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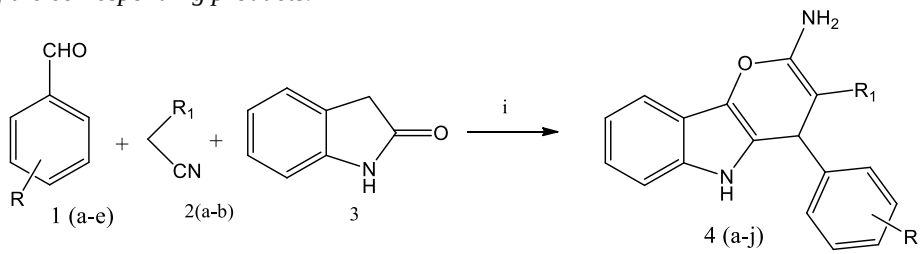
Facile one – pot three component green synthesis of pyrano [2,3-b] indoles and its derivatives

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Abstract
An efficient and convenient one-pot three-component synthesis of 2-amino-4,9-dihydro-4-phenyl pyrano[2,3-b]indole-3-carbonitrile/ethyl carboxylate derivatives were achieved using Copper nanoparticles grafted on carbon microsphere catalyst. The three components which take part in reaction are substituted aromatic aldehydes, malononitrile and oxindole. The protocol was carried out under mild reaction conditions with operational simplicity, affording good to excellent yield of the corresponding products.



Scheme 1: *Reagent and conditions*: (i) 10 mg Cu-NP/C, 10 mL 1:1 (water: ethanol), 70-80^{0}C.

Key words: Multi-component reaction, Cu-NP/C, pyrano indole.

Introduction

The organic synthesis is prominently directed towards “Greenery” due to growing interest among researchers who consequently show the development of new environmentally benign procedures, such as the use of the aqueous medium, multi-component reaction (MCR) strategy and reusable catalysts to save resources and energy [1]. In recent years, the efficient synthesis of complex molecules from simple and readily available materials has become one of the important aspects of organic synthesis. Attempts have been made to develop several techniques for the efficient use of reusable catalysts and multi-component reactions [2-4]. Being powerful and bond-forming efficient tools in organic, combinatorial, and medicinal chemistry, MCRs have attracted researchers with increasing awareness to develop high atom economy, eco-friendly, one-pot, single step, energy minimized, and negligible waste production strategies. These features encourage MCRs as well-suited for the easy construction of diversified arrays of valuable bioactive heterocycles.

4H-Pyran skeleton containing compounds is an important class of organic compounds exhibiting a wide range of pharmacological and biological properties.[5] Pyran is one of the important structural motifs found widely in natural products, such as coumarins, benzopyrans, sugars, flavonoids, xanthones, etc.[6] Epicalyxins F and G, which are isolated from the seeds of Alpinia blepharocalyx, are the most potent members of this class that act as anticancer agents against human HT-1080 fibrosarcoma and murine 26-L5 carcinoma. Some biologically significant 4H-pyran derivatives are depicted in Figure 1.

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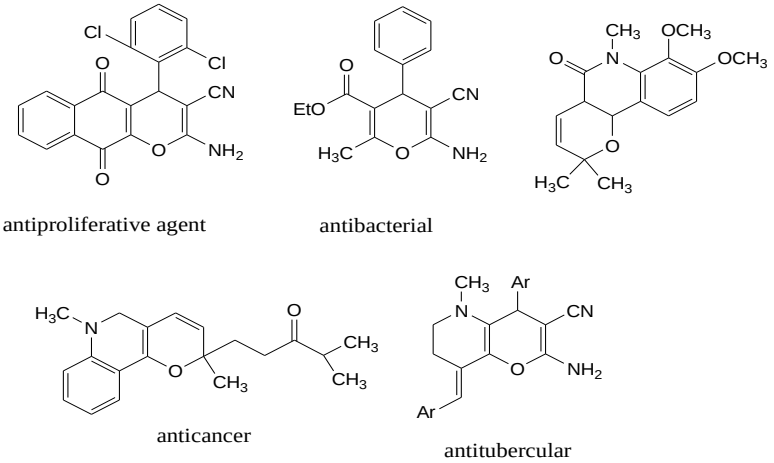


Figure 1. Some representative examples of biologically potent pyrano-pyrans.

The synthesis of such compounds has attracted a strong interest owing to their biological potential.[7] Various methods have been reported for the synthesis of these compounds and their analogues such as the use of 1H-imidazol-3-ium tricyanomethanamide,[8] iron oxide/phenyl sulfonic acid, [9] $PtCl_4$,[10] KF/Al_2O_3,[11] NH_4OAc,[12] ultrasonic irradiation,[13] β-cyclodextrin,[14] Cu NP/C [15], ES/ $Cu(OH)_2$ nano-composite.[16], basic catalyst piperidine [17] and immobilized ionic liquid [18]. These reported methodologies have shown good results in many instances. However, some of them also have limitations in terms of the metal catalyst, expensive reagents, long reaction time, environmentally hazardous, harsh reaction conditions, tedious work-up procedure, unsatisfactory yield and homogeneous catalysts, which are difficult in separation from the reaction mixture.

Heterogeneous catalysts have gained extensive applications as eco-friendly, economically viable, and easily separable catalysts in organic transformations [19]. Among the heterogeneous catalysts, various nanoparticles (NPs) have received considerable attention for their high catalytic activity and selectivity in various fields of synthetic organic and bioorganic chemistry.[20] Copper nanoparticles are an important group of nano-catalysts. Copper nanoparticle catalyzed reactions are advantageous over the conventional metal-catalyzed reactions in terms of low catalyst loading, high atom economy, better yields, inexpensive, shorter reaction times, and recyclability of the catalyst.[21] Nanoparticles may undergo self-aggregation; therefore, it is difficult to separate them from the reaction medium. To avoid the limitation of nanoparticles, they can be supported on some supports. These developed catalytic metallic nanoparticles are inexpensive, non or minimally poisonous, highly active, stable, and easily separable from reaction mixture are highly useful. In our previous work, copper nanoparticles grafted on carbon microsphere (Cu-NP/C) were found to be useful for organic transformations [22-24]. As a part of ongoing program on the development of novel methods in organic synthesis, we report herein a simple, rapid and high yielding one pot three component reaction protocol for the synthesis of pyrano[2,3-b]indoles derivatives employing environmentally friendly Cu-NP/C catalyst.

Experiental

General details:

All chemicals were purchased from Sigma Aldrich and Spectrochem companies and used without further purification. The reactions were monitored by TLC using aluminum sheets 20 x 20 cm, Silica gel 60 F254, Merck grade. Products were characterized by 1H and ^{13}C NMR spectra recorded on a Bruker spectrometer using $CDCl_3$ & DMSO-d6 as a solvent and tetramethylsilane as an internal standard. Mass spectrometric data was recorded by an electron spray ionisation (EST) technique on a Q-tof-micro quadruple mass spectrometer (Micro mass). Melting points were determined on DBK-programmable melting point apparatus.

General procedure for the synthesis of 2-amino-4, 9-dihydro-4-aryl pyrano [2,3b] indole-3-carbonitrile

A mixture of aromatic aldehyde (1mmol), malononitrile/ethyl cyano acetate (1.1mmol), oxindole (1mmol) was refluxed at 80^0C with constant stirring in 1:1water: ethanol (5mL) in the

presence of Cu-NP/C (10 mg) for an appropriate time as mentioned in Table 2. The progress of the reaction was monitored by TLC using 10% ethyl acetate: n- hexane as the mobile phase. After completion of the reaction, the reaction mixture was diluted with hot ethanol (10mL) and filtered off to separate catalyst as the residue. The residue was further washed with hot ethanol (2-5mL) and the combined filtrates were concentrated on rotary evaporator to get the desired products which were of enough purity that required no purification.

Results and Discussion

In the present work, we report an efficient and facile protocol for the synthesis of 2-amino-4, 9-dihydro-4-aryl pyrano [2,3b] indole-3-carbonitrile derivatives by the one-pot three-component condensation from aromatic aldehydes, malononitrile/ ethyl cyano acetate, and oxindole by using Cu NP/C as a reusable and safe catalyst in 1:1 water-ethanol mixture at 80^0C. The present work was carried by using Cu NP/C catalyst for the synthesis of pyrano indole derivatives. Initially, 4-tolualdehyde (1 mmol), malononitrile / ethyl acetate (1.1 mmol), oxindole (1 mmol) were selected for the optimization of reaction conditions at 80^0C in a 5mL water-ethanol (1:1). The effect of solvent and amount of catalyst was also studied. A better yield was found using 10 wt% of the catalyst in 1:1 H_2O:EtOH **(Table 1)**.

Table 1: Optimization of reaction conditions

Entry	Solvent	Catalyst (mg)	Temperature (^{0}C)	Time (min.)	Yield (%)
1	EtOH	-	70-80	12 hr	30
2	CH_3CN	10	80-90	78	65
3	CH_2Cl_2	10	40	100	68
4	H_2O	05	80-90	70	55
5	EtOH	05	70-80	45	70
6	1:1 H_2O – EtOH	05	70-80	40	75
7	1:1 H_2O– EtOH	10	**70-80**	**25**	**90**
8	1:1 H_2O – EtOH	15	70-80	27	92

Afterwards, a series of reactions was carried out using diversely substituted aldehydes under optimized reaction conditions. All the aldehydes underwent three-component reaction with malononitrile or ethyl cyano acetate and oxindole to produce a library of pyrano [2, 3-b] indole derivatives in good to excellent yields **(Table 2)**. The reactions of aromatic aldehydes with electron withdrawing groups such as chloro, nitro, proceeded at faster rates and gave better yields than those with electron donating groups such as methoxy and methyl.

Table 2: Synthesis of 2-amino-4, 9-dihydro-4-aryl pyrano [2,3b] indole-3-carbonitrile catalysed by copper nanoparticles grafted on carbon microsphere.

Entry	Aldehyde	Enolisable Ketone	Time (min.)	Product	Yield[b] (%)	MP (^{O}C)
1	4-Tolualdehyde	CN	27	4a	90	170-172[17]
2	4-Anisaldehyde	CN	30	4b	84	188-190[17]
3	3,4-Dimethoxy benzaldehyde	CN	33	4c	90	184-186[17]
4	2,5-Dimethoxy benzaldehyde	CN	32	4d	90	188–191[17]
5	2,3,5-Trimethoxy benzaldehyde	CN	35	4e	88	180-182[17]
6	4-Tolualdehyde	COOEt	25	4f	90	182-183[17]
7	4-Anisaldehyde	COOEt	28	4g	93	188-191[17]
8	3,4-Dimethoxy benzaldehyde	COOEt	30	4h	88	218-220[17]
9	2,5-Dimethoxy benzaldehyde	COOEt	32	4i	85	148-151[17]
10	2,3,5-Trimethoxy benzaldehyde	COOEt	36	4j	82	198-200[17]

[a]substituted aromatic aldehyde (1 mmol), malononitrile / ethyl cyano acetate(1mmol), oxindole (1 mmol) and Cu NP/C 10 mg, H_2O : EtOH (1:1) 5 mL, reflux.
[b]isolated yield.

Spectral data:

2-amino-4,9-dihydro-4-p-tolylpyrano[2,3-b]indole-3-carbonitrile (4a)

Mp. 170-172^{0}C; **IR (cm-1)**: 3477 (N-H stretching of free primary amine), 3229 (N-H stretching of pyrrole ring), 3117 (C-H stretching of aromatic ring), 2200 (C≡N stretching of the nitrile group), 1602 (N-H deformation pyrrole ring), 1055 (C-H in plane bending of aromatic ring), 808 (C-H out of plane bending for 1,4-disubstituted aromatic ring); **^{1}H NMR(DMSO-*d*6, 400 MHz):** δ (ppm) 2.20-2.24 (t, *J*= 1.1 Hz, 3H), 5.1-5.15 (d, *J* = 1.0 Hz, 1H), 6.82-6.90 (td, *J* = 7.5, 1.5 Hz, 1H), 7.0-7.07 (td, *J* = 7.5, 1.5 Hz, 1H), 7.10-7.18 (dq, *J* = 7.3, 1.1 Hz, 2H), 7.50-7.60 (m, 2H), 7.60-7.66 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.75-7.83 (dd, *J* = 7.5, 1.6 Hz, 1H) **MS**: *m/z* 301.

2-amino-4,9-dihydro-4-(4-methoxyphenyl)pyrano[2,3-b]indole-3-carbonitrile (4b)

Mp 188-191^{0}C; **IR (cm-1):** 3472 (N-H stretching of free primary amine), 3222 (N-H stretching of pyrrole ring), 3103 (C-H stretching of aromatic ring), 2191 (C≡N stretching of the nitrile group), 1622 (N-H deformation pyrrole ring), 1050 (C-H in plane bending of aromatic ring), 806 (C-H out of plane bending for 1,4-disubstituted aromatic ring); **^{1}H NMR(DMSO-*d*6, 400 MHz):** δ (ppm) 3.78-3.80 (s, 3H), 5.1-5.14 (t, *J* = 0.9 Hz, 1H), 6.80-6.89 (m, 3H), 7.00-7.08 (td, *J* = 7.5, 1.5 Hz, 1H), 7.31-7.38 (m, 2H), 7.62-7.67 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.72-7.80 (dd, *J* = 7.4, 1.6 Hz, 1H); **MS:** *m/z* 317.

Ethyl-2-amino-4,9-dihydro-4-(3,4-dimethoxyphenyl)pyrano[2,3-b]indole-3-carboxylate (4h)

Mp 218-220^{0}C; **IR (cm-1)**: 3468 (N-H stretching of free primary amine), 3230 (N-H stretching of pyrrole ring), 3112 (C-H stretching of aromatic ring), 2190 (C≡N stretching of the nitrile group), 1577 (N-H deformation pyrrole ring), 1052 (C-H in plane bending of aromatic ring), 817 (C-H out of plane bending for 1,4-disubstituted aromatic ring); **^{1}H NMR(DMSO-*d*6, 400 MHz):** δ (ppm) 1.1-1.17 (t, *J* = 5.9 Hz, 3H), 3.73-3.78 (s, 3H), 3.80-3.84 (s, 3H), 4.00-4.10 (q, *J* = 5.9 Hz, 2H), 5.5-5.54 (t, *J* = 0.9 Hz, 1H), 6.80-6.88 (td, *J* = 7.5, 1.5 Hz, 1H), 6.98-7.16 (m, 3H), 7.22-7.30 (dd, *J* = 7.7, 2.0, 1.0 Hz, 1H), 7.60-7.68 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.78-7.86 (dd, *J* = 7.5, 1.6 Hz, 1H) **MS**: *m/z* 394.

Conclusion:

In summary, in the present work, we report an efficient and rapid method for one-pot three component synthesis of 2-amino-4, 9-dihydro-4-aryl pyrano [2,3b] indole-3-carbonitrile catalyzed by Cu-NP/C under heterogeneous conditions. The present method provides a valuable addition to the synthesis of these biologically significant heterocycles in terms of mild, environmentally benign reaction conditions and good to excellent yields of the products.

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