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Green synthesis of tetrahydrobenzo[*b*]pyrans, pyrano[2,3-*c*]pyrazoles and spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazoles catalyzed by nano-structured diphosphate in water†

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A green and recoverable nano-structured diphosphate ($Na_2CaP_2O_7$) was synthesized and fully characterized using FT-IR spectra, X-ray diffraction patterns (XRD), scanning electron microscopy (SEM), and energy-dispersive X-ray spectroscopy (EDX) analysis. The nanostructured catalyst has been successfully used as reusable nanostructured catalyst for green, simple and efficient synthesis of tetrahydrobenzo[*b*]pyrans, pyrano[2,3-*c*]pyrazoles and spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazoles in aqueous media. The catalyst shows environmentally benign character, which can be easily prepared, stored, and recovered several times without obvious significant loss of catalytic activity.

Introduction

One important symbol of green chemistry is reducing the use of organic solvents because of the economical and environmental concerns associated with them. Water plays an essential role in life processes and also a medium for the organic synthesis.[1,2] Water is clean, non-toxic, and hazard-free in handling, non-inflammable, cheap and a readily available solvent. Furthermore, because of its highly polarity, high surface tension, high specific heat capacity and network of hydrogen bonds, water plays a significant role in many reactions.[3] In 1980, Breslow discovered that Diels–Alder reactions could be performed in water with a huge acceleration.[4,5] This discovery led to a considerable interest of synthetic organic chemists in the study of using water as a reaction solvent.[6,7] To date, a great number of organic reactions have been carried out in water successfully.[8]

The pyran ring system is present in numerous biologically active natural products as well as many synthetic compounds.[9] Tetrahydrobenzo[*b*]pyrans and pyrano[2,3-*c*]pyrazoles have a broad spectrum of biological and pharmacological activity, such as anticancer, anti-coagulant, antimicrobial, anti-inflammatory, anti-anaphylactic, and molluscicidal activity.[10–13]

Conventionally, the synthesis of tetrahydrobenzo[*b*]pyrans has been performed through a one-pot reaction of three components in the presence of various catalysts such as the Fe_3O_4@SiO_2–imid–PMA nanoparticle,[14] choline hydroxide based ionic liquid [Ch][OH],[15] red sea sand under microwave or ultrasonic irradiation,[16] hexadecyltrimethyl ammonium bromide (HTMAB),[17] sodium bromide (NaBr),[18] ionic liquids,[19–22] tetra-methyl ammonium hydroxide,[23] molecular iodine (I_2),[24] *N*-methylimidazole,[25] sodium selenite,[26] tetrabutylammonium bromide (TBAB),[27] amine or amino acid,[28] potassium phosphate (K_3PO_4),[29] magnetic core–shell titanium dioxide nanoparticles (Fe_3O_4@SiO_2@TiO_2),[30] nano α-Al_2O_3 supported ammonium dihydrogen phosphate ($NH_4H_2PO_4/Al_2O_3$),[31] phenylboronic acid [$PhB(OH)_2$],[32] cerium(iii) chloride ($CeCl_3 \cdot 7H_2O$),[33,34] nanosized TiO_2,[35] silica coated magnetite–polyoxometalate nanoparticles (Fe_3O_4@SiO_2@NH-NH_2–$H_3PW_{12}O_{40}$),[36] meglumine,[37] magnetic $La_{0.7}Sr_{0.3}MnO_3$ nanoparticles,[38] $RuBr_2(PPh_3)_4$,[39] lactose,[40] and silica coated magnetic $NiFe_2O_4$ nanoparticles supported $H_3PW_{12}O_{40}$ (NFS-PWA).[41]

However, a number of these methods suffer from certain drawbacks such as poor yields, difficult workups, long reaction times, high temperatures, the utilization of alternative energy source (microwave or ultrasonic), and the use of volatile or hazardous organic solvents. Therefore, it seemed desirable to develop a more efficient and a general method for the synthesis of tetrahydrobenzo[*b*]pyrans and pyrano[2,3-*c*]pyrazoles.

On the basis of the information obtained from the nano-structured diphosphate $Na_2CaP_2O_7$ (DIPH), we predicted that the DIPH can be used as an efficient catalyst for the promotion of the reactions which requires the use of a catalyst to speed-up. So, we were interested to investigate the applicability of this reagent in the promotion of the synthesis tetrahydrobenzo[*b*]pyrans and pyrano[2,3-*c*]pyrazoles.

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For the present study, the synthesis of the DIPH has been carried out from Na_2CO_3, $CaCO_3$ and $NH_4H_2PO_4$ in 1 : 1 : 2 proportion, respectively, by following the literature procedure.[42] In recent years, the DIPH has been used as catalyst in organic synthesis[43,44] as it has been shown to be non-toxic, green and stable, inexpensive, safe, non-volatile, non-corrosive and reusable.

In our progressive program to develop efficient and environmentally benign protocols for the synthesis of various products,[45–59] we tried to report a highly efficient method for the synthesis of tetrahydrobenzo[*b*]pyrans and pyrano[2,3-*c*]pyrazoles catalyzed by a DIPH in water (Scheme 1).

Nanostructured diphosphate ($Na_2CaP_2O_7$) was characterized by several methods including FT-IR, SEM, XRD and EDX. The existence of P_2O_7 units was confirmed by the symmetrical vibration bands of P–O–P at 720 cm^{-1} as well as the antisymmetric vibration bands at 890 cm^{-1}. The related vibrations of the PO_4 groups were shared between two fields: a field of symmetrical vibrations at 990 cm^{-1} and 1030 cm^{-1} and another that ranged from 1130 to 1280 cm^{-1} (Fig. S1†).[42–44] Scanning Electronic Microscopy (SEM) was used to study the morphology of the surface of $Na_2CaP_2O_7$ (Fig. S2†). Also, to confirm the formation of $Na_2CaP_2O_7$ nanostructure, the XRD patterns of sample was studied (Fig. S3†). The XRD pattern of $Na_2CaP_2O_7$ nanostructure indicates that these nanostructures have synthesized well and all of the major peaks matching with the previous literatures.[42–44] Moreover, the elemental analysis obtained from the EDX spectra of catalyst (Fig. S4†), shows the existence of all of the elements in the $Na_2CaP_2O_7$ nanostructures and these results are in agreement with other results.

At first, we selected the benzaldehyde (1 mmol), dimedone (1 mmol), and malononitrile (2 mmol) as model substrates to establish optimum reaction conditions in the presence of DIPH (Table 1). When the reaction was performed under solvent-free conditions, a low yield of target product was obtained (Entry 1).

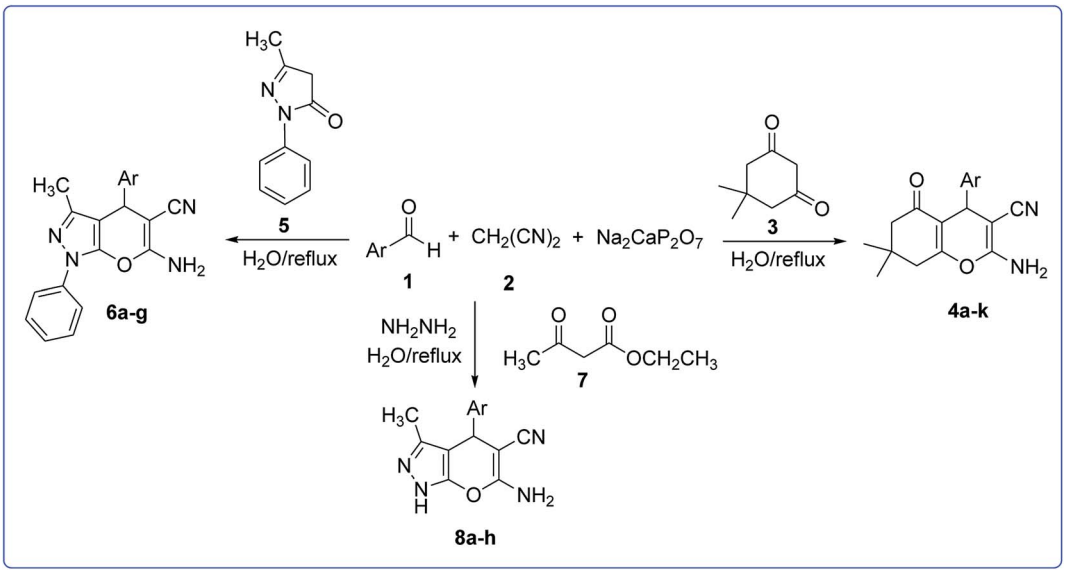
Table 1 Optimization of reaction conditions[a]

Entry	Catalyst (mol%)	Conditions	Time (min)	Yield[b] (%)
1	20	Solvent-free/100 °C	15	72
2	20	MOH/reflux	10	80
3	20	EtOH/reflux	10	82
4	20	EtOH : water/reflux	10	88
5	20	Water/reflux	10	94
6	10	Water/reflux	10	84
7	30	Water/reflux	10	94
8	None	Water/reflux	60	None

[a] Benzaldehyde (1 mmol), dimedone (1 mmol), malononitrile (1 mmol) in refluxing water. [b] Isolated yields.

To find the best solvent for this transformation, the present three-component reaction was screened in methanol, ethanol, and water (Table 2, Entries 2–4). Among these solvents, water was found to be the best one and afforded the highest yield (Entry 5). Then, the amount of the catalyst was evaluated in the model reaction in refluxing water (Entries 6–7). The results showed that 20 mol% of DIPH was the best choice for completing the reaction (Entry 5) and the use of excessive catalyst had no impact either on the rate of the reaction or on the product yield (Entry 7). When the reaction was attempted without a catalyst, it was found that no product was obtained even after 1 h (Entry 8).

Under these optimal conditions (Table 1, Entry 4), the scope and specificity of this protocol was further investigated. At first, a broad range of structurally diverse aldehydes were treated with malononitrile and dimedone (see Table 2) in order to synthesis of tetrahydrobenzo[*b*]pyrans derivatives **4a–k**. As shown in Table 2, all reactions proceeded efficiently and the desired products were obtained from high to excellent yields in relatively short times without any formation of by-products. The



Scheme 1 Synthesis of tetrahydrobenzo[*b*]pyrans and pyrano[2,3-*c*]pyrazoles catalyzed by a DIPH in water.

Table 2 Green synthesis of tetrahydrobenzo[*b*]pyran and pyrano[2,3-*c*]pyrazoles derivatives catalyzed by DIPH in refluxing water

Entry	Ar	Product	Time (min)	Yield[a] (%)	Mp (°C)	Lit. Mp (°C)	[Ref.]
1	Ph	**4a**	10	94	231–233	231–233	18
2	4-ClC_6H_4	**4b**	10	90	207–209	203–206	21
3	4-$CH_3C_6H_4$	**4c**	10	89	212–214	210–213	23
4	3-ClC_6H_4	**4d**	10	92	230–232	230–232	23
5	3-$MeOC_6H_4$	**4e**	10	90	192–194	188–190	20
6	2-$CH_3C_6H_4$	**4f**	15	86	212–214	211–212	41
7	4-CNC_6H_4	**4g**	10	95	226–228	225–228	23
8	4-$NO_2C_6H_4$	**4h**	10	95	177–179	177–179	23
9	3-$NO_2C_6H_4$	**4i**	10	94	210–212	211–214	18
10	4-BrC_6H_4	**4j**	10	91	202–204	203–205	26
11	2,4-ClC_6H_4	**4k**	10	90	183–185	180–182	27
12	Ph	**6a**	10	93	164–166	169–171	17
13	4-ClC_6H_4	**6b**	15	86	180–182	175–177	17
14	4-BrC_6H_4	**6c**	15	90	187–188	185–186	31
15	4-$CH_3C_6H_4$	**6d**	20	80	174–177	176–178	31
16	4-$CH_3OC_6H_4$	**6e**	20	82	171–173	170–172	31
17	3-$NO_2C_6H_4$	**6f**	15	90	189–191	190–192	31
18	4-$NO_2C_6H_4$	**6g**	20	87	195–197	197–199	31
19	Ph	**8a**	10	92	244–245	244–245	19
20	4-$CH_3OC_6H_4$	**8b**	15	86	213–215	211–213	19
21	4-BrC_6H_4	**8c**	15	85	246–248	248–250	19
22	2-Thienyl-C_6H_4	**8d**	10	92	225–226	224–226	37
23	4-Pyridin-C_6H_4	**8e**	20	90	215–217	216–217	37
24	3-BrC_6H_4	**8f**	15	90	224–226	222–223	19
25	4-$NO_2C_6H_4$	**8g**	10	90	250–252	248–249	37
26	3-$NO_2C_6H_4$	**8h**	15	89	228–230	232–233	22

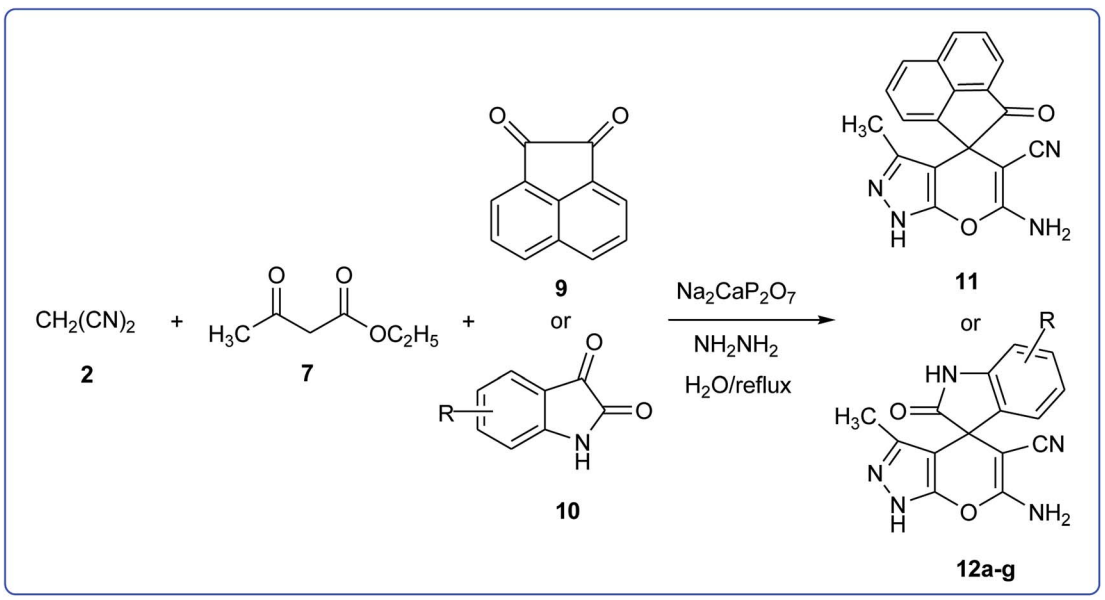
[a] Isolated yields.

reaction of aromatic aldehyde carrying electron donating or electron-withdrawing groups was also successfully carried out with this method (Table 2, Entries 1–11). The reactions showed corresponding compounds in excellent yields.

Encouraged by these results, we extended this study for three component synthesis of pyrano[2,3-*c*]pyrazoles (**6a–g**) in the presence of a catalytic amount of DIPH. Considering the reaction time and the yield, the DIPH (20 mol%) was selected as the optimum catalyst used in the refluxing water. Using the optimized reaction conditions, a range of substituted pyrano[2,3-*c*]pyrazoles were synthesized (Table 2, Entries 12–18). Moreover, the one-pot, four-component synthesis of pyrano[2,3-*c*]pyrazoles could be successfully used for the synthesis of corresponding compounds (**8a–h**). This method was found to be effective for aromatic aldehydes bearing either electron donating or electron-withdrawing substituents (Entries 19–21, 24–26) as well as for the heterocyclic aldehyde (Entries 22, 23).

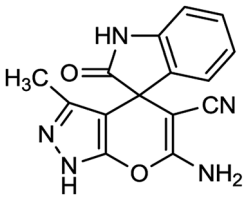
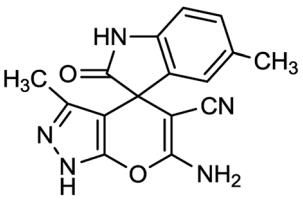
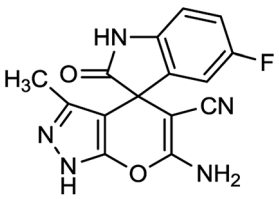
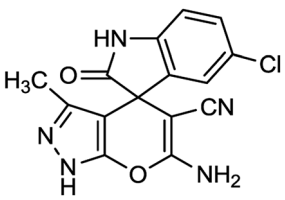
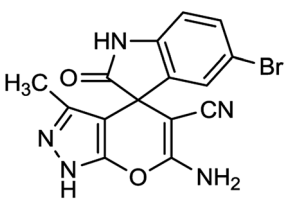
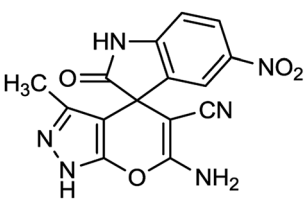
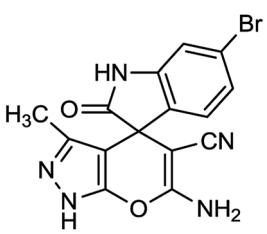
Spiro heterocycles, especially spirocyclic oxindole nucleus, are a substantial category of natural alkaloids that possess various biological and pharmacological activities, such as spirotryptostatin A, B, which are isolated from the fermentation broth of *Aspergillus fumigatus*, inhibits of cell cycle at G2/M phase and koumine,[60] which is one of the alkaloids isolated from the *Gelsemium sempervirens* plant that has antitumor and analgesic activities.[61] Chitosenine as a *Gardneria multiflora* oxindole alkaloid has ganglioblocking action.[62] These interesting properties promoted us to widen the applicability of this procedure with isatins.[63]

To explore the scope of this reaction to form a spiroheterocyclic compound, we investigated the use of acenaphthylene-1,2-dione (**9**) or isatin (**10**) as a substrate to react with the hydrazine hydrate, malononitrile, ethyl acetoacetate under the optimized conditions. As expected the reaction proceeded well to afford spiro[acenaphthylene-1,4′-pyrano[2,3-*c*]pyrazole (**11**) in 60 min with 64% yield and spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole] derivatives (**12a–g**) (Scheme 2 and Table 3). These successful results clearly indicate that the present catalytic approach is extendable to a wide variety of substrates.



Scheme 2 Synthesis of spiro-pyrano[2,3-*c*]pyrazole derivative.

Table 3 Green synthesis of spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole] derivatives (**12a–h**) using DIPH in refluxing water

				Mp (°C)		
Entry	Products (**12a–g**)	Time (min)	Yield[a] (%)	Found	Reported	[Ref.]
12a		50	78	284–286	285–286	37
12b		70	74	278–280	279–281	37
12c		40	85	274–276	274–275	37
12d		40	87	296–298	297–298	37
12e		40	90	280–282	282–283	37
12f		35	91	272–274	270–271	37
12g		40	82	>300	>300	63

[a] Isolated yields.

Table 4 Comparison of the efficiencies of various catalysts used in the synthesis of tetrahydrobenzo[*b*]pyrans and pyrano[2,3-*c*]pyrazoles

Product	Catalyst	Reaction conditions	Time (min)	Yield[a] (%)	[Ref.]
4a	Fe_3O_4@SiO_2–imid–PMA	H_2O/reflux	20	94	14
	Red sea sand	EtOH/reflux	360	84	16
	[Ch][OH]	H_2O/80 °C	60	92	15
	NaBr/MWI	Solvent-free, 70 °C	10	91	18
	DIPH	H_2O/reflux	10	94	This study
8a	[bmim]OH	Solvent-free/60 °C	10	88	19
	L-Proline/$[Bmim]BF_4$	Solvent-free/50 °C	10	90	22
	$NH_4H_2PO_4/Al_2O_3$	EtOH/reflux	15	80	31
	NFS-PWA	EtOH/reflux	45	90	41
	DIPH	H_2O/reflux	10	92	This study

[a] Isolated yields.

The reusability of the catalyst was also investigated. For this purpose, the same model reaction was again studied under optimized conditions. After the completion of the reaction, the acetone was added to the reaction mixture to dissolve the product. Then, the catalyst was removed by filtration. It was re-used directly in the model reaction to give **4a** in yields of 94%, 92%, 91%, 91%, 90% and 89% for six consecutive runs at 10 min.

In order to illustrate the efficiency of our procedure, results for the preparation of tetrahydrobenzo[*b*]pyrans and pyrano[2,3-*c*]pyrazoles previously reported are compared with our data (Table 4). The present method using DIPH as catalyst offers several advantages such as excellent yields, a simple procedure, short reaction times, facile work-up and greener conditions. The green aspect of the DIPH catalyst has been discussed in terms of being non-corrosive, presenting fewer disposals problem, facile isolation of the products, and recyclability.

Conclusion

In conclusion, we have developed a green and simple protocol for the synthesis of tetrahydrobenzo[*b*]pyran and pyrano[2,3-*c*] pyrazole derivatives *via* a three or four component condensation reaction in the presence of DIPH in water. This method was found not only to be applied to aromatic and heteroaromatic aldehydes, but also to be useful for the synthesis of ketone-derived dihydropyrano[2,3-*c*]pyrazole, spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole] and spiro[acenaphthylene-1,4′-pyrano[2,3-*c*] pyrazole]. This procedure provides several advantages such as high yields, wide scope of substrates, short reaction times, non-volatile, non-corrosive, absence of side-reactions, simple work-up procedure, non-toxic, evasion of hazardous catalysts or solvents, and the minimization of cost and waste generation owing to the recycling of the catalyst.

Experimental section

All reagents were obtained from commercial sources and were used without purification. IR spectra were recorded as KBr pellets on a Shimadzu 435-U-04 spectrophotometer. ^{1}H and ^{13}C NMR spectra were determined on a Bruker DRX-300 Avance spectrometer in DMSO-d_6 or $CDCl_3$, and shifts are given in δ downfield from tetramethylsilane (TMS) as an internal standard. Melting points were determined using an Electrothermal 9200 apparatus and are uncorrected.

General procedure for the synthesis of tetrahydrobenzo[*b*]pyrans (4a–k)

The catalyst, DIPH (20 mol%), was added to a mixture of the aldehydes (1 mmol), malononitrile (1.2 mmol), and dimedone (1 mmol), and 1 ml of water in a 5 ml flask fitted with a reflux condenser. The resulting mixture was heated to reflux (an oil bath) for the appropriate time (see Table 2) with stirring (spin bar). After the completion of the reaction as determined by TLC (hexane–ethyl acetate, 4 : 1), the acetone (2 ml) was added and the mixture stirred for 2 min. The catalyst was removed by filtration and washed with acetone and calcined at 500 °C for 1 h before re-use. Then the resulting crude reaction mixture was poured onto crushed ice and the precipitated solid was collected and recrystallized from ethanol (96%, 5 ml) to afford the pure tetrahydrobenzo[*b*]pyrans derivatives **4a–k**. The products were identified by their melting points, ^{1}H-NMR, and IR spectroscopies.

General procedure for the synthesis of pyrano[2,3-*c*]pyrazoles (6a–g)

The catalyst, DIPH (20 mol%), was added to a mixture of the aldehydes (1 mmol), malononitrile (1.2 mmol), and 3-methyl-1-phenyl-2-pyrazoline-5-one (1 mmol), and 1 ml of water in a 5 ml flask fitted with a reflux condenser. The resulting mixture was heated to reflux (an oil bath) for the appropriate time (see Table 2) with stirring (spin bar). After the completion of the reaction as determined by TLC (hexane–ethyl acetate, 4 : 1), the acetone (2 ml) was added and the mixture stirred for 2 min. The products and catalyst were isolated as described above and recrystallized from 96% ethanol (20 ml) to afford pyrano[2,3-*c*]pyrazoles **6a–g**.

General procedure for the synthesis of pyrano[2,3-*c*]pyrazoles (8a–h)

The catalyst, DIPH (20 mol%), was added to a mixture of the aldehydes (1 mmol), malononitrile (1.2 mmol), hydrazine hydrate (2 mmol), ethylacetoacetate (1 mmol), and 1 ml of water in a 5 ml flask fitted with a reflux condenser. The resulting mixture was heated to reflux (an oil bath) for the appropriate time (see Table 2) with stirring (spin bar). After the completion of the reaction as determined by TLC (hexane–ethyl acetate, 4 : 1), the acetone (2 ml) was added and the mixture stirred for 2 min. The products and catalyst were isolated as described above and recrystallized from 96% ethanol (20 ml) to afford pyrano [2,3-*c*]pyrazoles **8a–h**.

General procedure for the synthesis of spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazoles (12a–g)

The catalyst, DIPH (20 mol%), was added to a mixture of the isatins (1 mmol), malononitrile (1.2 mmol), hydrazine hydrate (2 mmol), ethylacetoacetate (1 mmol), and 1 ml of water in a 5 ml flask fitted with a reflux condenser. The resulting mixture was heated to reflux (an oil bath) for the appropriate time (see Table 2) with stirring (spin bar). After the completion of the reaction as determined by TLC (hexane–ethyl acetate, 4 : 1), the acetone (2 ml) was added and the mixture stirred for 2 min. The products and catalyst were isolated as described above and recrystallized from 96% ethanol (20 ml) to afford pyrano[2,3-*c*] pyrazoles **12a–g**.

Spectroscopic data of representative compounds

2-Amino-3-cyano-4-phenyl-7,7-dimethyl-5-oxo-4*H*-5,6,7,8-tetrahydrobenzo[*b*]pyran (4a). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 1.04 (s, 3H), 1.13 (s, 3H), 2.11–2.21 (m, 2H), 2.42 (s, 2H), 4.67 (s, 1H), 6.52 (brs, 2H, D_2O exchangeable), 7.14–7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 26.32, 27.65, 31.24, 35.09, 39.08, 49.98, 59.74, 113.09, 118.42, 125.86, 126.63, 127.54, 142.68, 158.54, 162.32, 194.24; IR (KBr disc, cm^{-1}): 3314, 3202, 2214, 1688, 1624, 1507, 1482, 1370.

2-Amino-3-cyano-4-(3-methoxyphenyl)-7,7-dimethyl-5-oxo-4*H*-5,6,7,8-tetrahydrobenzo[*b*]pyran (4e). ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 0.92 (s, 3H), 1.01 (s, 3H), 2.05 (d, 2H), 2.66 (d, 2H), 3.45 (s, 3H), 4.17 (s, 1H), 7.06 (brs, 2H, D_2O exchangeable), 7.13–7.26 (m, 3H), 7.34 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ 27.30, 28.78, 32.33, 35.52, 35.58, 38.43, 50.44, 58.41, 112.74, 120.19, 128.91, 129.63, 131.80, 144.16, 158.98, 163.61, 197.00; IR (KBr disc, cm^{-1}): 3370, 3180, 2185, 1660, 1624, 1509, 1492, 1380.

6-Amino-3-methyl-5-cyano-4-(phenyl)-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole (6a). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.77 (s, 3H), 5.16 (s, 1H), 7.28–7.48 (m, 10H), 7.78 (brs, 2H, D_2O exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 25.02, 40.43, 50.45, 59.13, 113.24, 118.67, 126.45, 126.06, 127.67, 128.03, 128.98, 129.14, 130.14, 140.05, 154.05, 162.34; IR (KBr disc, cm^{-1}): 3425, 3332, 2200, 1620, 1590, 1484, 1386.

6-Amino-3-methyl-5-cyano-4-(4-methylphenyl)-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole (6d). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 1.01 (s, 3H), 2.46 (s, 3H), 5.12 (s, 1H), 5.98 (brs, 2H, D_2O exchangeable), 7.11–7.79 (m, 9H); ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ 25.18, 26.56, 41.04, 50.25, 60.63, 113.24, 118.04, 125.13, 126.45, 127.52, 128.18, 129.89, 130.68, 131.43, 141.67, 153.69, 160.11; IR (KBr disc, cm^{-1}): 3413, 3321, 2196, 1620, 1589, 1448, 1381.

6-Amino-3-methyl-5-cyano-4-(3-nitrophenyl)-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole (6f). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 1.79 (s, 3H), 5.16 (s, 1H), 6.05 (brs, 2H, D_2O exchangeable), 7.19–7.68 (m, 8H), 8.01 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ 25.67, 41.12, 51.61, 61.05, 113.78, 119.14, 125.79, 126.54, 126.98, 127.32, 128.12, 128.67, 129.34, 130.78, 131.05, 140.67, 154.67, 159.89; IR (KBr disc, cm^{-1}): 3420, 3310, 2198, 1618, 1598, 1568, 1490, 1386.

6-Amino-3-methyl-4-(4-methoxyphenyl)-1,4-dihydro-pyrano[2,3-*c*]pyrazole-5-carbonitrile (8b). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 1.79 (s, 3H), 3.45 (s, 3H), 4.56 (s, 1H), 6.88 (brs, 2H, D_2O exchangeable), 7.10 (d, 2H), 7.19 (d, 2H), 12.01 (s, 1H, D_2O exchangeable); ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ 10.22, 35.17, 36.01, 57.64, 97.82, 121.31, 126.04, 128.64, 136.19, 136.07, 141.64, 155.22, 161.35; IR (KBr disc, cm^{-1}): 3483, 3254, 2191, 1641, 1608, 1492, 1390.

6-Amino-3-methyl-4-(4-bromophenyl)-1,4-dihydro-pyrano[2,3-*c*]pyrazole-5-carbonitrile (8c). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 1.75 (s, 3H), 4.81 (s, 1H), 6.48 (brs, 2H, D_2O exchangeable), 7.09 (d, 2H), 7.32 (d, 2H), 12.12 (s, 1H, D_2O exchangeable); ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ 10.12, 33.62, 55.69, 96.23, 120.01, 128.45, 129.79, 132.54, 133.30, 135.21, 140.54, 155.89, 161.98; IR (KBr disc, cm^{-1}): 3444, 3238, 2195, 1637, 1600, 1491, 1394.

6′-Amino-3′-methyl-2-oxo-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitrile (12a). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 1.54 (s, 3H), 6.91 (s, 1H), 7.02 (s, 2H), 7.17 (s, 2H, D_2O exchangeable), 7.23 (s, 1H), 10.55 (s, 1H, D_2O exchangeable), 12.25 (s, 1H, D_2O exchangeable); IR (KBr disc, cm^{-1}): 3420, 3390, 3330, 3130, 2680, 2180, 1710, 1640, 1580, 1520, 1420, 1320, 1210, 1160, 1050.

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