

IR (cm^{-1}) 3238, 3047, 2922, 2360, 1681, 1266; ^{1}HNMR (300MHz, $CDCl_3$) δ 1.79(3H,s,CH_3), 2.26 (3H,s,CH_3), 4.52(1H,s,CH), 6.84(2H,s,NH_2), 7.02-7.05 (2H,d,Ar-H), 7.10-7.12 (2H,d,Ar-H),12.07(1H,s,NH); ^{13}C–NMR (300MHz, $CDCl_3$) 163.5, 139.0,113.5,177.1, 25.2,132.3, 59.4, 135.3,128.4, 125.6, 117.1,13.5, 22.2 m/z 267 (M^{+} ,100%)

6-amino-4-(4-chloro phenyl) 3-methyl-1, 4 dihydropyrano [2,3-c] pyrazole 5-carbonitrile

IR (cm^{-1}) 3409, 3305, 3174, 2185, 1649; ^{1}HNMR (300MHz, $CDCl_3$): δ 1.79 (3H,s,CH_3), 4.63 (1H,s,CH), 6.91 (2H,s,NH_2), 7.18-7.20 (2H,d,Ar-H), 7.36-7.39 (2H,d,Ar-H), 12.14 (1H,s,NH);

^{13}C–NMR (300MHz, $CDCl_3$) 163.9, 140, 113.2, 130.9, 176.2, 26.1, 133.1, 59.1, 126.1, 130.2, 117.2, 13.4

m/z 287 ($M^{+\cdot}$)

6-amino-4-(2, 4-dichloro phenyl) 3-methyl-1, 4 dihydropyrano [2,3-c] pyrazole 5-carbonitrile

IR (cm^{-1}) 3478, 3246,3118, 2188, 1640, 1593; ^{1}HNMR (300MHz, $CDCl_3$) δ1.738 (3H,s , CH_3), 4.54 (1H, s, CH),7.02 (1H, s, ArH), 7.15 (2H, s, NH_2), 7.66 (2H, d,ArH), 7.69 (2H, d, ArH), 11.82 (1H,s , NH). m/z-320($M^{+\cdot}$).

6-amino-4-(4-hydroxy-3-methoxy phenyl) 3-methyl-1, 4 dihydropyrano [2,3-c] pyrazole 5-carbonitrile

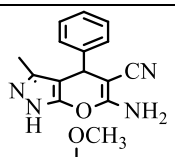
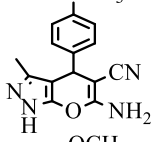
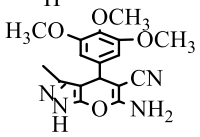
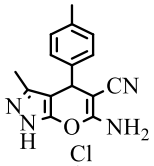
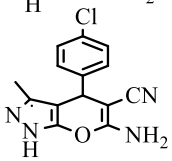
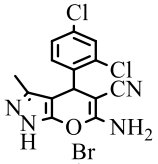
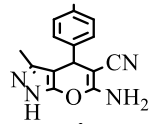
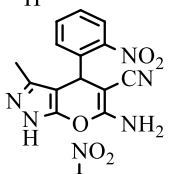
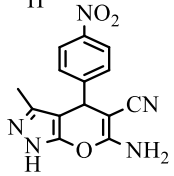
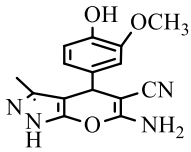
1H NMR (300 MHz,CDCl3): *δ* 1.83 (*s*, 3H, CH_3), 3.71 (*s*, 3H, OCH_3), 4.48 (*s*, 1H, CH), 6.54 (d, 1H, OH), 6.73 (*t*, 2H, CH_2), 6.77 (*s*, 2H, CH_2), 8.82 (*s*, 1H), 12.03.(*s*, 1H, NH); 13C NMR (300 MHz, $CDCl_3$) *δ* 9.8, 35.5, 55.6, 57.6, 97.9, 111.6, 115.4, 119.7, 135.4, 135.8, 145.2, 147.3, 160.

3.2 Catalytic Activity

In order to study catalytic activity of the catalyst for the synthesis of pyranopyrazole from aromatic aldehyde, malononitrile, ethyl acetate and phenyl hydrazine. We performed the synthesis of pyrano-pyrazole under optimized condition and the result is displayed in Table 1.

In the beginning of the scheme benzaldehyde, malononitrile, ethyl acetate, phenyl hydrazine reacted together undergo cyclization to give 82% of selective yield in 3 hrs (Table 1, Entry 1). Further in order to study the effect electron donating group during the cyclo-condensation process for the synthesis of pyranopyrazole. So in next attempt 4- methoxy benzaldehyde, 3,4,5- tri-methoxy benzaldehyde and 4-methyl benzaldehyde taken in separate round bottom flask is allowed to react with malonitrile, ethyl acetate and phenyl hydrazine at 60^0C to yield 78%, 80%, 76% of pyranopyrazole derivative in 3.5hr., 3 hr., 4hrs. Respectively (Entry 2,3,4). So this result confirmed the presence of electron releasing group on benzaldehyde retard the rate of reaction with decrease in yield. Moving on, the same steps of reaction is carried with 4-chlorobenzaldehyde, 2,4-dichlorobenzaldehyde, 4-bromobenzaldehyde in a separate container with malononitrile, ethyl acetate and phenyl hydrazine to produce 84%, 88% and 89% of yield in 3,2 and 2 hrs respectively (Entry 5, 6 and 7). Soon after effect of electron withdrawing group is studied with 2-nitrobenzaldehyde and 4-nitrobenzaldehyde in a separate flask of reaction with following same state of reaction as described above and very surprising output was obtained with 94% and 92% of yield within very short of time 1.5 hr. for both the reaction (Entry 8 and 9). These results clearly indicates that electron withdrawing group increases rate of reaction with increase in yield with reduction in the time required for proceeding the reaction.

Table1- Synthesis of different substituted pyrano-pyrazole derivative by using SiO_2-TiCl4 under optimized reaction

Entry	Product	Time (hr.)	Yield (%)[x]
1		3	82
2		3.5	78
3		3	80
4		4	76
5		3	84
6		2	88
7		2	89
8		1.5	94
9		1.5	92
10		3	76

a) All reaction performed with equimolar reactant (1mmol) and with 10 mol % of catalyst.

b) x Refers to an isolated yield.

4. Result and Discussion-

In summary, a green, effective and environmentally friendly approach was considered for the synthesis pyranopyrazole. pyranopyrazole derivatives was synthesized by four component condensation reaction of various aromatic aldehydes, malononitrile, ethyl acetate and phenyl hydrazine under aqueous condition at 60^0C. Considerable advantages of the presented investigation are reasonably high yield, cleaner reaction profile, short

reaction time, simple work up procedure, recycle and reusability of SiO_2-TiCl4. The whole reaction situation made close agreement with the green chemistry disciplines. The isolation and purification of catalyst at the end of reaction was also easy. The referred catalyst also produces surprising result of good to excellent yield of pyranopyrazole within short of time.

5.References-

1. J. Basset , C.Coperet ,D.Soulivong ,M. Taoufik, T.Cazat, (2010), Metathesis of Alkanes and Related Reactions, Acc. Chem. Res., 43, 323–334.

2. M. Bihani, P.P Bora., G. Bez, H. Askari, (2013), Amberlyst A21 Catalyzed Chromatography-Free Method for Multicomponent Synthesis of Dihydropyrano[2,3-*c*]pyrazoles in Ethanol, ACS Sustainable Chem.Eng., 1, 440-447.

3. R. N. Butler, A. G. Coyne, (2010), Water: Nature's Reaction Enforcer—Comparative Effects for Organic Synthesis In-Water and On-Water, Chem. Rev., 110, 6302–6337.

4. D.S. Fischer, G.M. Allan, C. Bubert, N. Vicker, A. Smith, H.J. Tutill, A. Purohit, L. Wood, G. Packham, (2005), E-Ring Modified Steroids as Novel Potent Inhibitors of 17â-Hydroxysteroid Dehydrogenase Type 1, J. of Med. Chem., 48, 5749-5770.

5. V.K. Ahluwalia, A. Dahiya, V.K. Garg, (1997), Reaction of 5-amino-4-formyl-3-methyl (or phenyl)-1-phenyl-1H-pyrazoles with active methylene compounds: Synthesis of fused heterocyclic rings, Cheminform, 36, 88–90.

6. M. E. A. Zaki, H. A. Soliman, O. A. Hiekal, A. E. Z, Zeitschrift, Naturforschung, (2006), Pyrazolopyranopyrimidines as a Class of Anti-Inflammatory Agents, 61, 1–5.

7. T. N. Bansode, R. M. Ansari, Y. K. Gawale, (2011), Synthesis and biological activity of some new pyrazole derivatives, J. of Pharm. Res., 4, 1141–1152.

8. J. L Wang., D. Liu, Z. J. Zhang, S. Shan, X. Han, S. M. Srinivasula, C. M. Croce, E. S. Alnemri, Z. Huang, Structure-based discovery of an organic compound that binds Bcl-2 protein and induces apoptosis of tumor cells Proc. of the Nat. Acad. of Sci., 2000, 97, 7124–7129.

10. Z. H. Ismail, G. M. Aly, M. S. El-Degwi, H. I. Heiba, M. M. Ghorab, (2003), Synthesis and insecticidal activity of some new pyranopyrazoles, pyrazolopyranopyrimidines, and pyrazolopyranopyridines. Egypt. J. of Biotechn., 13, 73–82.

11. M. Beerappa, K. Shivashankar, (2018), Synthesis of 4,6-diarylpyrimidin-2(1H)-one derivatives from benzyl halides and (1-bromoethyl)benzene under solvent-free conditions, Synth. Communi., 48, 146–154.

12. A. Domling, (2006), Recent Developments in Isocyanide Based Multicomponent Reactions in Applied Chemistry Chem. Rev., 106, 17-89.

13. D.M. D'Souza, T.J.J. Mueller, (2007), Multi-component syntheses of heterocycles by transition-metal catalysis, Chem. Soc. Rev., 36, 3169-3210.

14. A. Alizadeh, F. Mobahedi, A. Esmaili, (2006), Glucose Catalysed and Ultrasound Assisted Synthesis of Pharmaceutically Potent Azomethine Analogues in Water Medium: A Complete Green Approach, Tetrahedron Lett., 47, 4469-4471.

15. M. Umkeherer, C. Kalinski, J. Kolb, C. Burdack, (2006), copper nitrate trihydrate catalyzed efficient one pot synthesis of amidoalkylnaphthol derivatives, Tetrahedron Lett., 47, 2391-2393.

16. A. Shaabani A., Sarvary A. H., Rezayan, Keshipour S., (2009), Synthesis of fully substituted pyrano [2, 3-c] pyrazole derivatives via a multicomponent reaction of isocyanides,Tetrahedron, 65, 3492–3495.

17. Enders D., Grossmann A., Gieraths B., Duzdemir M., Merkens C., Organocatalytic one-pot asymmetric synthesis of 4H,5H-pyrano[2,3-c]pyrazoles, (2012), Org. Lett., 14, 4254–4257.

18. A. Keyume, Z. Esmayil, L. Wang, F. Jun, (2014), Convenient DABCO-catalyzed one-pot synthesis of multi-substituted pyrano [2, 3-c] pyrazole dicarboxylates, Tetrahedron, 70, 3976–3980.

19. S. Gogoi, C. G. Zhao, (2009), Organocatalyzed enantioselective synthesis of 6-amino-5-cyanodihydropyrano [2, 3-c] pyrazoles , Tetra. Lett., 50, 19, 2252–2255.