A Four Components, One-Pot Synthesis of New Imidazole Molecular Tweezers Based on 2,4,6-Triarylpyridine as Hinge Region

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ABSTRACT: *In the present study, some new bis-imidazole derivatives have been prepared through four-components condensation of 2,6-bis (4-aminophenyl)-4-p-tolylpyridine, benzaldehyde derivatives, benzil and ammonium acetate in presence of acetic acid. The present methodology offers several advantages such as good yields, simple procedure, milder conditions and the possibility of introducing a variety of substituents at different positions of the imidazole and pyridine rings. These new compounds were confirmed by spectral methods ^{1}H NMR, ^{13}C NMR, FT-IR, and elemental analyses. Also, optimized geometries and chemical shifts have been calculated for the synthesized compounds using Density Functional Theory (DFT) method. Their optimized geometries are not planar.*

KEYWORDS: *Bis-imidazole; One-pot reaction; Triaryl pyridine; Heterocycles; Molecular tweezers.*

INTRODUCTION

Multi-Component Reactions (MCRs) are efficient way to access heterocycles due to their environmental friendliness, and the ease of access to a wide range of diverse, highly functionalized molecules, in a single event without need to isolate any intermediate, which reduces time, saves initial reactants, and increases yield [1].

Compounds containing aromatic heterocyclic segments, e.g. pyridine and imidazole, are used as pharmaceuticals, agrochemicals, veterinary, dyes, light-emitting devices, and also in qualititative and quantitative analysis [2-9].

It has also been reported that derivatives of imidazole and pyridine condensed nucleus used for explosive detection [10]. The method has been reported for synthesis of these compounds, have suffered from one or more drawbacks like low yields, longer reaction times, use of expensive reagents, lack of generality and were not suitable for, or were not applied for the synthesis of structurally diverse molecular tweezers [11].

The most convenient procedure for the synthesis of bis-imidazole derivatives is based on the reaction of benzil, dialdehyde and ammonium acetate in refluxing acetic acid [12].

Nevertheless, to date there have been no report that produces the bis-imidazole derivatives containing triaryl pyridines. We report herein the experimental procedures

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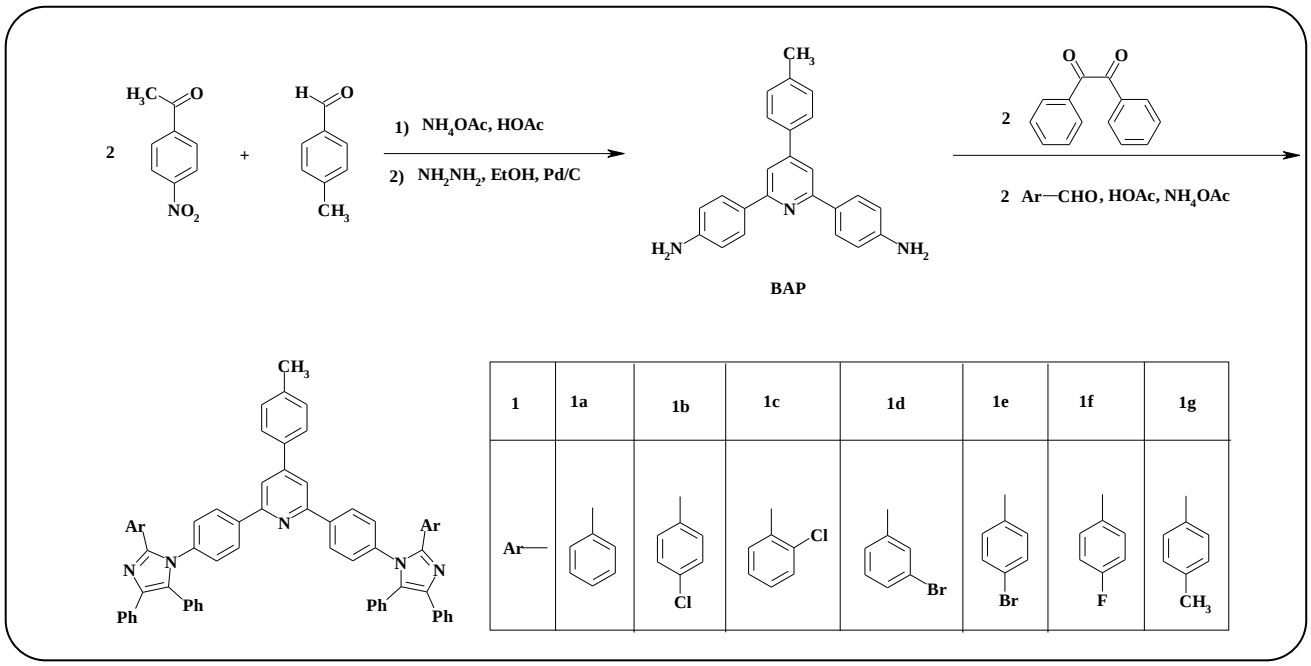

Fig. 1: Synthesis route to 2,6-bisimidazole derivatives.

for synthesis of new bis-imidazole derivatives from benzil, various aromatic aldehydes, 2,6-bis (4-aminophenyl)-4-*p*-tolylpyridine and ammonium acetate in acetic acid (Fig. 1). This method offers some advantages such as, produces bis-imidazoles with tetra-substituted aryl ring, instead of three-substituted ring and diamine as reactant is more available than dialdehyde.

EXPERIMENTAL SECTION

All yields refer to isolated products. Melting points were measured on an Electro Thermal Stuart SMP3 apparatus and uncorrected. The IR spectra were recorded as KBr pellets on a Bruker Tensor 27 FT-IR spectrophotometer. The NMR spectra were recorded with a DRX 500-MHZ spectrometer operating at a resonance frequency of 499.89 MHz for the ^{1}H-NMR spectra and 125.71 MHz for the ^{13}C-NMR spectra in $CDCl_3$ as solvent, using TMS as an internal standard. Chemical shifts are expressed as ppm δ units. The mass spectra were scanned on a Varian Mat CH-7 instrument at 70 eV. Elemental analysis was run in a Flash EA 1112 series analyzer.

Typical procedure

In a round-bottomed flask (25 ml) equipped with a reflux condenser, a mixture of 2,6-bis (4-aminophenyl)-4-*p*-tolylpyridine (1 mmol, 0.351 g), aromatic aldehyde (2 mmol), benzil (2 mmol, 0.42 g), ammonium acetate (2 mmol, 0.16 g) and acetic acid (10 ml) was refluxed for 2 h. Upon cooling, crystals separated which were filtered and washed with cold ethanol and then dried at 60 °C under vacuum.

COMPUTATIONAL DETAILS

All the calculations have been performed by using the gradient-corrected DFT method with the B3LYP functional [13], where the 6-31G(d,p) basis set was employed. The Gaussian 03 program package was used with its default procedures.

First, geometry of the compound (**1b**) was fully optimized in the gas phase. The optimized geometry was confirmed to have no imaginary frequency. Then, the gas phase optimized geometry was used to compute the ^{1}H- and ^{13}C-NMR chemical shifts of the compound. The chemical shifts were predicted with respect to tetramethylsilane. The GIAO method was used for prediction of the DFT nuclear shielding [14].

NMR spectra

For more clarification, the optimized geometry of the compound (**1b**) is shown in Fig. 2 in two different views.

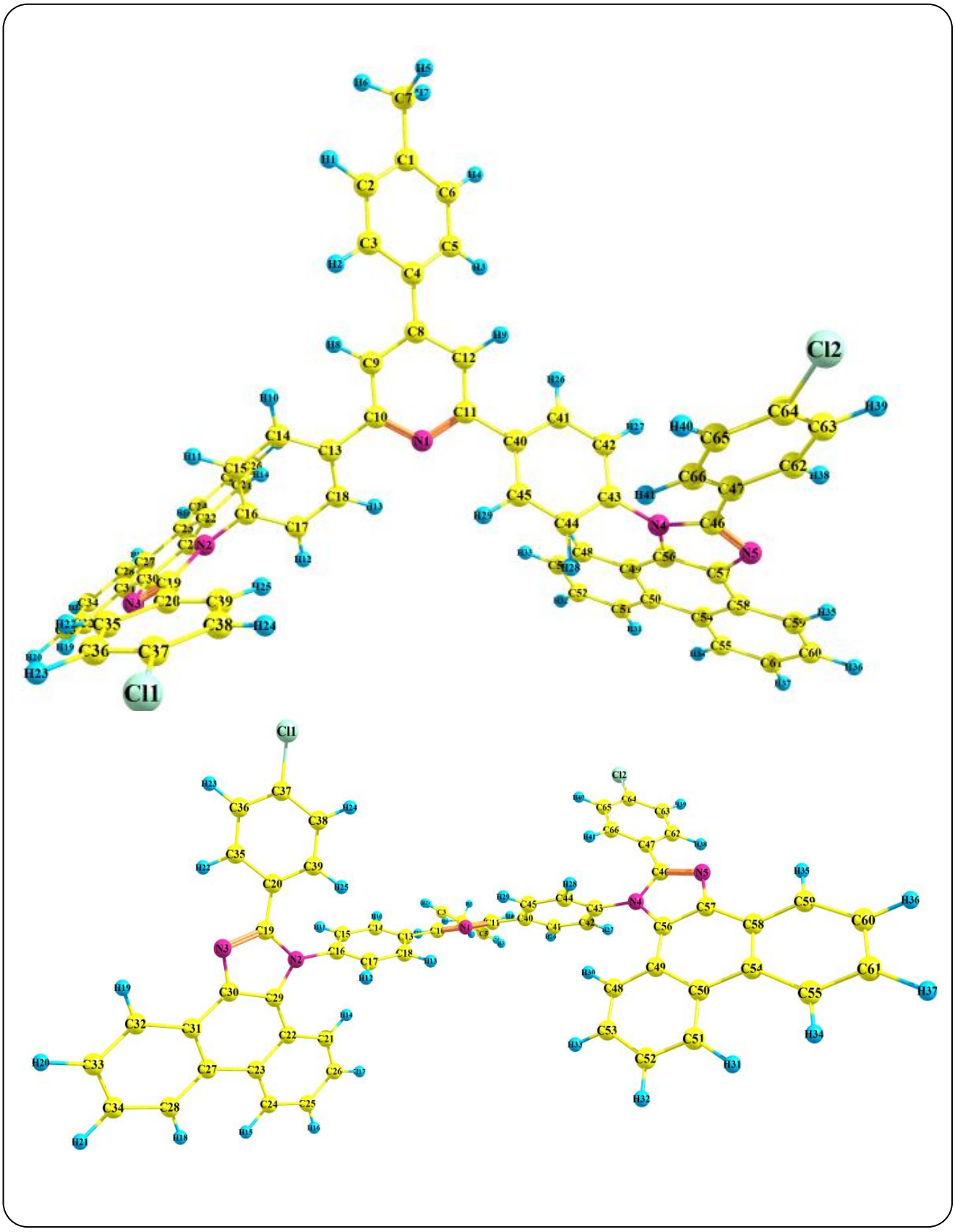

Fig. 2: The B3LYP optimized geometry of the compound (1b).

All of the bond lengths are in the expected ranges. The molecule is not planar, but, both side of the molecule are roughly perpendicular to the central part of the molecule. The C58-C49-C44-C41, C49-C48-C45-C40, C32-C21-C17-C14 and C30-C29-C18-C30 dihedral angles are 107.9, 109.9, -110.4 and -105.4º, respectively. While, the aromatic rings of the central section are roughly in the same plane. The calculated C2-C3-C9-C10 and C6-C5-C12-C11 dihedral angles are 174.5and 173.9º, respectively. Also, the calculated C9-C10-C13-C18, C12-C11-C40-C45 and C40-C45-C18-C13 dihedral angles are 154.3, 153.3 and -43.0º, respectively.

Nowadays, Theoretical assignment of the IR and NMR spectra can be employed as an useful method for identification of chemical species [15-18]. The theoretical ^{1}H- and ^{13}C-NMR chemical shifts (δ) of the compound (**1b**) are given in Table 1, where the atom positions are numbered as in Fig. 2. As seen, the calculated chemical shifts are in good agreement with the experimental values, confirming suitability of the optimized geometry for the compound (**1b**).

RESULTS AND DISCUSSION

As the starting material, 2,6-bis (4-aminophenyl)-4-*p*-tolylpyridine (BAP) was prepared in two step as formerly described [19]. Firstly, the corresponding dinitro compound was synthesized by an Aldol condensation of 4-nitroacetophenone with 4-methylbenzaldehyde and after losing of water and Michael addition to the second mole of 4-nitroacetophenone, leading to an intermediate (1,3,5-triaryl-1,5-diketone). Then through the ring closure by ammonium acetate as nitrogen source and air oxidation, the dinitro compound can be obtained [20]. Diamine (BAP) was readily obtained in high yield by the Pd/C-catalyzed reduction of the dinitro compound with hydrazine monohydrate in refluxing ethanol.

The structures of bis-imidazoles (**1a-g**) were confirmed by FT-IR, ^{1}H NMR, ^{13}C NMR spectroscopy and elemental analysis. The ^{1}H NMR spectra of **1a-g** showed the expected multiplicity and integration values. The ^{1}H NMR spectra of the compounds **1a-g** showed two characteristic singlet signals at δ ~ 2.5 ppm that was attributed to the methyl protons (CH_3), and another at δ ~ 8.2 ppm, was assigned to the protons in pyridine ring. Other signals attributed to 40 protons of aromatic rings. Data from elemental analysis were in good agreement with the calculated values.

4-p-tolyl-2,6- bis(4-(2,4,5-triphenyl-1H-imidazol-1-yl) phenyl)pyridine (1a)

Yield 85%, m.p. 339-341 °C; FT-IR (υ_{max}. cm^{-1}): 3053 (Aromatic C-H stretch), 2917 (Methyl C-H stretch), 1542 (C═N), 1598 (C═C).

^{1}H NMR δ (ppm): 2.44 (s, 3H, —CH_3), 7.15-7.28 (m, 20H, Ar—H), 7.32-7.39 (m, 10H, Ar—H), 7.80 (s, 2H, Pyridine), 7.77 (d, 8H, J = 8 Hz, Ar—H), 8.15 (d, 4H, J = 8.36 Hz, Ar—H).

^{13}C NMR δ (ppm): 21.31, 117.24, 126.78, 126.91, 127.51, 127.59, 128.16, 128.23, 128.46, 128.59, 128.69, 129.15, 129.94, 130.27, 130.45, 130.77, 131.19, 134.17, 137.77, 138.36, 138.82, 139.57, 146.97, 150.50, 155.79.

Anal. Calcd. for $C_{66}H_{47}N_5$: C, 87.10; H, 5.21; N, 7.70 Found: C, 87.33; H, 5.05, N, 7.56., MS (m/z): 909.

2,6-bis (4-(2-(4-chlorophenyl)-4,5-diphenyl-1H-imidazol-1-yl)phenyl)-4-p-tolylpyridine(1b)

Yield 79%, m.p. 336-369 °C; FT-IR (υ_{max}. cm^{-1}): 3060 (Aromatic C-H stretch), 2922 (Methyl C-H stretch), 1542 (C═N), 1600 (C═C), 697 (C—Cl).

^{1}H NMR δ (ppm): 2.44 (s, 3H, —CH_3), 7.15-7.29 (m, 20H, Ar—H), 7.80 (s, 2H, Pyridine), 7.32 (d, 2H, J = 8 Hz, Ar—H), 7.41 (d, 4H, J = 8.4 Hz, Ar—H),7.57-7.62 (m, 6H, Ar—H), 8.12 (d, 4H, J = 8.4 Hz, Ar—H).

^{13}C NMR δ (ppm): 20.25, 116.36,125.77, 125.90, 126.37, 126.68, 127.20, 127.47, 127.52, 127.62, 127.99, 128.93, 129.22, 129.37, 130.05, 130.13, 133.19, 133.42, 136.64, 137.69,138.02, 138.57, 144.82, 154.73.

Anal. Calcd. for $C_{66}H_{45}Cl_2N_5$: C, 80.97; H, 4.63; N, 7.15 Found: C, 81.13; H, 4.45, N, 7.36., MS (m/z): MS (m/z): 981 (M+4).

2,6-bis (4-(2-(2-chlorophenyl)-4,5-diphenyl-1H-imidazol-1-yl)phenyl)-4-p-tolylpyridine(1c)

Yield 76%, m.p. 263-266 °C; FT-IR (υ_{max}. cm^{-1}): 3057 (Aromatic C-H stretch), 2916 (Methyl C-H stretch), 1543 (C═N), 1598 (C═C), 758 (C═Cl).

^{1}H NMR δ (ppm) : 2.41 (s, 3H, —CH_3), 7.06 (d, 4H, J = 8.5 Hz, Ar—H), 7.18-7.31 (m, 24H, Ar—H), 7.72 (s, 2H, Pyridine), 7.53 (t, 4H, J = 8 Hz, Ar—H), 7.59-7.61 (m, 4H, Ar—H), 7.92 (d, 4H, J = 8.25 Hz, Ar—H).

Table 1. Experimental and theoretical ^{1}H- and ^{13}C-NMR chemical shifts of the compound (1b) in $(CD_3)_2SO$ solution, δ [ppm].

Atom position	Theo.	Exp.	Atom position	Theo.	Exp.	Atom position	Theo.	Exp.
C7	22.15	20	C36,C63	124.03	129	H7[a]	2.20, 2.64	2.44
C9	114	116	C15	124.8	129	H65,H66	6.86	7.15-7.29
C12	114.27	116	C42,C54	124.89	129	H21,H36,H53,H63	7.33	7.15-7.29
C21	117.26	125	C6,C27	125.13	130	H2,H6,H15,H25,H42,H48,H52	7.49-7.59	7.15-7.29
C28	118.43	125	C2	125.29	130	H3,H5,H33,H34,H60,H61	7.74-7.82	7.15-7.29
C49	119.29	125	C18,C20,C45	126.06	130	H9,H12,H17,H44	8.01-8.07	7.15-7.29
C52,C22,C25	119.41	125	C44,C56	126.41	130	H9,H8	8.07	7.31-7.33
C51,C24	119.79	125	C17	126.62	130	H41	8.19	7.57-7.62
C26,C32	120.15	126	C23,C50	126.67	130	H14	8.25	7.57-7.62
C34,C53,C59,C61	120.38	126	C35,C62	128.29	130	H62	8.49	7.57-7.62
C60	121.94	126	C4	132.86	133	H35	8.57	7.57-7.62
C33,C65	122.05	127	C30	135.9	136	H28,H55	8.72	7.57-7.62
C38	122.14	127	C57	136.13	136	H24,H51	8.81	7.8
C5	122.68	127	C13,C16,C40, C43	137.66	137	H18,H45,H32,H59	9.11	8.11-8.13
C3	122.8	127	C37,C64	139.01	138			
C39	123.32	128	C19,C46	144.6	138			
C14,C41	123.66	128	C8	148.05	144			
C31,C58	123.88	128	C10,C11	154.05	154			

^{13}C NMR δ (ppm): 20.23, 116.07, 125.53, 125.66, 125.81, 125.99, 126.49, 127.03, 127.13, 127.55, 128.58, 128.67, 128.83, 129.47, 129.73, 130.01, 131.91, 133.27, 133.77, 134.41, 136.03, 137.25, 137.34, 138.42, 144.05, 149.28, 154.74.

Calcd. for $C_{66}H_{45}Cl_2N_5$: C, 80.97; H, 4.63; N, 7.15 Found: C, 81.21; H, 4.72, N, 7.06., MS (m/z): 981 (M+4).

2,6-bis (4-(2-(3-bromophenyl)-4,5-diphenyl-1H-imidazol-1-yl)phenyl)-4-p-tolylpyridine(1d)

Yield 80%, m.p. 275-280 °C; FT-IR (υ_{max}. cm^{-1}): 3060 (Aromatic C-H stretch), 2920 (Methyl C-H stretch), 1542 (C═N), 1598 (C═C).

^{1}H NMR δ (ppm): 2.41 (s, 3H, ——CH_3), 6.96 (d, 4H, J = 8 Hz, Ar—H), 7.20-7.29 (m, 20H, Ar—H), 7.32 (d, 2H, , J = 8 Hz, Ar—H), 7.31 (s, 2H, Pyridine —H), 7.50 (t, 4H, J = 8.4 Hz, Ar—H), 7.60 (d, 6H, J = 8.3 Hz, Ar—H), 8.11 (d, 4H, J = 8.4 Hz, Ar—H).

^{13}C NMR δ (ppm): 20.23, 114.6, 114.78, 116.57, 125.42, 125.67, 125.86, 126.16, 126.43, 126.71, 127.43, 127.92, 128.04, 128.46, 128.67, 129.62, 129.98, 130.08, 133.53, 133.87, 135.61, 135.80, 138.93, 144.51, 154.34.

20,114,114,116,125,125,125,126,126,127,127,127,127,128,128,129,129,130,138,154.

Calcd. for $C_{66}H_{45}Br_2N_5$: C, 74.23; H, 4.25; N, 6.56 Found: C, 74.12; H, 4.47, N, 6.28., MS (m/z): 1069 (M+4).

2,6-bis (4-(2-(4-bromophenyl)-4,5-diphenyl-1H-imidazol-1-yl)phenyl)-4-p-tolylpyridine(1e)

Yield 83%, m.p. 334-337 °C; FT-IR (υ_{max}. cm^{-1}): 3056 (Aromatic C-H stretch), 2923 (Methyl C-H stretch), 1542 (C═N), 1599 (C═C).

^{1}H NMR δ (ppm): 2.44 (s, 3H, ——CH_3), 7.15-7.28 (m, 20H, Ar—H), 7.87 (s, 2H, Pyridine), 7.42 (d, 4H, J = 8 Hz, Ar—H), 7.32 (d, 2H, J = 8 Hz, Ar—H), 7.57-7.65 (m, 6H, Ar—H), 8.16 (d, 4H, J = 8.4 Hz, Ar—H)

^{13}C NMR δ (ppm): 20.27, 116.38, 121.73, 125.78, 125.90, 126.37, 126.69, 127.20, 127.52, 127.60, 128.41, 128.92, 129.33, 129.45, 130.11, 130.41, 133.15, 136.60, 138.02, 138.57, 149.50, 154.72.

Calcd. for $C_{66}H_{45}Br_2N_5$: C, 74.23; H, 4.25; N, 6.56 Found: C, 74.38; H, 4.15, N, 6.78., MS (m/z): 1069 (M+4).

2,6-bis(4-(2-(4-fluorophenyl)-4,5-diphenyl-1H-imidazol-1-yl)phenyl)-4-p-tolylpyridine(1f)

Yield 75%, m.p. 320-323 °C; FT-IR (υ_{max}. cm^{-1}): 3057 (Aromatic C-H stretch), 2920 (Methyl C-H stretch), 1513 (C═N), 1606 (C═C).

^{1}H NMR δ (ppm): 2.43 (s, 3H, ——CH_3), 6.96 (t, 4H, J = 8.4 Hz), 7.15-7.33 (m, 24H, Ar—H), 7.51 (t, 4H, J = 8 Hz), 7.60 (d, 4H, J = 8 Hz, Ar—H), 7.87 (s, 2H, Pyridine), 8.12 (d, 4H, J = 8.4 Hz, Ar—H).

^{13}C NMR δ (ppm): 20.26, 114.31, 114.53, 116.41, 125.88, 126.54, 126.69, 127.18, 127.26, 127.59, 127.62, 128.92, 129.76, 130.14, 132.34, 1135.45, 135.86, 136.78, 136.98, 137.56, 138.03, 138.62, 139.32, 144.56, 154.67.

Calcd. for $C_{66}H_{45}F_2N_5$: C, 83.79; H, 4.79; N, 7.40 Found: C, 83.42; H, 4.46, N, 7.26. MS (m/z): 945.

2,6-bis (4-(4,5-diphenyl-2-p-tolyl-1H-imidazol-1-yl) phenyl)-4-p-tolylpyridine(1g)

Yield 86%, m.p. 225-228 °C; FT-IR (υ_{max}. cm^{-1}): 3059 (Aromatic C-H stretch), 2921 (Methyl C-H stretch), 1518 (C═N), 1598 (C═C).

^{1}H NMR δ (ppm): 2.34 (s, 3H, ——CH_3), 2.44 (s, 6H, ——CH_3), 7.05-7.30 (m, 30H, Ar—H), 7.94 (s, 2H, Pyridine), 7.60 (d, 6H, J = 8 Hz, Ar—H), 8.01 (d, 4H, J = 8 Hz, Ar—H).

^{13}C NMR δ (ppm): 20.34, 21.31, 117.38, 126.78, 126.91, 127.51, 127.59, 128.16, 128.23, 128.26, 128.49, 128.54, 128.69, 129.16, 129.94, 130.27, 130.49, 130.72, 131.19, 134.17, 135.43, 138.39, 139.57, 146.97, 155.79.

Calcd. for $C_{68}H_{51}N_5$: C, 87.06; H, 5.48; N, 7.46 Found: C, 83.86; H, 5.55, N, 7.28. MS (m/z): 937.

CONCLUSIONS

In summary, a facile and convenient route of synthesis for highly substituted bis-imidazole based on the reactions of diamine, benzil, aldehyde and ammonium acetate in acetic acid has been developed. The present methodology will be beneficiary in organic synthesis for the synthesis of highly substituted bis-imidazoles for molecular tweezers in easy way and high yield.

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REFERENCES

[1] Zhu J., Bienayme H., "Multicomponent Reactions", Wiley-VCH: Weinheim, Germany (2005).

[2] Kim B.Y., Ahn J.B., Lee H.W., Kang S.K., Lee J.H., Shin J.S., Ahn S.K., Hong C.I., Yoon S.S., Synthesis and Biological Activity of Novel Substituted Pyridines and Purines Containing 2,4-Thiazolidinedione, *Eur. J. Med. Chem.* **39** (5): 433-447 (2004).

[3] Davood A., Alipour E., Shafiee A., Efficient Synthesis of Imidazole Derivatives: An Important Synthon for the Preparation of Biologically Active Compounds, *Turk. J. Chem.* **32**: 389-395 (2008).

[4] Shalini K., Sharma P.K., Kumar N., Imidazole and Its Biological Activities: A Review, *Der Chemica Sinica*, **1**(3): 36-47 (2010).

[5] Chawla A., Sharma A., Sharma A. K., Review: A Convenient Approach for the Synthesis of Imidazole Derivatives Using Mcrowaves, *Der Pharma Chemica*, **4** (1):116-140 (2012).

[6] Bhatnagar A., Sharma, P. K., Kumar N., A Review on Imidazoles: Their Chemistry and Pharmacological Potentials, *Int. J. Pharm. Tech. Res.*, **3** (1): 268-282 (2011).

[7] Enyedy I. J., Sakamuri S., Zaman, W. A., Johnson K. M., Wang, S., Pharmacophore-Based Discovery of Substituted Pyridines as Novel Dopamine Transporter Inhibitors, *Bioorg. Med. Chem. Lett.*, **13**(3): 513-517 (2003).

[8] Liu W., Chen Z., Zheng C. J., Liu X. K., Wang K., Li F., Dong Y. P., Ou X. M., Zhang X. H., A Novel Nicotinonitrile Derivative as an Excellent Multifunctional Blue Fluorophore for Highly Efficient Hybrid White Organic Light-Emitting Devices, *J. Mater. Chem. C*, **3** (34): 8817-8823 (2015).

[9] Li N., Wang P., Lai S.L., Liu W., Lee C.S., Lee S.T., Liu Z., Synthesis of Multiaryl-Substituted Pyridine Derivatives and Applications in Non-Doped Deep-Blue OLEDs as Electron-Transporting Layer with High Hole-Blocking Ability, *Adv. Mater.*, **22** (4): 527-530 (2010).

[10] Hisamatsua Y., Aihara H., Diverse Dimerization of Molecular Tweezers with a 2,4,6-triphenyl-1,3,5-triazine Spacer in the Solid State, *Chem. Commun.*, **46** (27): 4902-4904 (2010).

[11] Krebs F.C., Functionalization of the Hinge Region in Receptor Molecules for Explosive Detection, T*etrahedron Lett.*, **44** (35): 6643-6646 (2003).

[12] Wang Z., Lu P., Chen S., Gao Z., Shen F., Zhang W., Xu Y., Kwok H. S., Ma Y., Phenanthro[9,10-d] Imidazole as a New Building Block for Blue Light Emitting Materials, *J. Mater. Chem.*, **21**: 5451-5456 (2011).

[13] Lee C., Yang W., Parr R.G., Development of the Colle-Salvetti Correlation-Energy Formula Into a Functional of the Electron Density, *Phys. Rev. B*, **37**(2): 785-789 (1988).

[14] Ditchfield R., Self-Consistent Perturbation Theory of Diamagnetism, *Mol. Phys*., **27** (4): 789-807 (1974).

[15] Karabacak M., Sinha L., Prasad O., Bilgili S., Sachan Alok K., Asiri A.M., Atac A., Spectral Investigation and Theoretical Study of Zwitterionic and Neutral Forms of Quinolinic Acid, *J. Mol. Struct*., **1095**: 100-111 (2015).

[16] Beyramabadi S.A., Eshtiagh-Hosseini H., Housaindokht M.R., Shirzadi S., Morsali A., Naseri M.A., Experimental and Theoretical Characterization of N,N' -bis(2,4-dihydroxybenzylidene)-1,2-Diaminobenzene Schiff base and Its Cu(II) Complex, *J. Struct. Chem*., **54** (6): 1055-1062 (2013).

[17] Alkorta I., Elguero J., Roussel C., A Theoretical Study of the Conformation, Basicity and NMR Properties of 2,2´-, 3,3´- and 4,4´-Bipyridines and Their Conjugated Acids, *Comput. Theor. Chem*. **966**: 334-339 (2011).

[18] Beyramabadi S.A., Morsali A., Javan-Khoshkholgh M., Esmaeili A.A., N,N'-dipyridoxyl Schiff Bases: Synthesis, Experimental and Theoretical Characterization, *Spectrochim. Acta Part A*, **83** (1): 467-471 (2011).

[19] Tamami B., Yeganeh H., Synthesis and Characterization of Novel Aromatic Polyamides Derived from 4-aryl-2,6-bis(4-aminophenyl) Pyridines, *Polymer*, **42** (2): 415-420 (2001).

[20] Behmadi H., Naderipour S., Saadati S. M., Barghamadi M., Shaker M., Tavakoli-Hoseini N., Solvent-Free Synthesis of New 2,4,6-Triarylpyridines Catalyzed by a Brønsted Acidic Ionic Liquid as a Green and Reusable Catalyst, *J. Heterocyclic Chem.*, **48**: 1117-1121 (2011).