

Original Article: Simple, Highly Efficient Synthesis 2-Amino-4-Phenyl-4,5,6,7-Tetrahydropyrano[3,2-c]Carbazole-3-Carbonitrile Derivatives Using Silica Supported Dodeca-Tungstophosphoric Acid DTP/SiO₂



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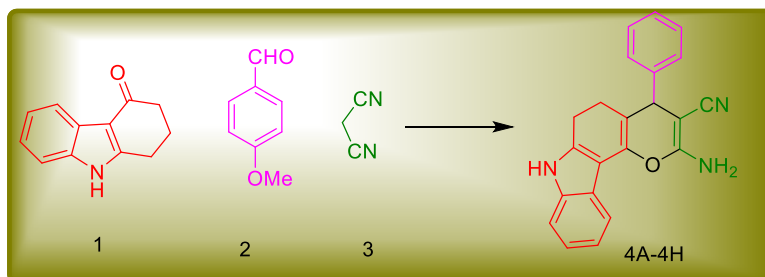
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ABSTRACT

The one-pot multicomponent efficient and easily operational protocol has been developed for the synthesis of tetrahydropyrano[2,3-c]pyrazole-5-carbonitrile derivatives. The methods work via the multicomponent reaction between 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one, aldehyde and malononitrile catalyzed by the silica-supported dodeca tungstophosphoric acid (DTP/SiO₂) catalyst. The protocol is practically green, milder reaction condition, higher yield, with short reaction times and recyclability of the catalyst.



Introduction

The heterocyclic chemistry and their pharmacological application is the key connection of the molecules for their wild

range of biological application[1]. There are many heterocyclic moieties in nature having a range of biological properties among them pyranopyrazoles are significant scaffolds

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because of a broad range of medicinal properties like anti-inflammatory [2], anticancer[3] and analgesic[4] antimicrobial [5], antiplatelet [6], anti-inflammatory [7-8], antitumor [9,10], analgesic [11], molluscicidal [12], cholinesterases inhibitory activity [13], vasodilator [14], and human Chk1 kinase inhibiting activity [15] therefore the synthesis of their analogs has valuable important in the pharmaceutical chemistry. Besides this PY

scaffolds have also important in the field of agrochemistry because of their herbicidal fungicidal and bactericidal properties, [16,17]. Therefore, for the preparation of PY moiety has a great interest in the research for finding novel derivatives. The dihydropyrano[2,3-c]pyrazole molecule is a significant intermediate that exists in four isomeric forms with a high bioactive profile (**Figure 1**).

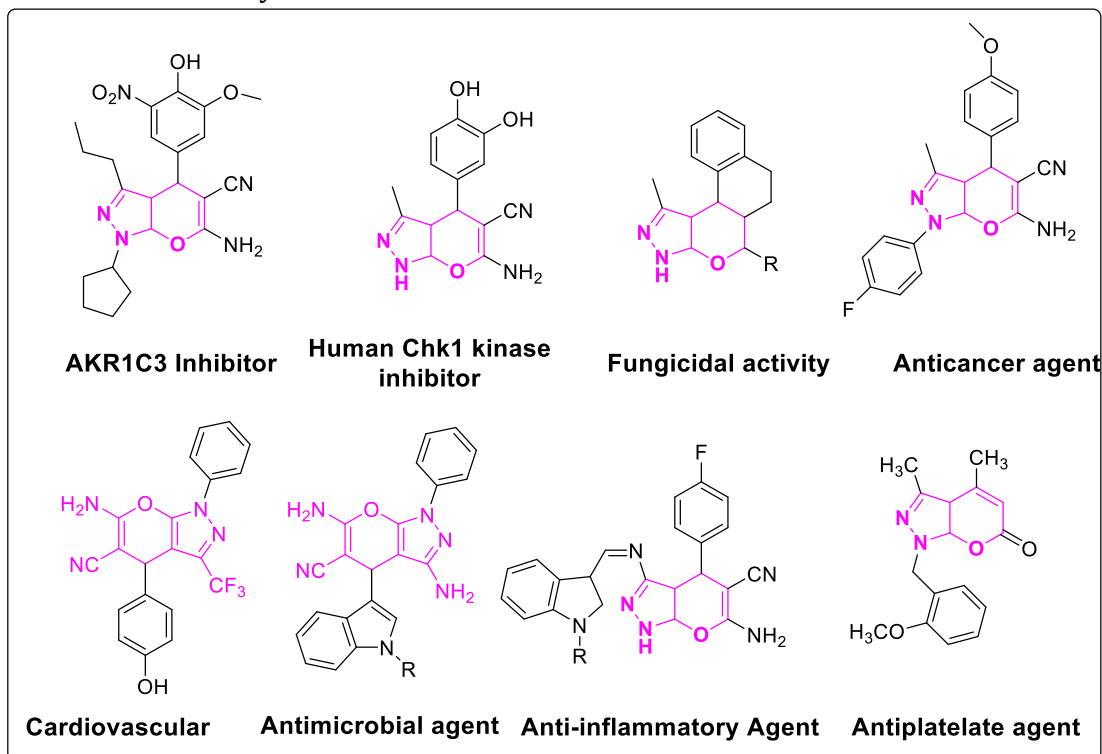


Figure 1. Bioactive dihydropyrano[2,3-c]pyrazole agent

As per the pharmaceutical importance of pyranopyrazole, the various synthetic protocols have been described for the preparation of bioactive modified medicinal active heterocyclic derivatives[18]. The synthetic protocol consists of the mono or multistep, and di-component or multicomponent reactions to get the desired pyranopyrazole moiety. Out of these methods, the Multicomponent reaction is one of the excellent protocols for the preparation of bioactive heterocyclic compounds. The reaction proceeds via all the reactants are mixed together to give the final product, without purification of intermediates compounds. The principle of MCRs, is highly productive, simple protocol, low cost, low

wastages, reducing reaction times, and no byproduct.26, the multicomponent is the better reaction as compared with traditional methods. Along with the MCRs are eco friendly, and usually performed by excellent chemoselectivity [19–22]. Recently, various techniques, protocols are available for the efficient preparation of PY derivatives by using multicomponent reactions. The DPy is usually prepared from the MCR of using $\text{NH}_2\text{-NH}_2\text{-H}_2\text{O}$, ethyl acetoacetate, $\text{CH}_2(\text{CN})_2$, and aromatic aldehydes by using catalyst-free [23], using acid catalyst [24], using base catalyst [25], using organ catalyst [26], using inorganic catalyst [27], using DTP/SiO₂ [28] catalyst that includes.

We are always interested in the development of novel bioactive heterocyclic[29-35], herein we have reported the synthesis of Simple, Highly efficient synthesis of 2-amino-4-phenyl-4,7-dihydropyrano[3,2-c]carbazole-3-carbonitrile derivatives using silica-supported dodecylphosphoric acid DTP/SiO₂.

Experimental

All the apparatus and chemicals were used as per standard laboratory guidelines. The M.P. of the novel compound has been done with melting point apparatus thermal IA9100 (Bibby Scientific Limited, Staffordshire, UK). The FTIR of the compound was recorded over the Bruker FTIR instruments. The ¹H NMR, ¹³C NMR recorded over the Bruker-300MHz, Bruker-400 MHz instruments.

Synthesis of 2-amino-4-phenyl-4,5,6,7-tetrahydropyrano[3,2-c]carbazole-3-carbonitrile derivatives (4A).

A mixture of 1,2,3,9-tetrahydro-4H-carbazol-4-one (1mol), aldehyde (2A-2J) (1.1 mol), malononitrile 3 (1.1 mmol), and DTP/SiO₂ (25 wt %) in DMF (10 mL) was stirred at room temp about 30-60 Minute (Table 1). The progress of reaction was checked by TLC. After completing the conversion of reactant into product (by TLC), the catalyst was filtered off To this reaction mixture, ice cold water (40 mL) was added and stirred mechanically for 10-15 min. The solid was separated out, filtered and recrystallized from ethanol to afford the pure products **4 A-4H**.

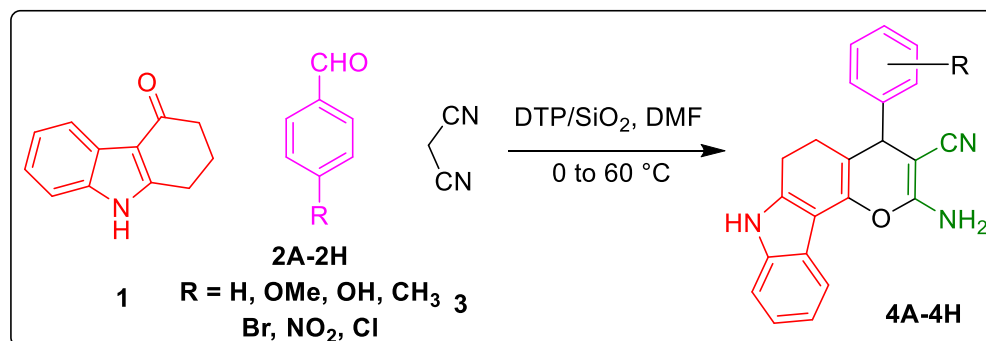
(4A). MP: 244-246 °C; ¹H NMR (300 MHz, DMSO-d₆): δ 11.54 (s, 1H), 8.56 (d, 1H, *J*=7.4 Hz), 7.42 (d, 1H, *J*=8.2), 7.40 (t, 1H, *J*=8.2 Hz), 7.35 (t, 1H), 7.28-7.16 (m, 5H), 6.80 (s, 2H), 4.87 (s, 1H), 2.54 (m, 2H), 2.34 (m, 2H); ¹³C NMR (75 MHz, DMSO-d₆): 160.1, 149.2, 142.3, 136.1, 135.2, 128.4, 127.7, 126.2, 126.2, 125.6, 122.1, 121.7, 119.8, 119.1, 117.2, 111.2, 111.1, 56.4, 43.2, 29.2, 24.7. LCMS (ESI+) calcd. for C₂₂H₁₇N₃O 339.13; found 340.01 (M+H)⁺

2-amino-4-(4-chlorophenyl)-4,5,6,7-tetrahydropyrano[3,2-c]carbazole-3-carbonitrile (4F).

MP: 253-260 °C; ¹H NMR (300 MHz, DMSO-d₆): δ 11.56 (s, 1H), 8.34 (d, 1H, *J*=7.4 Hz), 7.12 (d, 1H, *J*=8.1), 7.20 (t, 1H, *J*=8.3 Hz), 7.10 (t, 1H), 7.05-7.21 (m, 5H), 6.82 (s, 2H), 3.92 (s, 1H), 2.32 (m, 2H), 2.45 (m, 2H); ¹³C NMR (75 MHz, DMSO-d₆): 160.1, 149.0, 141.2, 135.6, 135.1, 131.2, 130.4, 128.3, 126.1, 121.6, 119., 119.2, 117.1, 111.0, 111.1, 56.1, 42.4, 29.1, 24.5 LCMS (ESI+) calcd. for C₂₂H₁₆ClN₃O (M+H)⁺: 373.09; found 374.0

Results and Discussion

The synthesis of carbazole-3-carbonitrile derivatives was achieved by reacting substituted aromatic benzaldehydes (**2a**) with malononitrile (**3**) and 1,2,3,9-tetrahydro-4H-carbazol-4-one (**1**) in DMF solvent in the presence of DTP/SiO₂ as a catalyst. The product was obtained after stirring the reaction mixture for 60 minutes at room temperature. carbazole-3-carbonitrile derivatives (**4a-4H**) were obtained with high purity and better to excellent yields, as shown in **Scheme 1**.



Scheme 1. Synthesis of 6A PyCarbazole carbonitriles

Firstly, we have considered solvent parameters and observed reactions in different solvents like water, methanol, PEG-400, and ethanol as aprotic solvents as well as DCM, DMF, and acetonitrile as aprotic solvents. We observed that the solvent has an important role in the progress of the reaction. The reaction with DMF gave the corresponding product in good yields, whereas the findings with other

solvents such as DCM, ethanol, and acetonitrile, yielded the product **4A** in fewer quantities, neither PEG-400 nor water were particularly given good results. Further, it has been decided the impressive and ideal solvent for this conversion was DMF.

The structures of all the newly synthesized 2APyCarbazole carbonitriles derivatives (**4A-4J**) are depicted in **Table 1**.

Table 1. Comparison of catalytic activity of various catalysts for synthesis of pyrano[3,2-c]chromene-3-carbonitrile derivatives

Sr/No	Solvent	Catalyst	Reaction time	Yield
	Water	DTP/SiO ₂	120	45
	Methanol	DTP/SiO ₂	120	50
	Ethanol	DTP/SiO ₂	120	65
	PEG-400	DTP/SiO ₂	120	65
	DCM	DTP/SiO ₂	120	50
	DMF	DTP/SiO ₂	60	82
	CH ₃ CN	DTP/SiO ₂	120	65

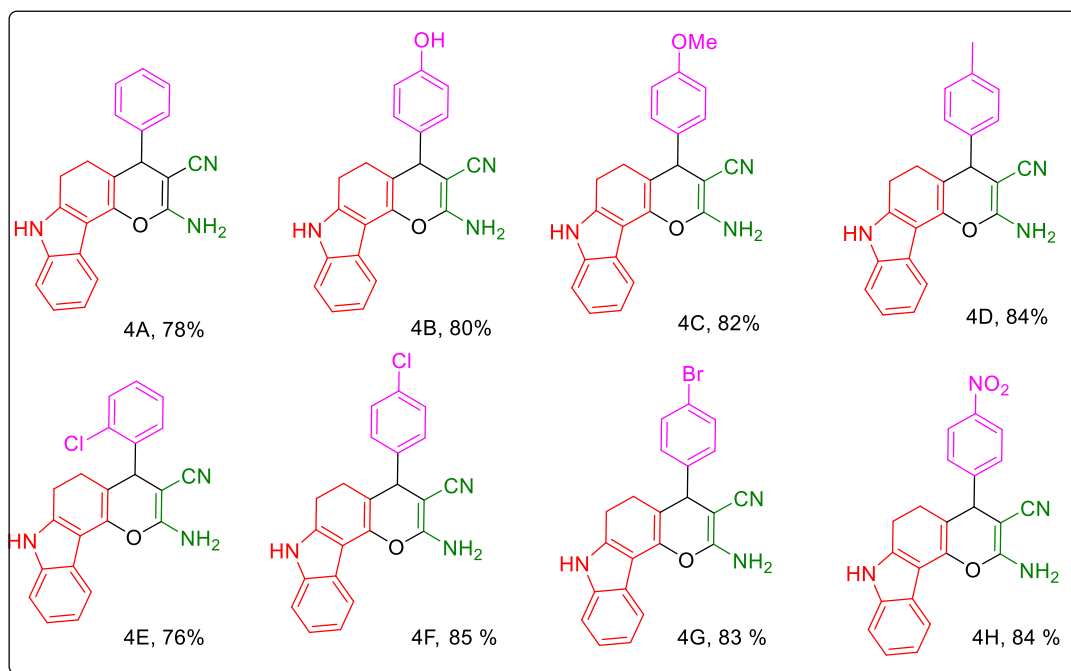
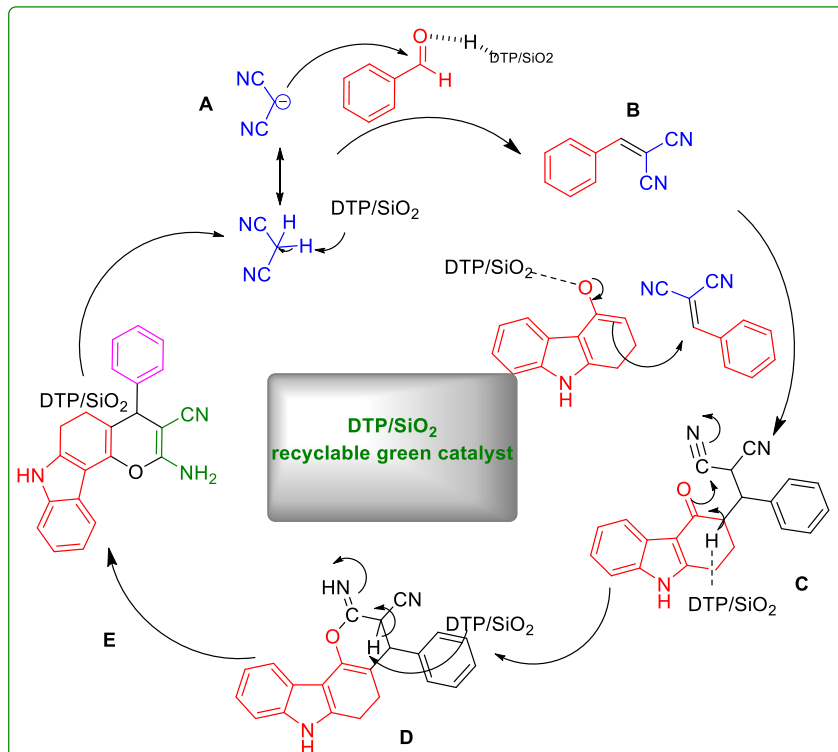


Table 2. DTP/SiO₂ catalyzed synthesis of 2-amino-4-phenyl-4,7-dihydropyrano[3,2-c]carbazole-3-carbonitrile.



Scheme 2. Plausible mechanism for the 2-Amino-4-Phenyl-4,5,6,7-Tetrahydropyrano[3,2-c]Carbazole-3-Carbonitrile

However, in the model reaction, the influence of catalyst loading was also investigated. The results revealed that a catalyst concentration of 10 mol% was a great choice for this process. Increasing the catalyst concentration 10 to 15 mol% resulted in a low effect on yield and not be further increased. When the reaction was conducted with reducing amounts of catalyst, the yield of **4A** could not be further increased. Under optimized conditions the optimized protocol was carried out in the absence of DTP/SiO₂ there was less conversion of reactants to products after stirring at room temperature.

This result motivates us to investigate the methods for synthesis of carbazole-3-carbonitrile derivatives from substituted benzaldehydes, malononitrile, and 1,2,3,9-tetrahydro-4*H*-carbazol-4-one using a 10 mol% DTP/SiO₂ catalyst and DMF as a solvent in an optimized reaction condition. After the completion of the reaction, the product was recovered and the catalyst was isolated by filtration. The Isolated catalyst was again used

after drying of catalyst. A series of aromatic aldehydes were selected to undergo the condensation in the presence of a DTP/SiO₂ catalyst. As shown in Table 1, aromatic aldehydes **2** carrying either electron-donating or electron-withdrawing substituent reacted efficiently and gave excellent yields Table 2, Therefore, the nature of the substituent's attached to the aromatic ring did not show a significant effect in this conversion. The experimental methods include efficient, eco-friendly, convenient, rapid properties and showed the ability to endure a variety of electron releasing and electron-withdrawing functional groups, such as methoxyl, nitro, hydroxyl, and halides.

Mechanism

The plausible mechanism for the synthesis of 2-amino-4-phenyl-4,5,6,7-tetrahydropyrano [3,2-c]carbazole-3-carbonitrile (**4A**) as shown in **Scheme 2**, involves the proton abstraction of the active methylene group of malononitrile by the DTP/SiO₂, the active methylene compounds react

with the nucleophilic sites of benzaldehyde simultaneously the resulted compound undergoes dehydration and produce compound **B** (Scheme 2), The intermediates B, which attack on the 1,2,3,9-tetrahydro-4H-carbazol-4-one (**1**) and form the **C**. In the presence of DTP/SiO₂, catalyst the intermediate undergoes intramolecular cyclization and isomerization results in desired product **E**.

Conclusion

Finally, 2-amino-4-phenyl-4,7-dihydropyrano[3,2-c]carbazole-3-carbonitrile derivatives (**4a-l**) was prepared from DTP/SiO₂ catalyst. we designed a mild, rapid, and environmentally sustainable synthesis process for 2-amino-4-phenyl-4,7-dihydropyrano[3,2-c]carbazole-3-carbonitrile derivatives (**4A-4H**) from aromatic benzaldehyde, malononitrile, and 1,2,3,9-tetrahydro-4H-carbazol-4-one. Simple reaction conditions, no side reactions, and high yield product formation are all essential features of the technique. For the synthesis of 2-amino-4-phenyl-4,7-dihydropyrano[3,2-c]carbazole-3-carbonitrile derivatives, the current technique is an alternative to traditional methods. The catalyst was retrieved several times without losing catalytic activity, resulting in a cost-effective method.

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Conflict of Interest

We have no conflicts of interest to disclose.

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