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$NiWO_4$ catalyzed expeditious synthesis of pyranopyrazoles

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In this paper, a multicomponent green rapid method for synthesis of pyranopyrazoles is reported using $NiWO_4$ in water in 15 min. Environment friendly features such as energy efficiency, aqueous medium, no hazardous solvent, no chromatography, in addition to the short reaction time, catalyst reusability and substrate tolerance without affecting yield proves the near perfectness of this method for synthesis of medicinally important pyranopyrazoles. $NiWO_4$, $ZnWO_4$ and $CuWO_4$ have been synthesized using extract of plant *Phyllantus amarus*. The prepared catalysts have been characterized by XRD, EDX and SEM.

Keywords: $NiWO_4$, Pyranopyrazoles, *Phyllantus amarus*, Multicomponent, Synthesis

2,4-Dihydropyrano[2,3-c]pyrazole compounds have emerged as most sought compounds for their medicinal prospects in Alzheimer's disease[1]. Also their promising biological properties such as antibacterial[2], anticancer[3], xanthine oxidase inhibition[4], antidiabetic[5], proteostasis regulation[6], *etc.* have attracted attention of synthetic chemist to develop efficient methods for their preparations.

The multicomponent one pot approach employing ethylacetoacetate, hydrazine, malononitrile and aldehyde has been a topic for extensive catalytic explorations using Nitrogen doped Graphene Oxide[7], 1-(carboxymethyl)pyridinium iodide[8], Ti-grafted polyamidoamine dendritic silica[9], $ZnFe_2O_4$ [10], Fe_3O_4 [11], Amberlyst-A21 [12], Et_4NBr [13], Lipase[14], Alumina[15], and many more[16].

Mixed metal tungstate particularly $NiWO_4$ are studied for their diverse properties such as photocatalyst for dye degradation[17], supercapacitors[18], electrochemical sensor[19], and many more[20].

Experimental Details

Preparation of plant extract

The collected *Phyllantus amarus* plant specimen (stem and leaves) were washed thoroughly with double distilled water. Plant specimen (120 g) was heated in double distilled water (600 mL) at 80°C for 30 min. The air cooled extract was filtered and used as such for further studies.

Preparation of $NiWO_4$ / $CuWO_4$ / $ZnWO_4$

$Ni(NO_3)_2.6H_2O$ (5.81 g, 0.02 mol) / $Cu(NO_3)_2.3H_2O$ (4.83 g, 0.02 mol) / $Zn(NO_3)_2.6H_2O$ (5.94 g, 0.02 mol) and $Na_2WO_4.2H_2O$ (3.29 g, 0.01 mol) were dissolved separately in double distilled water (50 mL) each. Tungstate solution was added dropwise to metal salt solution with constant stirring giving precipitate. To this precipitate, plant extract (50 mL) was added and stirred for 2 h. The homogenised precipitate was filtered and washed with hot distilled water and dried in oven at 80°C for 5 h. The obtained residue was calcined at 500°C for 1 h. The formed $NiWO_4$ / $CuWO_4$ / $ZnWO_4$ was characterised by chemical analysis, IR, XRD, SEM and EDX.

Synthesis of pyranopyrazoles

In a 100 mL round bottom flask, malononitrile (10 mmol), ethylacetoacetate (10 mmol), aldehyde (10 mmol), water (10 mL), and $NiWO_4$ (1 g), were mixed at RT and hydrazine hydrate (15 mmol), was added under stirring at RT. Reaction content was stirred at RT for 15 min. After completion of reaction, solid residue was washed with excess water. Catalyst was recovered by adding boiling EtOH and filtering. Product in EtOH was poured into the same quantity of water and isolated by filtration. Analytically pure product was obtained by recrystallization with EtOH.

6-Amino-3-methyl-4-phenyl-2,4-dihydropyrano [2,3-*c*]pyrazole-5-carbonitrile 1a: ^1H NMR (400 MHz, DMSO-d_6): δ 1.78 (s, 3H), 4.59 (s, 1H), 6.90 (s, 2H), 7.17 (m, 3 H), 7.32 (m, 2 H), 12.12 (s, 1H).

6-Amino-3-methyl-4-(4-nitrophenyl)-2,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitrile 1c: ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.79 (s, 3H), 4.82 (s, 1H), 7.05 (s, 2H), 7.45 (d, *J=8.4 Hz*, 2 H), 8.19 (d, *J=8.4 Hz*, 2 H), 12.20 (s, 1H).

6-Amino-3-methyl-4-(3,4,5-trimethoxyphenyl)-2,4-dihydropyrano- [2,3-*c*]pyrazole-5-carbonitrile 1f: ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.87 (s, 3H), 3.63 (s, 3H), 3.71 (s, 3H), 3.72 (s, 3H), 4.58 (s, 1H), 6.47 (s, 2H), 6.90 (s, 2 H), 12.11 (s, 1H).

6-Amino-4-(4-hydroxy-3-methoxyphenyl)-3-methyl-2,4-dihydro-pyrano[2,3-*c*]pyrazole-5-carbonitrile 1g: ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.81 (s, 3H), 3.70 (s, 3H), 4.49 (s, 1H), 6.53 (d, *J*=7.6 Hz, 1H), 6.69 (m, 2H), 6.82 (s, 2H), 8.88 (s, 1H), 12.07 (s, 1H).

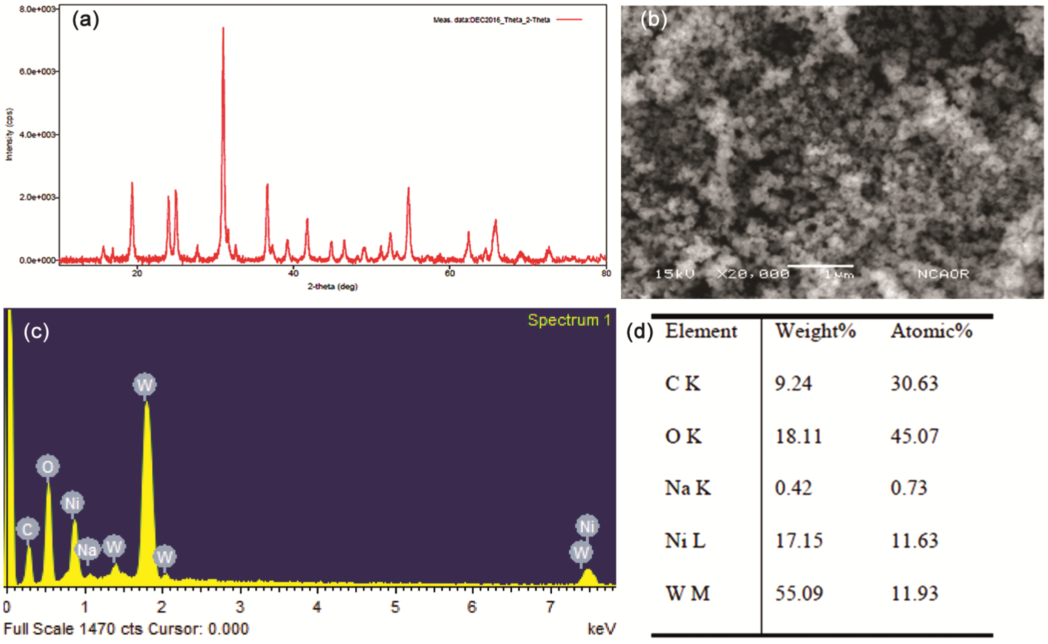
6-Amino-4-(4-fluorophenyl)-3-methyl-2,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitrile 1h: ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.79 (s, 3H), 4.64 (s, 1H), 6.93 (s, 2H), 7.15 (m, 4 H), 12.15 (s, 1H).

Results and Discussion

$NiWO_4$, $ZnWO_4$, $CuWO_4$ were synthesized using extract of plant *Phyllantus amarus*. Although the role of plant extract in this preparation is yet to be established, however, the effect of its constituents in maintaining uniform size and morphology and sample homogeneity is observed. The XRD of prepared $NiWO_4$ (Fig. 1), $CuWO_4$ (Fig. 2), and $ZnWO_4$ (Fig. 3) were in accordance with the literature data[21-23]. The SEM and EDX data as observed is included in Fig. 1, Fig. 2 and Fig. 3 for the prepared tungstates.

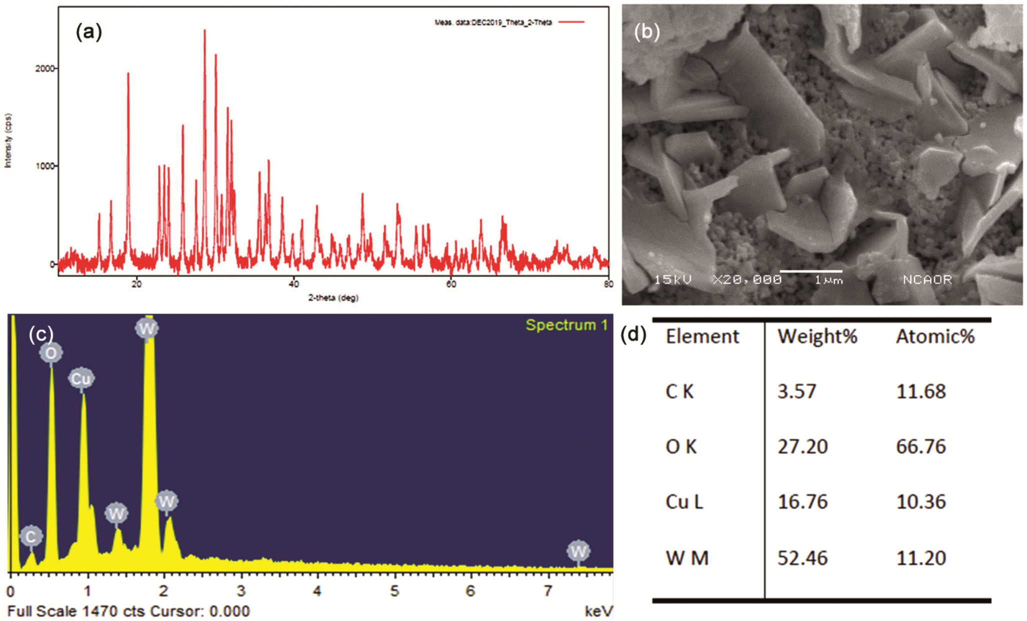
The prepared tungstates were explored (Scheme 1) for catalytic applications in multicomponent synthesis of pyranopyrazoles. Table 1 summarizes the effect of prepared tungstates on selectivity of product among the numerous possible intermediates, product yield and reaction time. The catalytic efficiency of tungstates in aqueous medium empowered this method with greener prospects. Among the prepared tungstates, $NiWO_4$ was observed to be a highly efficient catalyst for synthesis of pyranopyrazoles within 15 min reducing the catalyst quantity to less than 1 g, further affected the product yields. The optimized conditions were then extended to prepare various substituted pyranopyrazoles (Scheme 2) as described in Table 2 in good yields. The melting point and spectral data of the pyranopyrazoles were in accordance with the literature data[2,7,24-34].

Moreover, the versatility of this method with good yield irrespective of the aromatic substitution encouraged us to look into the mechanism of this multicomponent transformation. Based on the reactivity of all the components involved in this reaction, a probable mechanism is depicted in Scheme 3.



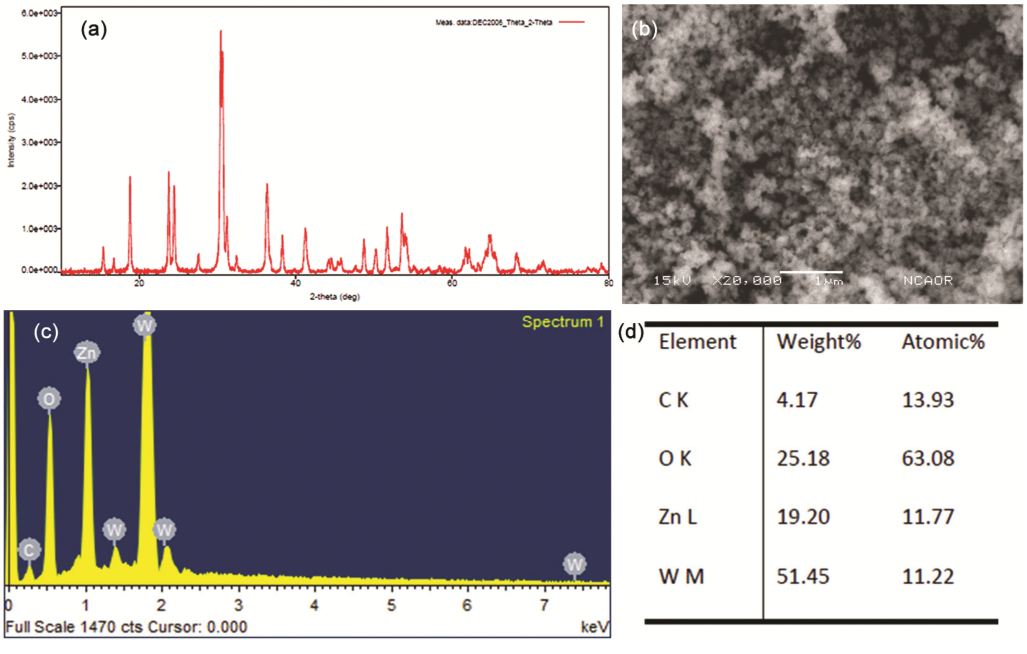
Element	Weight%	Atomic%
C K	9.24	30.63
O K	18.11	45.07
Na K	0.42	0.73
Ni L	17.15	11.63
W M	55.09	11.93

Fig. 1 — XRD, SEM and EDX of prepared $NiWO_4$



Element	Weight%	Atomic%
C K	3.57	11.68
O K	27.20	66.76
Cu L	16.76	10.36
W M	52.46	11.20

Fig. 2 — XRD, SEM and EDX of prepared $CuWO_4$



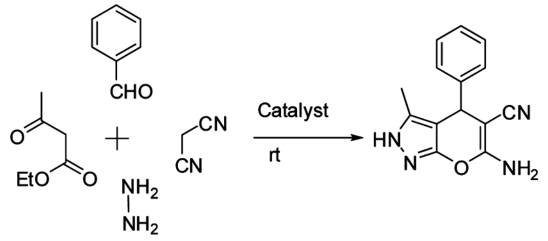
Element	Weight%	Atomic%
C K	4.17	13.93
O K	25.18	63.08
Zn L	19.20	11.77
W M	51.45	11.22

Fig. 3 — XRD, SEM and EDX of prepared $ZnWO_4$

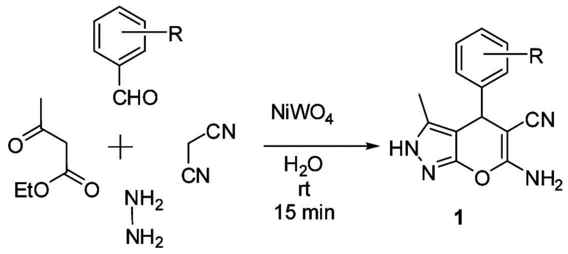
Table 1 — Optimization studies as per Scheme 1

Entry	Catalyst	Solvent	Time (min)	Isolated Yield (%) [a]
1	–	Water	15	17
2	$NiWO_4$	Water	15	86
3	$ZnWO_4$	Water	15	48
4	$CuWO_4$	Water	15	44
5	$NiWO_4$	Water:EtOH (1:1)	30	59
6	$NiWO_4$	Water	30	85
7	$NiWO_4$ (0.5 g)	Water	45	60

[a] Hydrazine hydrate (15 mmol), malononitrile (10 mmol), ethyl acetoacetate (10 mmol), benzaldehyde (10 mmol), water (10 mL), catalyst (1 g), RT, 15 min

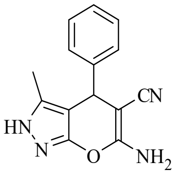
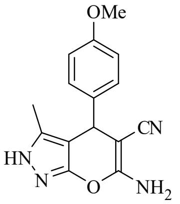
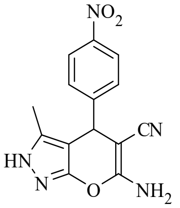
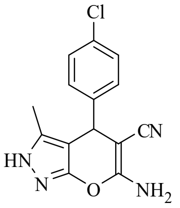
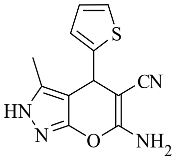


Scheme 1 — Optimization studies for synthesis of pyranopyrazoles



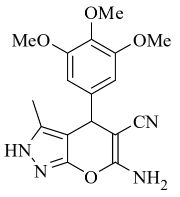
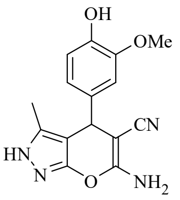
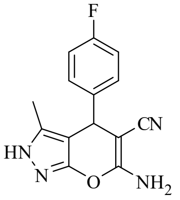
Scheme 2 — Substituted Pyranopyrazoles

Table 2 — Versatility of the method as per Scheme 2

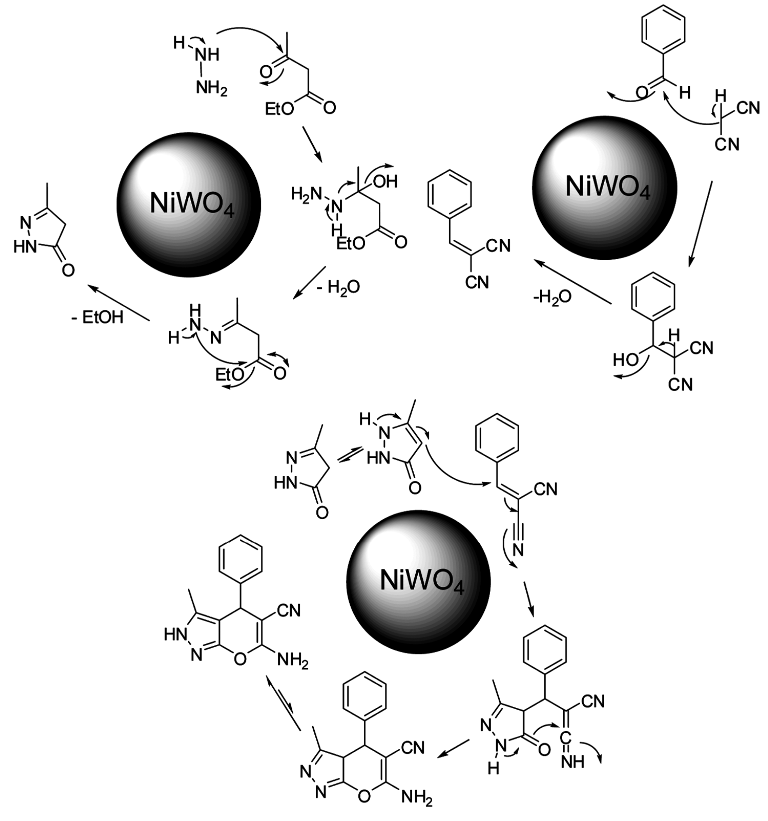
Entry	Product	Isolated Yield (%) [a]	Observed m.p. (°C)	Reported m.p. (°C)	[Ref. No.]
1	 **1a**	94	242-244	244-246	Datta *et al.* [2]
2	 **1b**	89	242-244	245-246	Karami *et al.* [27]
3	 **1c**	90	190-192	192-194	Kargar *et al.* [24]
4	 **1d**	88	260-262	267-268	Datta *et al.* [2]
5	 **1e**	91	192-194	190-192	Mishra *et al.* [26]

(*Contd.*)

Table 2 — Versatility of the method as per Scheme 2 (*Contd.*)

Entry	Product	Isolated Yield (%)[a]	Observed m.p. (°C)	Reported m.p. (°C)	[Ref. No.]
6	 **1f**	92	210-212	209-211	Vekariya *et al*. [33]
7	 **1g**	90	232-234	235-237	Ali *et al*. [34]
8	 **1h**	86	140-142	145-147	Kargar *et al*. [24]

[a] Reaction conditions: Hydrazine hydrate (15 mmol), malononitrile (10 mmol), ethylacetoacetate (10 mmol), aldehyde (10 mmol), water (10 mL), $NiWO_4$ (1 g), RT, 15 min



Scheme 3 — Probable mechanism

Conclusion

A multicomponent green rapid method for synthesis of pyranopyrazoles is reported using $NiWO_4$ in water in 15 min. Environment friendly features such as energy efficiency, aqueous medium, no hazardous solvent, no chromatography, in addition to the short reaction time, catalyst reusability and substrate tolerance without affecting yield proves the near perfectness of this method for synthesis of medicinally important pyranopyrazoles.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

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