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Efficient conjugate addition of 3-methyl-5-pyrazolones to chalcones in water extract rice straw ash (WERSA)

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Conjugate addition of 5-methyl-pyrazolones to chalcone has been described with Water Extract Rice Straw Ash (WERSA) as the reaction medium. Various chalcones have been used as Michael acceptors against 5-methyl-pyrazolones. The products have been isolated in analytically pure form by simple filtration in good to excellent yields under green reaction conditions with good substrate scope. This general eco-friendly method uses waste material for organic transformation. The synthesised compounds could be further utilised for the synthesis of bioactive molecules and pharmaceutical products.

Keywords: Chalcones, conjugate addition, 5-methyl-pyrazolones, WERSA

Conjugate addition reactions are one of the important and most reliable synthetic methods for C-C bond formation[1], these reactions have played a pivotal role in the synthesis of various complex natural products. Chalcones are basically employed as substrates in conjugate addition reactions and have captivated the synthetic chemist, as well as biologists due to its broad range of interesting therapeutic application such as cancer[2], inflammation[3], diabetes[4]. and some of them, were marketed such as Metochalcone marketed as a choleretic drug. Sofalcone was used as an antiulcer and Mucoprotective drug (Figure 1)[5]. Moreover, because of the conjugation, chalcones are fluorescent in nature, which makes them potential chemical probes[6].On the other hand, 5-methyl-pyrazolones are valuable synthons due to their reactivity and ease of transforming into other functional groups[7]. The pyrazole derivatives exhibit many biological and pharmacological activities like anticancer[8], candidature as a potential anti-HIV agent[9], inhibitor of hepatitis C virus (HCV) replication[10], p38 kinase inhibitors and selective inhibitory activity against COX-2 enzymes[11] which further influenced attention towards the synthesis. With many trade names metamizole, rimonabant and phenylbutazone are some of the commercially available drug molecules in the market which contains 4-alkyl-1*H*-pyrazoles as core moiety[12]. Apart from previously mentioned applications, these molecules have also been comprehensively rendered as bifunctional ligands for metal catalysis[13]. Wide scoped applications along with emphasizing the vital importance of these moieties have drawn the interest of synthetic chemists.In recent times a good share of research has been focused on these transformations[1]. However, most of the reports were mainly used organic solvents and harsh reaction conditions[14].

[2+3] Cycloaddition of alkenes[15] and alkynes[16] with 1,3-dipolar diazo compounds, reactions of nitroolefins with hydrazones[17], condensations of β-oxodithioesters[18] and 1,3-dicarbonyl compounds with hydrazines are frequently used as a synthetic approach for the synthesis of 4-alkyl-1*H*-pyrazoles[19]. Pioneering work by Etman and co-workers have reported the first Michael addition of 3-phenyl-2-pyrazolin-5-one to chalcones or the synthesis of 4-alkyl-1*H*-pyrazoles by utilizing pyridine as a catalyst in butanol[20]. Subsequently, Deka et al reported Michael addition of chalcone with pyrazolone catalysed by K_2CO_3 [21]. Relying on alumina graphite as inorganic nano promoter, a multicomponent strategy was described by Nikoofar et al.[22] Brief review of these methods reported accentuated various shortcomings like usage of toxic catalyst, high boiling solvent and expensive reaction sequences. Therefore, an appropriate yet inexpensive and environmentally friendly method to synthesise these compounds is a quest, yet to be deciphered. On the other hand, reactions under green conditions are always important. In recent time, greener reactions were

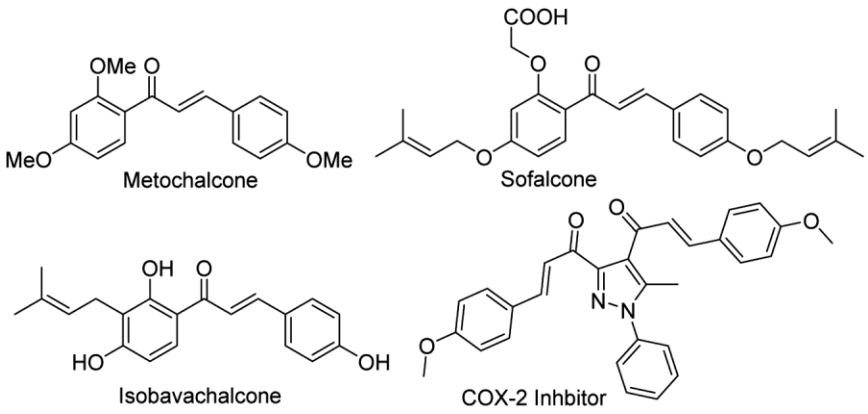
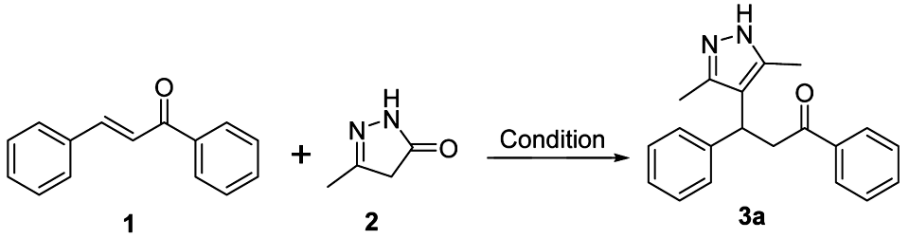


Figure 1 — Some bioactive chalcones and derivatives



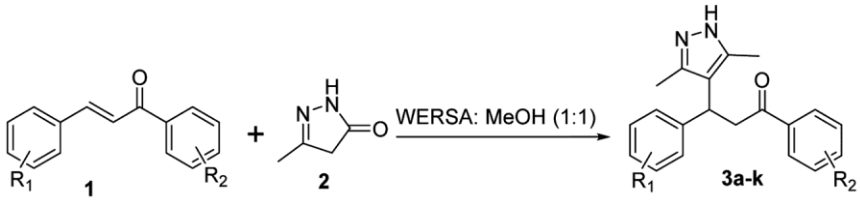
Scheme I — Michael addition of pyrazolones to chalcones

developed by employing naturally available waste materials such as rice straw, banana peels, teak leaves and lemon extracts, etc.[23] These materials are biocompatible and readily available in ample. Therefore, herein we wish to disclose a simple, efficient, high yielding, an inexpensive and eco-friendly method for synthesis of 5-methyl-1*H*-pyrazol-3-ol derivatives using Water Extract Rice Straw Ash (WERSA) as the reaction medium.

Results and Discussion

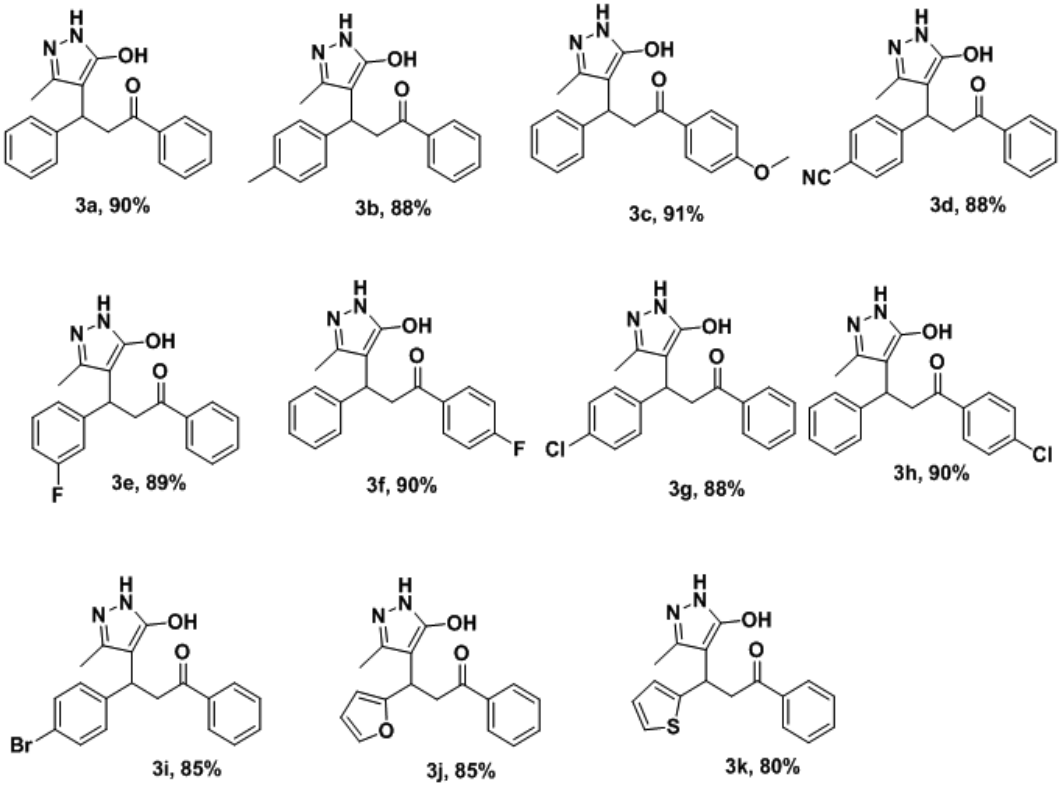
Water Extract Rice Straw Ash (WERSA) medium was prepared as per previous literature reports[24]. The dry rice straw was burnt to ash in the open air. The ash was added to a beaker containing de-ionized water (5gm/50ml) and stirred for 1hr. The residue was filtered using the sintered funnel and to obtain solution clear solution is named as WERSA. This extract has pH 11 which validates the previous report on the basic nature of the WERSA. Literature reports reveal that the WERSA consists of different metal oxide like Na, K, Ca, Mg,Ti, Al, Si, Fe and P etc. in various compositions[20].

Initially, the reaction was carried out by using chalcone **1**, and pyrazole **2**in water and stirred at rt for 6h did not yield any product. Similarly, the reaction was performed in organic solvents like MeOH, EtOH, DCM at rt only trace amount of product was obtained. The reaction in Water Extract of Rice Straw Ash (WERSA) afforded the desired product **3a** in 35% yield, Scheme I. Due to low solubility of the substrates in water, the reaction was conducted in 1:1 ratio of WERSA and MeOH which afforded the desired product **3a** in 80% yield. The product was precipitated was filtered by using Whatman filter paper and washed with cold methanol and dried under vacuum to afford the pure product. With these optimised conditions we further explored for the substrate scope and potential of the methodology. The reaction was performed with various substituted chalcones which afforded the products in good yield. Methyl, methoxy, nitrile substituted chalcone afforded the product **3b-d** in 88, 90% yield respectively (Scheme II, Table I). Similarly, the reaction with halogenated —chalcones yielded the products **3e-i** in good yield. Interestingly hetero aromatic chalcones also yielded the desired product in good yield. The methodology has advantages such as excellent yield, broad substrate scope, catalyst-free, easy purification by simple filtration without any workup,mild condition and does not require any organic solvent, ligand, base or any additives.



Scheme II — Substrate scope

Table I — Substrate scope[a,b]



[a] Reaction conditions: Chalcone **1** (1 mmol), pyrazole**2** (1 mmol) was added in a round bottom flask containing 4 mL of WERSA: MeOH (1:1) and stirred for 2h at room temperature.
[b] Isolated yield.

Mechanism

The Michael addition of 5-methyl-pyrazolone known to undergo keto-enol tautomerism**2** to **2a** in presence of base present in WERSA[25]. WERSA in water and methanol further promotes the reaction by strong hydrogen bonding with the substrates. Thus, restraining the substrates and bring the reactants into juxtaposition**4**. Subsequently, undergoes Michael addition **5** to afford the product **3a** as depicted in Figure 2.

Experimental Section

Chalcone **1** (1 mmol), pyrazole **2** (1 mmol) was added in a round bottom flask containing 4 mL of WERSA: MeOH (1:1). The mixture was stirred for 2 h at RT. Progress of the reaction was determined by thin layer chromatography (TLC). After completion of reaction, solid crude was filtered, washed with cold methanol and dried under vacuum to afford product **3a**in 90% yield as white solid. m.p.155-160°C. TLC (SiO_2): R_f = 0.7 (70% EtOAc/Hexane); IR (KBr): 3064, 3028, 2924, 2612, 1594, 1497, 1388.84, 1359.48, 1312.51, 1157.79, 1134.85, 1094.30, 1021.79, 907.12, 867.89, 836.02, 802.17 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ7.93 (d, *J* = 7.5 Hz, 2H), 7.53 (dd, *J* = 17.9, 11.4 Hz, 2H), 7.42 (d, *J* = 6.8 Hz, 4H), 7.30 – 7.20 (m, 3H), 7.18 – 7.11 (m, 1H),

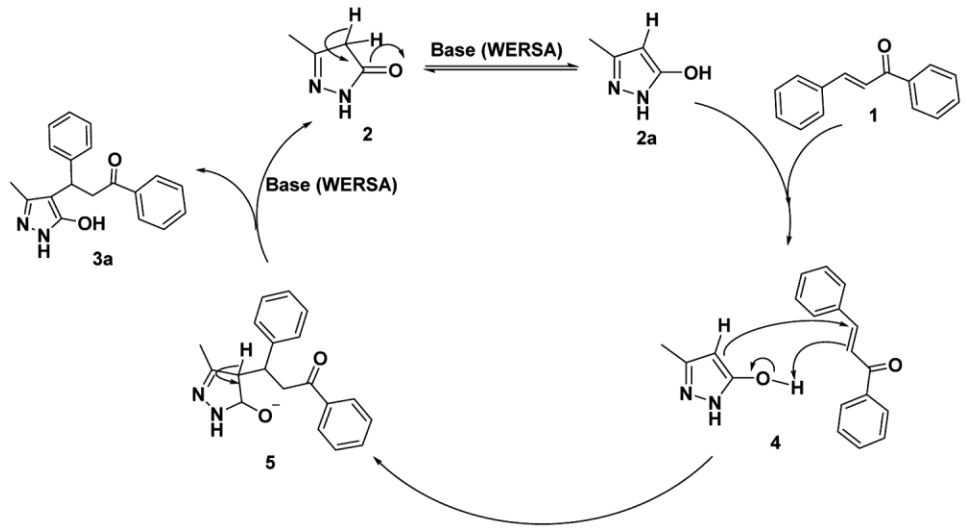


Figure 2 — Plausible mechanism

4.50 (d, *J* = 6.1 Hz, 1H), 4.07 (dd, *J* = 17.1, 8.1 Hz, 1H), 3.58 (dd, *J* = 17.3, 5.9 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 197.5, 159.1, 144.0, 135.9, 131.7, 127.3, 127.0, 126.7, 126.3, 124.6, 120.1, 117.3, 40.6, 24.5, 9.1; HRMS (ESI+): *m/z* Calcd for $C_{19}H_{19}N_2O_2$ $[M+H]^+$: 307.1446. Found: 307.1468.

Conclusion

In conclusion,we report herein, the Michael addition of chalcone and 5-methyl-pyrazolones in Water Extract Rice Straw Ash (WERSA). The products were isolated in analytically pure form by simple filtration in good to excellent yields. The methodology utilises waste material for organic transformation.

Conflicts of interest

There are no conflicts of interest to declare.

Supplementary Information

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

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