Simple and Convenient Approach to the Kr€ohnke Pyridine Type Synthesis of Functionalized Indol-3-yl Pyridine Derivatives Using 3-Cyanoacetyl Indole

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Access to privileged heterocyclic scaffolds involving 4-aryl-6-(1*H*-indol-3-yl)-2,2-bipyridine-5-carbonitriles and 6-(2-furyl)-2-(1*H*-indol-3-yl)-4-arylpyridine-3-carbonitriles frameworks has been achieved via a single-step multicomponent reaction of structurally diverse aldehydes, 2-acetylpyridine (or) 2-acetylfuran and 3-cyanoacetyl indole in ammonium acetate under neat condition. Also a series of 6,6′-di(1*H*-indol-3-yl)-4,4′-diaryl-2,2′-bipyridine-5,5′-dicarbonitrile and 7,7,7′,7′-tetramethyl-4,4′-bis(aryl)-4,6,7,8,4′,6′,7′,8′-octahydro-1*H*,1*H*-[2,2′]biquinolinyl-5,5′-dione derivatives are synthesized using cinnamil, 3-cyanoacetyl indole (or) dimedone and ammonium acetate.

1.0. Introduction

The structural diversity and biological importance of nitrogen containing heterocycles have made them attractive targets for synthesis over many years. They are found in various natural products and have been identified as products of chemical and biological importance. Multicomponent reactions (MCR) have emerged as a powerful tool for delivering the molecular diversity needed in the combinatorial approaches for the preparation of bioactive heterocyclic compounds.[1] MCR, such as the Biginelli,[2] Passerini,[3] Ugi,[4] and Hantzsch, provide a wide variety of important heterocycles.[5] For example, the Hantzsch reaction provides dihydropyridines with activity against calcium channels, multidrug resistance (MDR) proteins, 5-hydroxytryptamine(5-HT) receptors, and anti-inflammatory targets.[6,7]

Pyridine derivatives occupy a central position in modern heterocyclic chemistry particularly in the pharmaceutical and agrochemical fields.[8] Bipyridines have been well-known as highly interesting organic ligands for transition metals for more than a century. In particular, the 2,2′-bipyridines were used in investigations in analytical chemistry, medical chemistry, and energy conversion processes. Many applications of 2,2′-bipyridine derivatives have been reported in fields such as supramolecular chemistry, artificial photosynthesis systems, luminescent sensor materials, and non-linear optical materials.[9]

On the other hand, 3-substituted indole is the one of the "privileged medicinal scaffold" found in many natural products[10,11] and biologically active compounds especially with anticancer, antitumor,[12] hypoglycemic, anti-inflammatory, analgesic, and antipyretic activities.[13,14] These scaffolds are capable of providing ligands for a number of functionally and structurally discrete biological receptors through appropriate functional group modifications. Some of the biologically active 3-substituted indole representatives are shown in Figure 1.[10−14]

The wide-ranging biological activity associated with many pyridine and 3-substituted indole derivatives, both naturally occurring and synthetic, ensures that the synthesis of this important ring system remains a topic of current interest. Various methods for the preparation of these compounds have been reported. However, these methods suffer from tedious synthetic routes, longer reaction time, drastic reaction conditions, as well as narrow substrate scope.[15−19] To the best of our knowledge, there have been very few reports for the synthesis of 6-(indol-3-yl)-2,2′-bipyridine derivatives.[20] As part of our ongoing research on the development of novel synthetic routes for the synthesis of biologically active

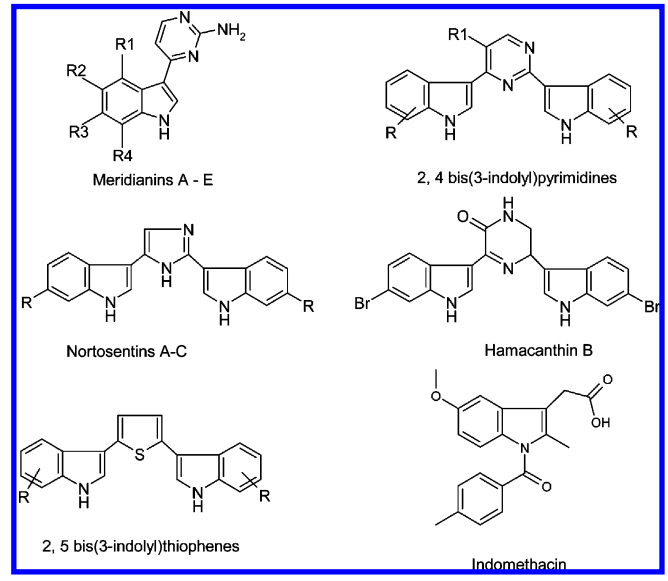

Figure 1. Representatives of 3-substituted indoles.

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Scheme 1

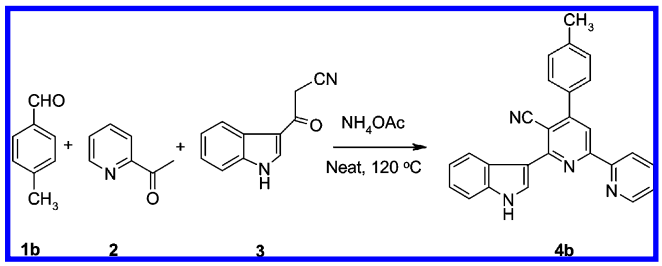


Table 1. Screening of Various Solvents

entry	solvent	yield (%)[a,b]
1	DMF	64
2	Methanol	79
3	Acetonitrile	78
4	Water	83
5	Ethanol	72
6	Neat (120 °C)	87

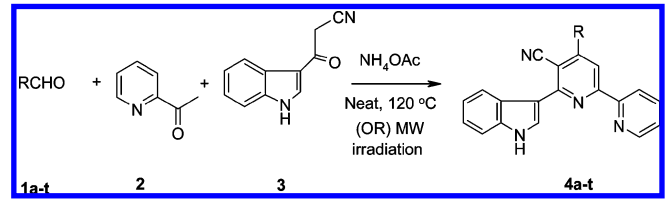
[a] Isolated yield after column chromatography. [b] All the reactions were carried out for 6 h.

heterocyclic compounds and use of green chemical techniques in organic synthesis,[21−23] herein, we report a simple and facile one pot procedure for the synthesis of indol-3-yl pyridine derivatives under neat condition.

2.0. Result and Discussion

Initial studies were carried out with a reaction of *p*-tolualdehyde (**1b**), 2-acetylpyridine (**2**), and 3-cyanoacetyl indole (**3**)[24] in the presence of ammonium acetate in various solvents at reflux temperature. (Scheme 1, Table 1) Excellent results were obtained under neat condition at 120 °C with high yield of the product in a shorter reaction time. (Table 1, entry 6) So we followed the reaction that employs the heating of mixture of aldehyde, 2-acetylpyridine, 3-cyanoacetyl indole, and ammonium acetate at 120 °C. Under these conditions, the reaction proceeded smoothly with a wide range of functionalized aldehydes, including those

Scheme 2. Synthesis of 6-(Indol-3-yl)-2,2′-bipyridine Derivatives from Various Substituted Aldehydes



containing ether, nitro, halogens, heterocyclic and polyaromatic groups.(Scheme 2) Then, we next extended our investigation to the microwave irradiated synthesis of 6-(indol-3-yl)-2,2′-bipyridine derivatives. The yield of the product is good on comparison with that obtained by the conventional method. The results are summarized in Table 2, Method A.

On the basis of the above results, a tentative mechanistic interpretation to explain the formation of 6-(indol-3-yl)-2,2′-bipyridine derivatives (Scheme 3) is proposed. Initially, aryl aldehyde **1** reacts with 3-(cyanoacetyl)indole **3** to form the unsaturated ketone **3a**, which in turn adds 2-acetylpyridine (**2**, in its enol form **2′**) to give compound **3b/3b′**. Then, the latter **3b′** reacts with ammonium acetate to form an intermediate **3c/3c′**, which by elimination of water gives the Hantzsch 1,4-dihydropyridine **3d**. Under the reaction conditions the latter undergoes ready dehydrogenation to the aromatized pyridine derivative **4**.

The structures of the products **4a-t** were deduced from their IR, ^{1}H NMR, and ^{13}C NMR spectral data. The mass spectra of these compounds displayed (M+H$^+$) peaks at the appropriate *m/z* values. Finally, the structure of **4h** was confirmed unambiguously by single crystal X-ray analysis (Figure 2).

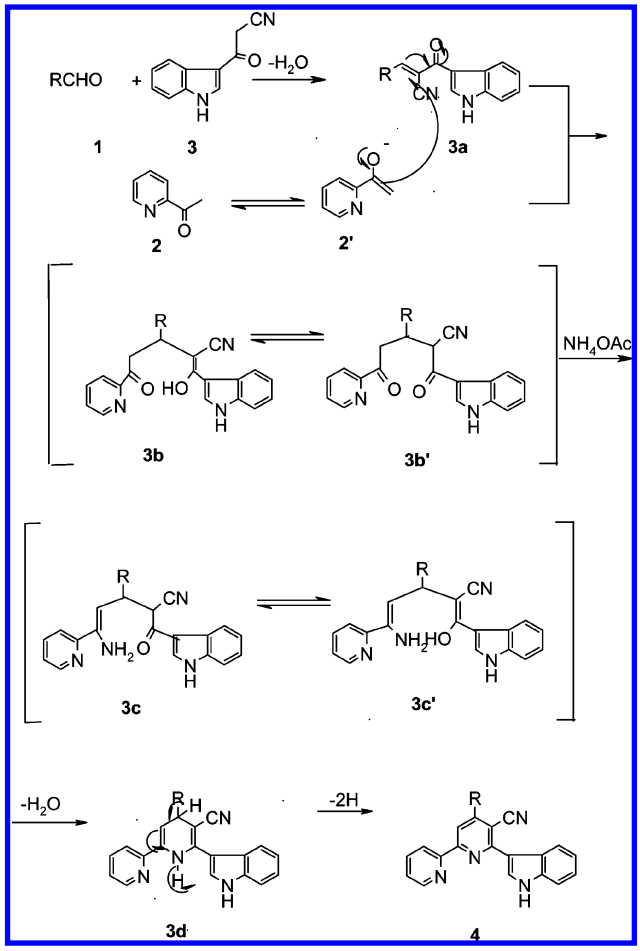
On the other hand, the same reaction proceeding with 2,4-dichlorobenzaldehyde under optimized conditions resulted in Hantzsch 1,4-dihydropyridine derivatives, whereas all other aldehydes yielded only pyridine derivatives. For entry **1u**, the conventional heating gave 78% yield of Hantzsch

Table 2. Synthesis of 6-(Indol-3-yl)-2,2′-bipyridine Derivatives

			method A[b]				method B[c]			
			conventional heating		microwave irradiation		conventional heating		microwave irradiation	
entry	R	product[a]	time (h)	yield (%)[d]	time (min)	yield (%)[d]	time (h)	yield (%)[d]	time (min)	yield (%)[d]
1	Phenyl (**1a**)	**4a**	6.0	86	17	88	5.0	90	12	93
2	4-Methylphenyl (**1b**)	**4b**	5.5	87	14	88	4.5	91	11	94
3	3-Methylphenyl (**1c**)	**4c**	6.0	81	15	82	5.5	86	12	88
4	4-Methoxyphenyl (**1d**)	**4d**	5.5	88	14	90	5.5	92	14	94
5	4-Dimethoxyphenyl (**1e**)	**4e**	5.5	89	13	91	5.0	92	12	92
6	1-Napthyl (**1f**)	**4f**	6.5	87	18	90	6.0	91	18	92
7	4-Chlorophenyl (**1g**)	**4g**	6.5	80	16	81	6.0	88	14	90
8	4-Bromophenyl (**1h**)	**4h**	6.5	79	17	82	5.5	86	15	89
9	4-Fluorophenyl (**1i**)	**4i**	6.0	78	16	79	6.0	87	16	87
10	3-Nitrophenyl (**1j**)	**4j**	6.5	76	17	77	5.5	86	13	86
11	3-Nitrophenyl (**1k**)	**4k**	6.5	76	17	78	5.5	82	14	84
12	3-Bromophenyl (**1l**)	**4l**	5.5	72	18	77	4.5	81	14	83
13	2-Bromophenyl (**1m**)	**4m**	7.5	71	18	76	6.5	76	14	78
14	2-Chrolophenyl (**1n**)	**4n**	7.5	71	18	75	6.5	80	14	84
15	2-Furo (**1o**)	**4o**	6.5	79	15	81	5.5	82	12	85
16	Indol-3-yl (**1p**)	**4p**	6.5	71	18	75	6.0	81	13	82
17	4-Pyridyl (**1q**)	**4q**	6.5	76	16	81	6.0	82	14	85
18	2-Pyridyl (**1r**)	**4r**	7.5	78	18	82	6.5	86	14	89
19	1-Imadazolyl (**1s**)	**4s**	6.5	67	16	72	5.0	77	12	84
20	2-Thienyl (**1t**)	**4t**	6.0	69	17	72	5.0	78	13	81

[a] All the products were characterized by IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopy. [b] All reaction were carried without urea nitrate under optimized condition. [c] All reaction were carried with urea nitrate under optimized condition. [d] Isolated yield of the product.

Scheme 3. Plausible Mechanism for the Formation of 6-(Indol-3-yl)-2,2′-bipyridine Derivatives



dihydropyridine derivative in 6 h, and the microwave reaction yielded up to 81% in 18 min. (Scheme 4).

The structure of Hantzsch 1,4-dihydropyridine (**5**) was thoroughly investigated with spectral (IR, ^{1}H NMR, ^{13}C NMR), elemental, and single crystal X-ray diffraction studies. The ORTEP diagram of compound **5** shown in Figure 3.

Non-aromatized dihydropyridine derivative (**5**) was further oxidized by using urea nitrate as the catalyst. Urea nitrate in solvent slowly releases nitric acid which is involved in the oxidation reaction. Since urea nitrate is inexpensive and easy to prepare, we explored the ability to catalyze the oxidation reaction in a shorter reaction time.[25] A 20 mol % of urea nitrate used for the oxidation of non-aromatized product (**5**) in ethanol gave 86% yield of pyridine derivative (**6**) under microwave irradiation.

The compound **6** was fully characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry. The spectral data was in good agreement with their structure. Further, the structure

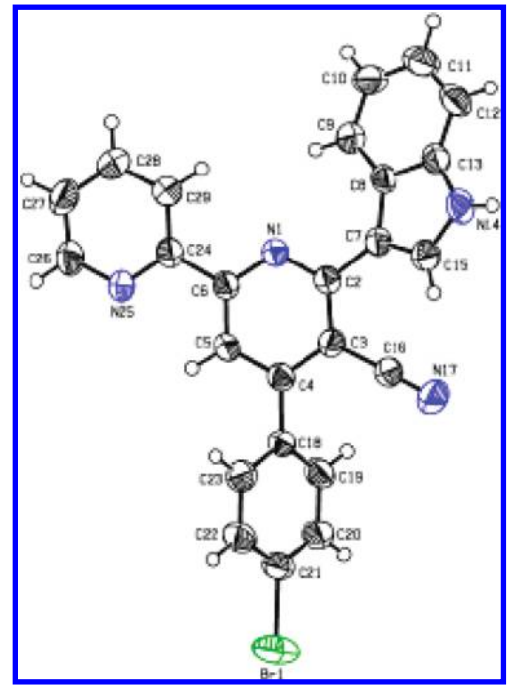


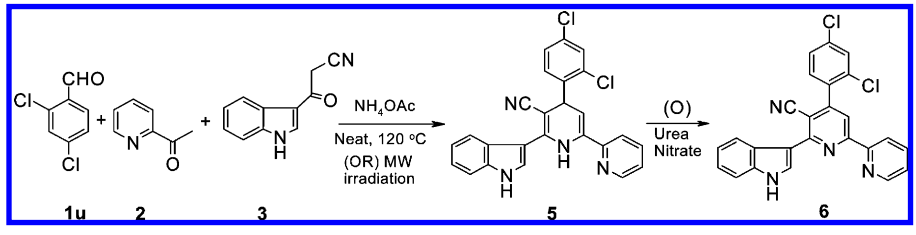
Figure 2. ORTEP diagram of compound **4h**.

of the compound was confirmed by single crystal X-ray diffraction analysis.[29] (Figure 4).

We modified the protocol by adding urea nitrate in the reaction mixture. (Table 2, entry 1−20) Addition of urea nitrate 20 mol % helped to improve the yield product (**4a**−**t**) considerably in a shorter reaction time. (Table 2, Method B).

Many bis(bipyridyl) derivatives are capable of forming multi nuclear complexes. Fused pyridines are useful substructures in the design of supramolecular compounds. These chelating ligands show high affinities for transition metal ions and which frequently stabilize unusually low oxidation state species because of both dπ*-pπ* back-bonding by the cations and their capacity to form ligated anion radicals.[26] We extended our protocol to the synthesis of bis(6-(indol-3-yl)-2,2′-bipyridine) derivatives under optimized conditions. Terephthaldialdehyde (0.5 mmol), 3-cyanoacetyl indole (1 mmol), and 2-acetyl pyridine under optimized conditions gave bis(6-(indol-3-yl)-2,2′-bipyridine) derivative in good yield. The reaction took a longer time for the complete formation of the product. The crude product was precipitated in ice cold water, filtered, washed with ethanol, and then dried. The isolated product was further purified by recrystallization with DMF, and the isolated yield was 68% in Method A. By the addition of 20 mol % of urea nitrate to the reaction mixture the yield of the product was increased up to 76%. (Method B, Scheme 5).

Scheme 4. Synthesis of Dihydro Pyridine Derivative



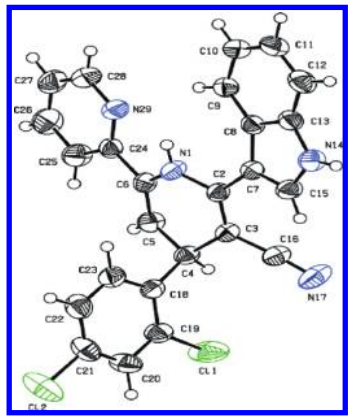


Figure 3. ORTEP diagram of compound **5**.

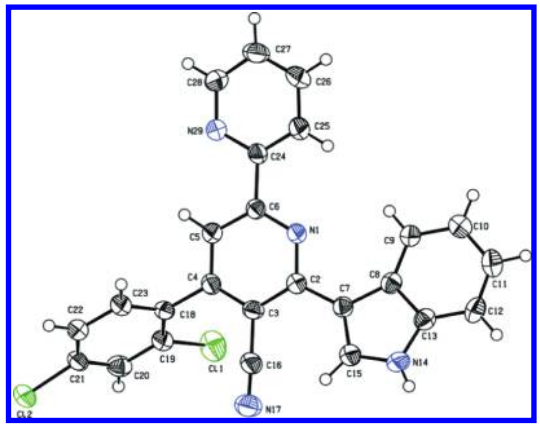


Figure 4. ORTEP diagram of compound **6**.

The structure of bis(6-(indol-3-yl)-2,2′-bipyridine) derivative was thoroughly characterized based on IR, ^{1}H NMR, ^{13}C NMR spectral studies, and elemental analysis. The mass spectra of products displayed (M+H$^+$) peaks at the appropriate *m/z* values.

To study the unique supramolecular properties of oligopyridinyl derivatives, we extended our protocol to the synthesis of bis(indol-3-yl pyridine) spacers under optimized conditions. Oligopyridines are extremely versatile ligands for the assembly of metallosupramolecular systems and enantioselective asymmetric synthesis.[27,28] 1,6-Diarylhexa-l,5-diene-3,4dione, 3-cyanoacetyl indole, and ammonium acetate under reflux condition gave bis(3-indolyl pyridine) in good yield. (Table 3, Method A and Scheme 6) To further explore the utility of bis(indol-3-yl pyridine) derivative, reaction under the optimized conditions were investigated, and the reaction was amendable to a variety of substituent's on cinnamils bearing ethers, chloro, bromo, and hydrocarbons. Addition of 20 mol % of urea nitrate was facilitated to improve the yield of all the products **10a**−**g** in a shorter reaction time. (Table 3, Method B).

The structures of compounds **(10a**−**g)** were evaluated based on detailed IR, ^{1}H NMR, ^{13}C NMR, mass spectral studies, and elemental analysis. The spectral data were in good agreement with their structures.

In contrast, the reaction proceeded with 1,6-diarylhexa-l,5-diene-3,4dione, dimedone, and ammonium acetate under optimized condition to give bis(indol-3yl dihydropydine) derivatives in moderate yields. The scope of the reaction was further extended to various substituted cinnamils bearing ethers, bromo, and hydrocarbons. (Table 4, Method A and Scheme 7**)** However, addition of 20 mol % of urea nitrate to reaction mixture of compounds **12a**−**f** did not lead to the formation of pyridine derivatives. The structures of compounds (**12a**−**f**) were examined based on detailed spectroscopic studies like IR, ^{1}H NMR, ^{13}C NMR spectral studies, and elemental analysis.

Encouraged by the above results, we extended our protocol to the synthesis of 2-(2-furo)6-(indol-3-yl)pyridine derivatives

Scheme 5. Synthesis of Bis(6-(indol-3-yl)-2,2′-bipyridine) Derivative

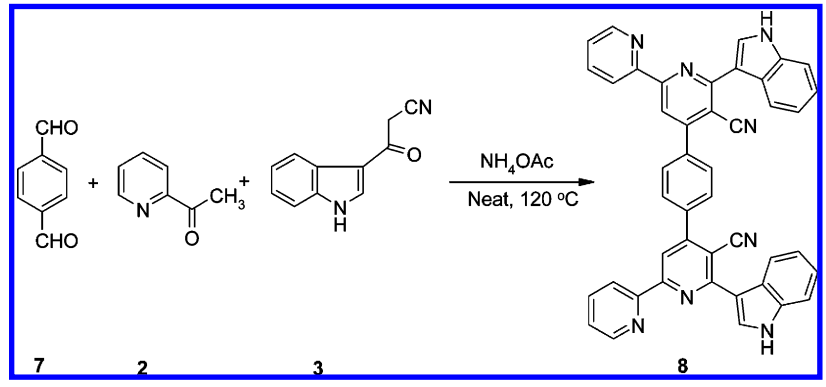


Table 3. Synthesis of 6,6′-Di(1*H*-indol-3-yl)-4,4′-diaryl-2,2′-bipyridine-5,5′-dicarbonitrile

			method A[b]		method B[c]	
entry	Ar	product[a]	time (h)	yield (%)[d]	time (h)	yield (%)[d]
1	Phenyl (**9a**)	**10a**	12.0	65	11.0	72
2	4-Methylphenyl (**9b**)	**10b**	11.0	66	10.5	74
3	3-Methylphenyl (**9c**)	**10c**	12.0	62	11.0	68
4	4-Methoxyphenyl (**9d**)	**10d**	10.0	68	9.0	74
5	3,4-Dimethoxyphenyl (**9e**)	**10e**	11.0	70	11.5	76
6	4-Chlorophenyl (**9f**)	**10f**	12.0	58	11.0	66
7	4-Bromophenyl (**9g**)	**10g**	12.0	55	11.0	64

[a] All the products were characterized by IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopy. [b] All reactions were carried without urea nitrate under optimized conditions. [c] All reactions were carried with urea nitrate under optimized conditions. [d] Isolated yield of the product.

Scheme 6. Synthesis of 6,6′-Di(1*H*-indol-3-yl)-4,4′-diaryl-2,2′-bipyridine-5,5′-dicarbonitrile Derivatives

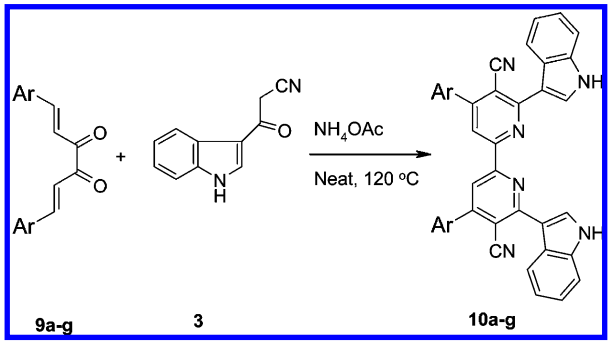


Table 4. Synthesis of 7,7,7′,7′-Tetramethyl-4,4′-bis(aryl)-4,6,7,8,4′,6′,7′,8′-octahydro-1*H*,1*H*-[2,2′]biquinolinyl-5,5′-dione derivatives

			method A[b]	
entry	Ar	product[a]	time (h)	yield (%)[c]
1	Phenyl (**9a**)	**12a**	12.0	55
2	4-Methylphenyl (**9b**)	**12b**	11.0	56
3	3-Methylphenyl (**9c**)	**12c**	11.5	48
4	4-Methoxyphenyl (**9d**)	**12d**	12.0	58
5	3,4-Dimethoxyphenyl (**9e**)	**12e**	11.0	52
6	4-Bromophenyl (**9f**)	**12f**	14.0	42

[a] All the products were characterized by IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopy. [b] All reaction were carried without urea nitrate under optimized conditions. [c] Isolated yield of the product.

under optimized conditions. 2-Acetylfuran (1 mmol) and aldehyde (1 mmol) in ammonium acetate were refluxed at 120 °C for 1−2 h (monitored by TLC). After complete disappearance of both starting materials, 3-cyanoacetyl indole (1 mmol) was added, and the refluxing was continued for 4−6 h. Finally the reaction mixture was poured into water and extracted with ethyl acetate, and the organic layer was dried with sodium sulfate. The crude product was purified using column chromatography. The isolated product was further purified by recrystallization in ethanol to obtain good yield of 2-(2-furo)6-(indol-3-yl)pyridine derivatives. (Table 5 Method A and Scheme 8) The scope of the reaction was further extended to various substituted aldehydes bearing ether, chloro, bromo, nitro, and heterocycles. Addition of 20 mol % of urea nitrate to the reaction mixture enhanced the yield of **14a**−**j** considerably as shown Table 5, Method B.

All aldehydes **1a**−**j** reacted with 2-acetylfuran to form the 2-furopyridine derivatives, whereas 2, 4-dichlorobenzaldehyde reacted with 2-acetylfuran to yield 64% of 2-furodihydropyridine derivative under optimized condition. (Scheme 9, Method A).

The structure of furo Hantzsch 1,4-dihydropyridine (**15**) was thoroughly characterized with IR, ^{1}H NMR, ^{13}C NMR spectral studies and elemental analysis. The mass spectra of products displayed (M+H$^+$) at the appropriate *m*/*z* values.

Furodihydropyridine derivative (**15**) was oxidized by using urea nitrate as a catalyst. A 20 mol % of urea nitrate used for the oxidation of non-aromatized product (**15**) in ethanol gave 78% yield of pyridine derivative (**16**) under microwave irradiation.

The structure and purity of the compound (**16**) was thoroughly analyzed with IR, ^{1}H NMR, ^{13}C NMR spectral studies and elemental analysis. The data was in agreement with their structure.

Scheme 7. Synthesis of 7,7,7′,7′-Tetramethyl-4,4′-bis(aryl)-4,6,7,8,4′,6′,7′,8′-octahydro-1*H*,1*H*-[2,2′]biquinolinyl-5,5′-dione Derivatives

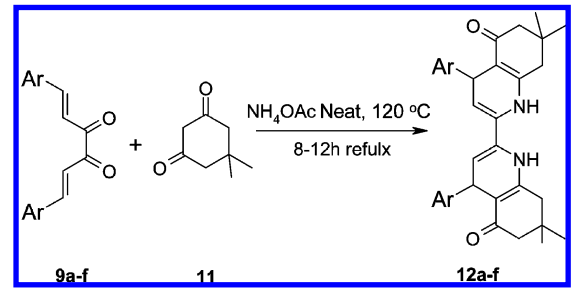
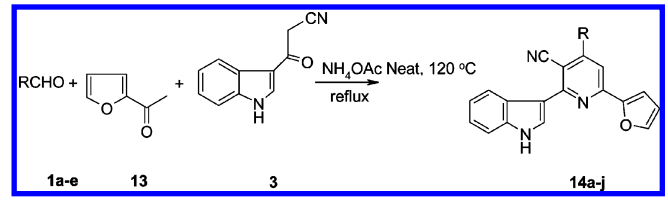


Table 5. Synthesis of 2-(Furo)-6-(indol-3-yl) Pyridine Derivatives

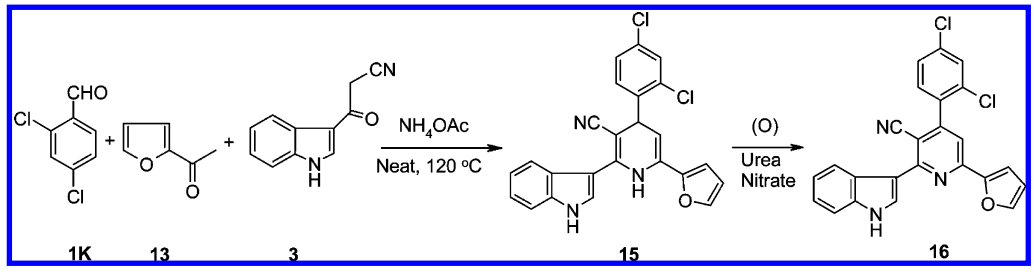
			method A[b]		method B[c]	
entry	Ar	product[a]	time (h)	yield (%)[d]	time (h)	yield (%)[d]
1	4-Methylphenyl (**1a**)	**14a**	6.0	74	5.0	79
2	4-Chlorophenyl (**1b**)	**14b**	7.0	71	6.0	77
3	3-Nitrophenyl (**1c**)	**14c**	7.5	68	6.5	74
4	4-Fluorophenyl (**1d**)	**14d**	7.0	70	6.5	75
5	4-Bromophenyl (**1e**)	**14e**	7.0	76	6.5	81
6	3-Bromophenyl (**1f**)	**14f**	7.5	76	6.0	78
7	4-Pyridinyl (**1g**)	**14g**	7.0	79	5.5	79
8	2-Pyridinyl (**1h**)	**14h**	6.5	73	6.0	81
9	2-Thienyl (**1i**)	**14i**	7.0	76	6.5	81
10	Indol-3-yl (**1j**)	**14j**	7.5	77	6.0	82

[a] All the products were characterized by IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopy. [b] All reaction were carried without urea nitrate under optimized conditions. [c] All reaction were carried with urea nitrate under optimized conditions. [d] Isolated yield of the product.

Scheme 8. Synthesis of 2-(Furo)-6-(indol-3-yl) Pyridine Derivatives



Scheme 9. Synthesis of 2-(Furo)-6-(indol-3-yl) Pyridine Derivatives



3.0. Conclusions

In summary, we have demonstrated a simple, facile, and eco-friendly synthetic methodology for indol-3-yl pyridinyl derivatives through multicomponent reaction. The versatility of this chemistry offers a valuable addendum to methodology for the synthesis of Kr€ohnke pyridines. Further studies to delineate the scope and limitations of the present methodology are underway.

4.0. Experimental Section

4.1. General Procedures. All the substituted aldehydes, 2-acetylpyridine, indole and DMSO-d_6 were purchased from Aldrich Chemicals. Acetic anhydride and other reagents were procured from S. D. Fine. Chem. Limited and were used as received. IR measurements were done as KBr pellets for solids using Perkin-Elmer Spectrum RXI FT-IR. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 using TMS as internal standard with JEOL ECA-500 MHz and Bruker 400 and 500 MHz high resolution NMR spectrometer. Multiplicities were abbreviated as follows: singlet (s), doublet (d), triplet (t), multiplet (m), and broad (br). The mass spectra were recorded using a Electrospray Ionization Method with a Thermo Finnigan mass spectrometer. Melting points were determined in capillary tubes and are uncorrected. Analytical TLC was performed on precoated plastic sheets of silica gel G/UV-254 of 0.2 mm thickness (Macherey-Nagel, Germany). Elemental analysis data were recorded using Thermo Finnigan FLASH EA 1112 CHN instrument.

4.2. Synthesis of 6-(Indol-3-yl)-2,2′-bipyridine Derivatives. Method: A. (i). Conventional Heating. A mixture of 3-cyanoacetyl indole (1 mmol), aldehyde (1 mmol) and 2-acetylpyridine (1 mmol) in 5 g of ammonium acetate under neat condition was refluxed at 120 °C for an appropriate time mentioned as in Table 2, Method A. After the completion of the reaction (as monitored by TLC), it was poured into water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated under vacuum. The crude product was chromatographed, and the isolated yield is shown in Table 2, Method A (90:10 petroleum ether/ethyl acetate). The isolated product was further purified by recrystallization in ethanol.

(ii). Microwave Irradiation. A mixture of 3-cyanoacetyl indole (1 mmol), aldehyde (1 mmol) and 2-acetylpyridine (1 mmol) in 5 g of ammonium acetate under neat condition in a sealed tube was irradiated in microwave oven (BPL BMG 800 TS model) at 80W for the appropriate time mentioned in the Table 2, Method A. After completion of the reaction (as monitored by TLC), it was poured into water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated under vacuum. The crude product was chromatographed, and the appropriate isolated yield is shown in Table 2, Method A (90:10, petroleum ether/ethyl acetate). The product was further purified by recrystallization in ethanol.

Method: B. (i). Conventional Heating. A mixture of 3-cyanoacetyl indole (1 mmol), aldehyde (1 mmol), 20 mol % of urea nitrate, and 2-acetylpyridine (1 mmol) in 5 g of ammonium acetate under neat condition was refluxed at 120 °C for an appropriate time as mentioned in Table 2, Method B. After the completion of the reaction (as monitored by TLC), it was poured into water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated under vacuum. The crude product was chromatographed, and the isolated yield is shown in Table 2, Method B (90:10 petroleum ether/ ethyl acetate). The isolated product was further purified by recrystallization in ethanol.

(ii). Microwave Irradiation. A mixture of 3-cyanoacetyl indole (1 mmol), aldehyde (1 mmol), 20 mol % of urea nitrate and 2-acetylpyridine (1 mmol) in 5 g of ammonium acetate under neat condition in a sealed tube was irradiated in a microwave oven (BPL BMG 800 TS model) at 80W for the appropriate time mentioned in the Table 2, Method B. After completion of the reaction (as monitored by TLC), it was poured into water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated under vacuum. The crude product was chromatographed, and the appropriate isolated yield is shown in Table 2, Method B (90:10, petroleum ether/ethyl acetate). The product was further purified by recrystallization in ethanol.

4.3. Oxidation of 4-(2,4-Dichlorophenyl)-6-(1*H*-indol-3-yl)-1,4-dihydro-2,2′-bipyridine-5-carbonitrile. A mixture of 4-(2,4-dichlorophenyl)-6-(1*H*-indol-3-yl)-1,4-dihydro-2,2′-bipyridine-5-carbonitrile **6a** (1 mmol) and urea nitrate (20 mol %) was irradiated in a microwave oven in ethanol for 5 min. After completion of the reaction (as monitored by TLC), it was poured into water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated under vacuum. The crude product was chromatographed and isolated in 86% yield (90:10 petroleum ether/ethyl acetate).

4.4. Synthesis of Phenyl-1,4-bis(6-(1*H*-indol-3-yl)-2,2′-bipyridine-5-carbonitrile). Method A. A mixture of 3-cyanoacetyl indole (1 mmol), aldehyde (0.5 mmol), and 2-acetylpyridine (1 mmol) in 5 g of ammonium acetate under neat condition was refluxed at 120 °C for 8 h. After the completion of the reaction (as monitored by TLC), it was poured into water and then filtered. The residue was washed with ethanol and then dried. The isolated product was further purified by recrystallization in ethanol.

Method B. A mixture of 3-cyanoacetyl indole (1 mmol), aldehyde (0.5 mmol), 20 mol % urea nitrate, and 2-acetylpyridine (1 mmol) in 5 g of ammonium acetate under neat condition was refluxed at 120 °C for 8 h. After the completion of the reaction (as monitored by TLC), it was poured into water and then filtered. The residue was washed with ethanol and then dried. The isolated product was further purified by recrystallization in ethanol.

4.5. Synthesis of 6,6′-bis-(1*H*-indol-3-yl)-4-4′-diaryl-[2,2′]bipyridinyl-5,5′-dicarbonitrile. Method A. A mixture of 3-cyanoacetyl indole or dimedone (2 mmol), cinnamil (1 mmol), and 5 g of ammonium acetate under neat condition was refluxed at 120 °C for appropriate time mentioned as in Table 3, Method A and Table 4. After the completion of the reaction (as monitored by TLC), it was poured into water and then filtered, washed with acetone, and then dried. The obtained crude solid was purified further by recrystallization

with DMF, and the appropriate isolated yield is shown in Table 3, Method A and Table 4.

Method B. A mixture of 3-cyanoacetyl indole (2 mmol), cinnamil (1 mmol), 20 mol % urea nitrate, and 5 g of ammonium acetate under neat condition was refluxed at 120 °C for an appropriate time as mentioned in Table 3, Method B After the completion of the reaction (as monitored by TLC), it was poured into water and then filtered, washed with acetone, and then dried. The obtained crude solid was purified further by recrystallization with DMF, and the appropriate isolated yield is shown in Table 3, Method B.

4.6. Synthesis of 2-(2-Furo)-6-(indol-3-yl)pyridine Derivatives. Method A. A mixture of aldehyde (1 mmol) and 2-acetylfuran (1 mmol) in 5 g of ammonium acetate under neat condition was refluxed at 120 °C for 1−2 h. After complete disappearance of the starting materials, 3-cyanoacetyl indole was added, and the reflux was continued for an appropriate time as mentioned in Table 5, Method A. After completion of the reaction (as monitored by TLC), it was poured into water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated under vacuum. The crude product was chromatographed and isolated yield is shown in Table 5, Method A (90:10 petroleum ether/ethyl acetate). The isolated product was further purified by recrystallization in ethanol.

Method B. A mixture of aldehyde (1 mmol) and 2-acetylfuran (1 mmol) in 5 g of ammonium acetate under neat condition was refluxed at 120 °C for 1−2 h. After complete disappearance of the starting materials, 3-cyanoacetyl indole and 20 mol % of urea nitrate was added, and the reflux was continued for appropriate time mentioned in Table 5, Method B. After the completion of the reaction (as monitored by TLC), it was poured into water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated under vacuum. The crude product was chromatographed, and the isolated yield is shown in Table 5, Method B (90:10 petroleum ether/ethyl acetate). The isolated product was further purified by recrystallization in ethanol.

4.7. Oxidation of 4-(2,4-Dichlorophenyl)-6-(2-furyl)-2-(1*H*-indol-3-yl)-1,4-dihydropyridine-3-carbonitrile. A mixture of 4-(2,4-dichlorophenyl)-6-(2-furyl)-2-(1*H*-indol-3-yl)-1,4-dihydropyridine-3-carbonitrile (1 mmol) and urea nitrate (20 mol %) was irradiated in a microwave oven in ethanol for 5 min. After completion of the reaction, (as monitored by TLC) it was poured into water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated under vacuum. The crude product was chromatographed and isolated in 78% yield (90:10 petroleum ether/ethyl acetate).

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Supporting Information Available. Additional information as noted in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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