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SYNTHESIS OF 4-(DIMETHYLAMINO)PYRIDINIUM-SUBSTITUTED PYRAZINE, PYRIDAZINE, 1,3,5-TRIAZINE, PURINE, AND IMIDAZOLE

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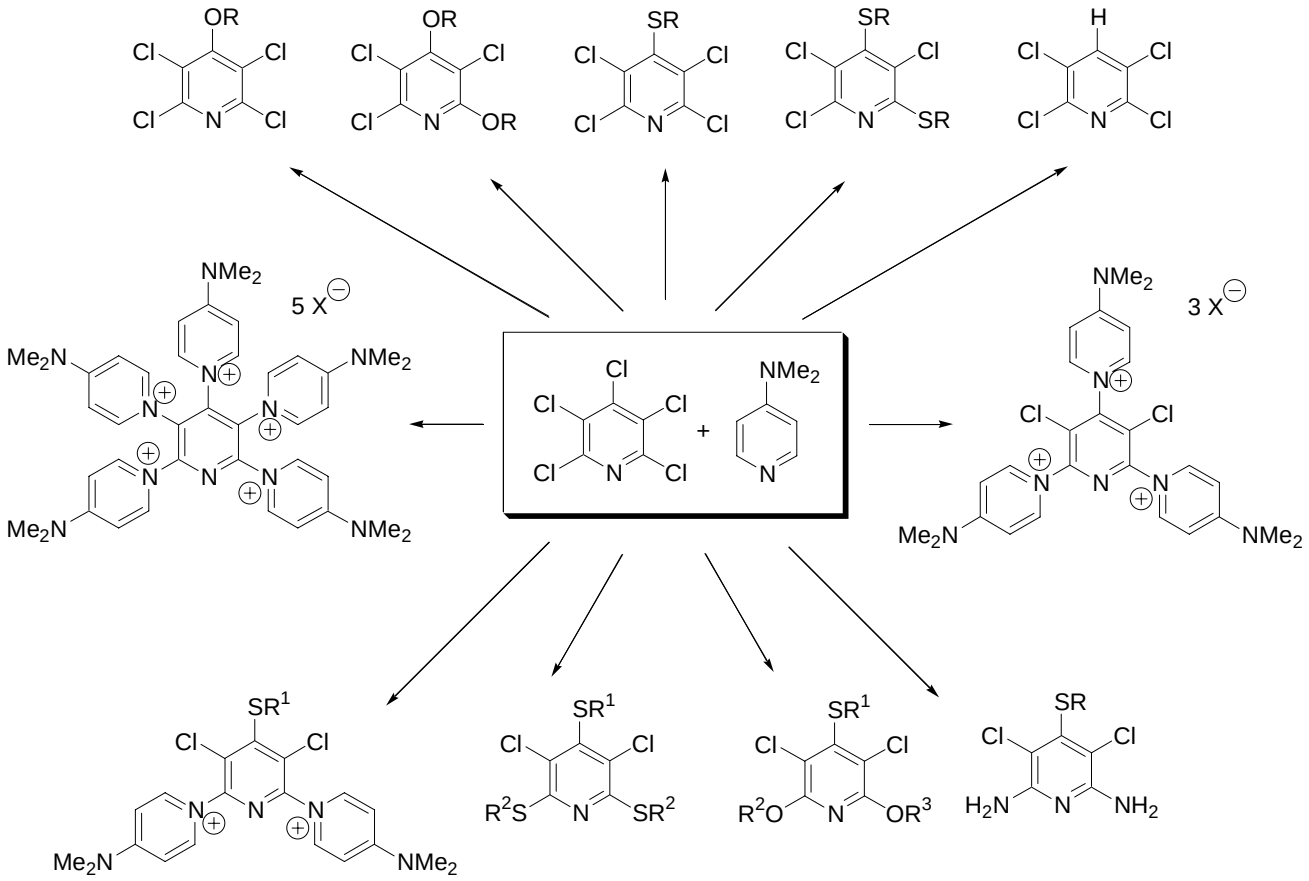
Abstract – Substitution reactions of 2,3-dichloropyrazine, 3,6-dichloropyridazine, 2,4,6-trichloro-1,3,5-triazine, 2,6-dichloropurine, and *N*-tosyl-2,4,5-tribromo-imidazole with 4-(dimethylamino)pyridine to monocationic, dicationic, and tricationic hetarenium salts are described.

INTRODUCTION

During the last decades, 4-(dimethylamino)pyridine (DMAP) has proved to be a very valuable tool in organic synthesis. In 1969 Steglich and Höfle reported DMAP as effective acylation catalyst,[1] and since then its application for acylations of a broad variety of alcohols, amines, phenols, and enolates,[2,3] Baylis-Hillman reactions,[4] Dakin-West reactions,[5] protection of amines,[6] C-acylations,[7] silylations,[3] and many other reactions has been described. Numerous other synthetic applications of DMAP were developed, among these the DMAP/ DCC activation as an efficient method for esterifications,[8] nucleophilic asymmetric catalysis[9] and reactions with polymeric DMAP reagents.[10] Streitwieser and co-workers reported that 4-(dimethylamino)pyridinium substituents are able to stabilize reactive anionic species such as the allyl anion[11] and the allyl radical.[12] We described DMAP-stabilized uracilates,[13] pyrimidinium-olates,[14] pyrimidinium-aminides,[15] and pyridinium-olates,[16] as well as 4-(dimethylamino)pyridinium-substituted heteroaromatics. As presented in Scheme 1, the mono-, tri-, or pentacationic hetarenium salts of pyridine are versatile starting materials for the regioselective synthesis of highly functionalized pyridines.[17] Thus, new pyridine ethers and thioethers with O^2,Cl^3,O^4,Cl^5,O^6-, S^2,Cl^3,S^4,Cl^5,S^6-, or O^2,Cl^3,S^4,Cl^5,O^6-substitution pattern and first representatives of N^2,Cl^3,S^4,Cl^5,N^6-pentasubstituted pyridine-amines[18] are available from DMAP-activated pentachloropyridine.



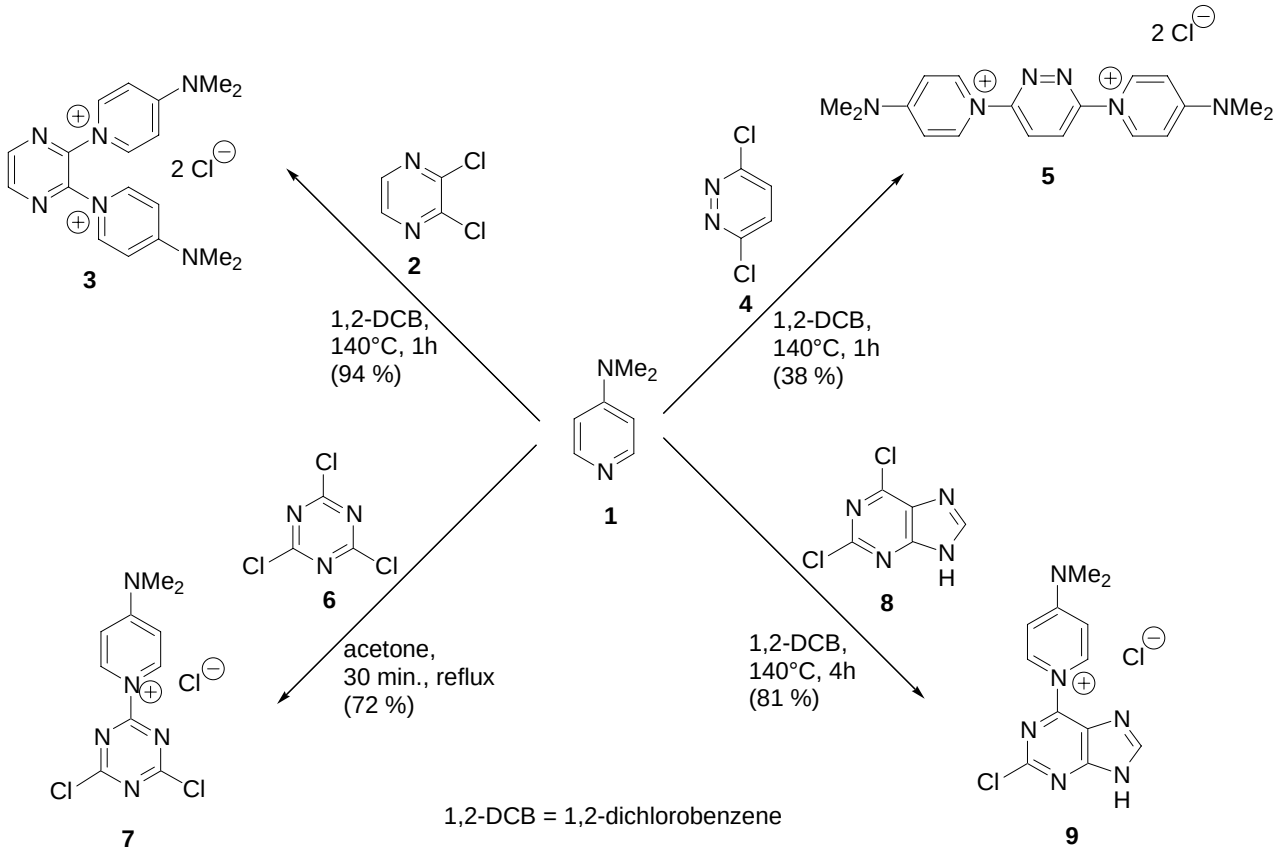
Scheme 1

Likewise, functionalized and hitherto unavailable pyrimidines were prepared.[19] We report here the syntheses of 4-(dimethylamino)pyridinium substituted pyrazine, pyridazine, 1,3,5-triazine, purine, and imidazole.

RESULTS AND DISCUSSION

2,3-Dichloropyrazine (**2**) reacted with two equivalents of 4-(dimethylamino)pyridine (**1**) in 1,2-dichlorobenzene (1,2-DCB) at 140 °C to give 1,1′-bis[4-(dimethylamino)(pyrazine-2,3-diyl)-pyridinium] dichloride (**3**) in 94 % yield as analytically pure solid. Under analogous reaction conditions, 3,6-dichloropyridazine (**4**) was converted into 1,1'-bis-[4-(dimethylamino)(pyridazine-3,6-diyl)-pyridinium] dichloride (**5**) by two equivalents of DMAP (Scheme 2). These colorless salts are stable on air. 2,4,6-Trichloro-1,3,5-triazine (**6**) reacted with excess DMAP in acetone or acetonitrile to give the monocationic salt 1-(4-dimethylamino)[4,6-dichloro-1,3,5-triazin-2-yl]pyridinium chloride (**7**) in 72 % yield, in addition to 5 % of higher substituted species. Three equivalents of DMAP in a broad variety of solvents (DMF, 1,2-dichlorobenzene, methanol, acetone, chloroform, ethyl acetate) resulted in the formation of mixtures of DMAP-substituted triazines which could not be separated chromatographically.

1,1′,1′′-Tris(1,3,5-triazine-2,4,6-triyl)pyridinium salts were described earlier as water-sensitive species which react to the tripole 2,4-pyridinio-1,3,5-triazin-6-olate chloride. The triazine-pyridinium salts are very interesting esterification agents for the preparation of penicillin esters.[20]

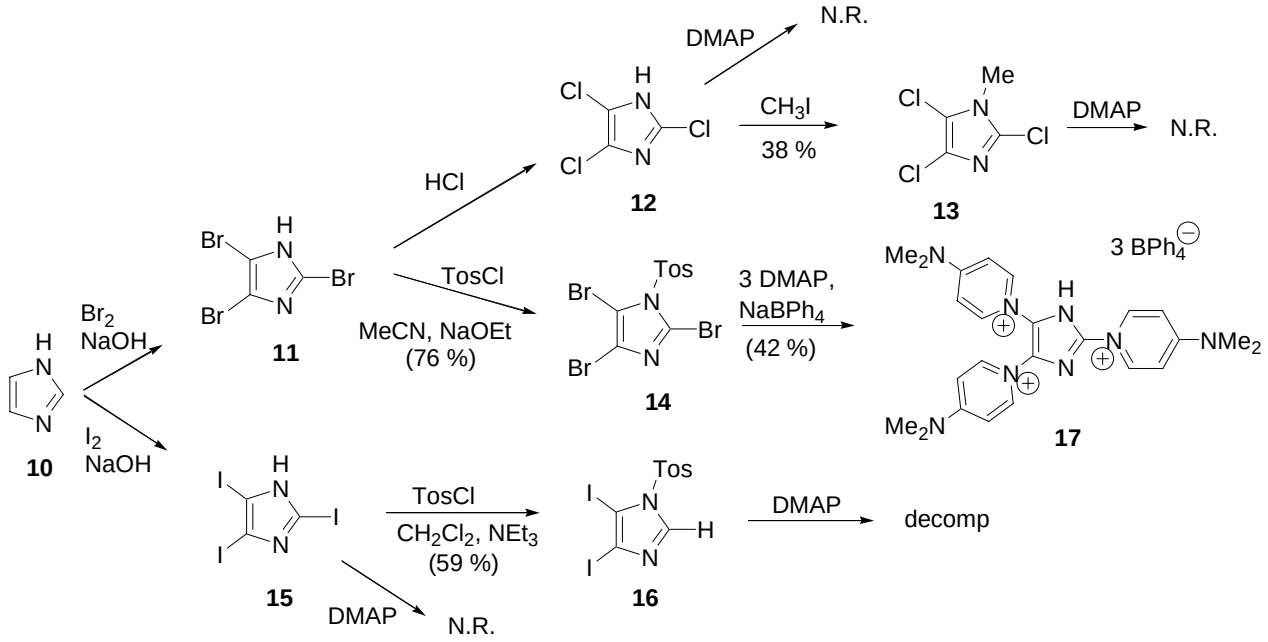


Scheme 2

2,6-Dichloropurine (**8**) reacted with two equivalents of DMAP in 1,2-dichlorobenzene at 140 °C to afford the monocationic salt (**9**) in 81 % yield. The regiochemistry, which was established by the chemical shift changes of the ^{13}C NMR resonance frequencies of the purine ring system in comparison with those of the starting material, is in accordance with the well-known leaving group tendency of the three chlorine atoms of 2,6,8-trichloropurine (C6 > C8 > C2).[21] Attempts to substitute the C(2)-Cl group by conducting the reaction with three equivalents of DMAP in the presence of trifluoromethansulfonic acid trimethylsilyl ester (TMSOTf) in 1,2-dichlorobenzene failed. This is in accord to our earlier results on purines.[22]

We next focussed our interest on imidazole derivatives and prepared 2,4,5-tribromoimidazole (**11**),[23] 2,4,5-trichloroimidazole (**12**),[24] 2,4,5-triiodoimidazole (**15**),[25] and 1-methyl-2,4,5-trichloroimidazole (**13**)[26] in order to avoid deprotonation reactions of the imidazole ring. As no reactions with DMAP were observable starting from these imidazole derivatives, we intended to improve the leaving group tendency of

the halogen atoms by tosylation of the acidic NH group. Thus, 2,4,5-tribromoimidazole (**11**) gave *N*-tosyl-2,4,5-tribromoimidazole (**14**) in 76 % yield. Tosylation of 2,4,5-triiodoimidazole in dichloromethane in the presence of triethylamine resulted in the formation of *N*-tosyl-4,5-diiodoimidazole (**16**) in 59 % yield. It is literature-known that C(2)-I group of triiodoimidazole is sensitive toward dehalogenations under basic conditions.[25,27]



Scheme 3

N-Tosyl-2,4,5-tribromoimidazole (**14**) reacted with three equivalents of DMAP to a 1,1',1''-tris[4-(dimethylamino)(imidazole-2,4,5-triyl)pyridinium] cation with a mixture of chloride and tosylate as anions. Anion exchange to tetraphenylborate gave compound (**17**) in 42 % yield which is yellow in color and scarcely soluble in common solvents except for acetone and DMF. On trying to perform analogous reactions with *N*-tosyl-4,5-diiodoimidazole (**16**) decomposition occurred. In accordance with the assigned structure, the NMR-spectra of **17** display two distinct types of pyridinium substituents in a 2:1 ratio. The tricationic structure was proved by the integration ratio (1:10) of the α- or β-hydrogen atoms of the pyridinium rings in comparison with the phenyl rings of the tetraphenylborate anion.

In summary we have described 4-(dimethylamino)pyridinium substituted heteroaromatics which are of interest as starting materials in heterocyclic synthesis.

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EXPERIMENTAL

General methods: The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Digital FT-NMR Avance 400 and Avance DPX 200 at 400 and 200 MHz, respectively. The chemical shifts are reported in ppm relative to internal tetramethylsilane (δ = 0.00 ppm). For the sake of clarity, the numbering is as follows: 2-H/C-2 etc. refers to the central heteroaromatic, whereas 2′-H/C-2′, 2′′-H/C-2′′, and 2′′′-H/C-2′′′ etc. refers to the first, second, or third 4-(dimethylamino)pyridinium substituent, or the tosyl group. FT-IR spectra were obtained on a Bruker Vector 22 in the range of 400 to 4000 cm^{-1} (2.5 % pellets in KBr). The GC-MS spectra were recorded on a GC Hewlett-Packard 5980, Serie II in combination with a MS Hewlett-Packard 5989 B, and on a Varian GC3900 with SAT2100T mass spectrometer. Solvents and reagents were obtained from commercial sources and used as received without further purification.

General procedure for the synthesis of bis[4-(dimethylamino)pyridinium substituted pyrazine and pyridazine (3) and (5).

A solution of the heteroaromatic [2,3-dichloropyrazine (**2**): 1.49 g, 10.0 mmol; 3,6-dichloropyridazine (**4**): 1.49 g, 10.0 mmol] and 4-(dimethylamino)pyridine (**1**) (2.44 g; 20.0 mmol) in 200 mL of DMF, respectively, was heated over a period of 1 h at 140 °C. After cooling, 100 mL of ethyl acetate was added to the solution, and the resulting precipitates were filtered off, washed with ethyl acetate and dried *in vacuo*.

1,1’-Bis[4-(dimethylamino)(pyrazine-2,3-diyl)pyridinium] dichloride (3)

Colorless solid, mp 309 °C. ^{1}H NMR (D_2O): δ = 8.92 (s, 2H; 5-H/6-H), 8.20 (d, ^{3}J = 7.9 Hz, 4H; 2′-H, 6′-H, 2′′-H, 6′′-H), 7.06 (d, ^{3}J = 7.9 Hz, 4H; 3′-H, 5′-H, 3′′-H, 5′′-H), 3.34 (s, 12H, Me) ppm; ^{13}C NMR (D_2O): δ = 157.0 (C-4′/C-4′′), 145.3 (C-5/C-6), 141.9 (C-2/C-3), 139.0 (C-2′/6′, C-2′′/6′′), 108.6 (C-3′/5′,C-3′′/5′′), 40.2 (Me) ppm; IR (KBr): 3364, 3043, 1650, 1578, 1423, 1308, 1221, 1181, 822 cm^{-1}; *Anal*. Calcd for $C_{18}H_{22}N_6Cl_2 \cdot 4\ H_2O$: C, 46.46; H, 6.50; N: 18.06. Found C, 46.06; H, 6.23; N, 17.80.

1,1’-Bis-[4-(dimethylamino)(pyridazine-3,6-diyl)pyridinium] dichloride (5)

Colorless solid, mp 308 °C. ^{1}H NMR (D_2O): δ = 8.63 (d, ^{3}J = 8.1 Hz, 4H; 2′-H, 6′-H, 2′′-H, 6′′-H), 8.37 (s, 2H, 4-H, 5-H), 7.06 (d, ^{3}J = 8.1 Hz, 4H; 3′-H, 5′-H, 3′′-H, 5′′-H), 3.28 (s, 12H; Me) ppm; ^{13}C NMR (D_2O): δ = 157.5 (C-4′, C-4′′), 155.5 (C-3, C-6), 137.9 (C-2′, C-2′′, C-6′, C-6′′), 124.6 (C-4, C-5), 108.2 (C-3′, C-5′, C-3′′, C-5′′), 40.1 (Me) ppm; IR (KBr): 3364, 3044, 1650, 1570, 1431, 1306, 1227, 1125, 1068, 1026, 831 cm^{-1}. *Anal*. Calcd for $C_{18}H_{22}N_6Cl_2 \cdot 2{,}5\ H_2O$: C, 49.32; H, 6.21; N, 19.17. Found: C, 49.44; H, 5.62; N, 19.17.

1-(4-Dimethylamino)[4,6-dichloro-1,3,5-triazin-2-yl]pyridinium chloride (7)

A solution of 2,4,6-trichloro-1,3,5-triazine (**6**) (3.68 g, 20.0 mmol) in 100 mL of acetone was heated at 50 °C. Then, a solution of 4-(dimethylamino)pyridine (**1**) (1.22 g, 10.0 mmol) in 40 mL of acetone was added and the mixture was heated for 30 min at reflux temperature. After cooling, the product was precipitated by addition of 100 mL of ethyl acetate to the solution. The precipitate was collected by filtration, washed with ethyl acetate and dried *in vacuo* to give a colorless solid, mp 150 °C. ^{1}H NMR (D_2O): δ = 8.87 (d, ^3J = 8.2 Hz, 2H; 2′-H, 6′-H), 6.90 (d, ^3J = 8.2 Hz, 2H; 3′-H, 5′-H), 3.24 (s, 6H; Me) ppm; ^{13}C NMR (D_2O): δ = 172.1 (C-2), 164.4 (C-4, C-6), 159.7 (C-4′), 137.2 (C-2′, C-6′), 109.1 (C-3′, C-5′), 42.0 (Me) ppm; IR (KBr): 3209, 3070, 1705, 1652, 1566, 1371, 1328, 1207, 1148, 1124, 810 cm^{-1}. Under the ESIMS-conditions, substitution of the chlorine substituents by the spraying solvent (MeOH) occurred: HRESIMS: Calcd for $C_{12}H_{16}N_5O_2^+$: 262.1299. Found: 262.1248.

1-(4-Dimethylamino)[2-chloropurin-6-yl]pyridinium chloride (9)[22]

A solution of 2,6-dichloropurine (**8**) (1.89 g, 10.0 mmol) and 4-(dimethylamino)pyridine (**1**) (1.83 g, 15.0 mmol) in 200 mL of DMF was heated at 140 °C for 4 h. The product precipitated partially during this time. After cooling, 100 mL of ethyl acetate were added, the precipitate was collected by filtration, washed with ethyl acetate and dried *in vacuo*. The salt (**9**) was obtained as yellow solid, mp > 350 °C (decomp). ^{1}H NMR [D_2O/DMSO-d_6 (1:1)]: δ = 9.28 (d, ^3J = 8.2 Hz, 2H; 2′-H, 6′-H), 8.60 (s, 1H, 8-H), 7.18 (d, ^3J = 8.2 Hz, 2H; 3′-H, 5′-H), 3.43 (s, 6H; Me) ppm; ^{13}C NMR [D_2O/DMSO-d_6 (1:1)]: δ = 156.7 (C-4′), 151.3 (C-2), 147.0 (C-4), 146.9 (C-8), 144.7 (C-6), 137.2 (C-2′, C-6′), 120.9 (C-5), 107.6 (C-3′, C-5′), 40.2 (Me) ppm; IR (KBr): 1656, 1562, 1378, 1312, 1227, 1178, 1123, 983 cm^{-1}. *Anal*. Calcd for $C_{12}H_{12}N_6Cl_2$: C, 46.32; H, 3.89; N, 27.01. Found: C, 46.19; H, 3.42; N, 27.18.

***N*-Tosyl-2,4,5-tribromoimidazole (14)**

A solution of 2,4,5-tribromoimidazole (**11**) (3.04 g, 10.0 mmol) and sodium ethoxide (1.04 g, 20.0 mmol) in 150 mL of anhydrous acetonitrile was stirred for 18 h at rt. Then, tosyl chloride (1.91 g, 10.0 mmol) was added and the solution was heated for 6 h at reflux temperature. After cooling, the solvent was distilled off *in vacuo* and the residue was chromatographed (silica gel, ethyl acetate / petroleum ether = 1/8). The product was obtained as a colorless solid, mp 157 °C. ^{1}H NMR ($CDCl_3$): δ = 8.00 (d, ^3J = 8.5 Hz, 2H, 2′-H, 6′-H), 7.41 (d, ^3J = 8.5 Hz, 2H, 3′-H, 5′-H), 2.48 (s, 3H, Me′) ppm; ^{13}C NMR ($CDCl_3$): δ = 147.6 (C-1′), 133.7 (C-4′), 130.5 (C-2′, C-6′), 128.4 (C-3′, C-6′), 127.0 (C-2), 121.5 (C-5), 117.6 (C-4), 21.9 (C-Me′) ppm; IR (KBr): 1592, 1510, 1395, 1225, 1196, 1180, 1161, 1092 cm^{-1}; GCMS: *m/z* = 301 ($C_3Br_3N_2$, 5), 155 ($C_7H_7O_2S$, 41), 91 (C_7H_7, 100). *Anal*. Calcd for $C_{10}H_7N_2O_2Br_3S$: C, 26.17; H, 1.54; N, 6.10; S, 6.99. Found: C, 26.78; H, 1.81; N, 6.05; S, 6.77.

N-Tosyl-4,5-diiodoimidazole (16)

A solution of 2,4,5-triiodoimidazole (**15**) (4.46 g, 10.0 mmol) and 4-tosyl chloride (1.91 g, 10.0 mmol) in 150 mL of dichloromethane and 10 mL of triethylamine was stirred at rt for 2 h. Then, the solvent was distilled off and the residue was chromatographed (silca gel, ethyl acetate / petroleum ether = 1/2). The product was obtained as a colorless solid, mp 102 °C. ^{1}H NMR ($CDCl_3$): δ = 8.32 (s, 1H, 2-H), 7.91 (d, ^3J = 8.5 Hz, 2H, 2′-H, 6′-H), 7.38 (d, ^3J = 8.5 Hz, 2H, 3′-H, 5′-H), 2.47 (s, 3H, Me′) ppm; ^{13}C NMR ($CDCl_3$): δ = 147.1 (C-1′), 141.1 (C-2), 133.0 (C-4′), 130.3 (C-2′, C-6′), 128.9 (C-3′-, C-5′), 121.7 (C-4), 102.9 (C-5), 21.9 (Me′) ppm; IR (KBr): 3125, 1593, 1378, 1192, 1169, 1137, 1089, 1030, 923, 812 cm^{-1}; GCMS: *m/z* = 474 (M, 100), 384 (M - C_7H_7, 91), 155 (M - Tos, 86). *Anal*. Calcd $C_{10}H_8N_2O_2I_2S$: C, 25.34; H, 1.70; N, 5.91; S, 6.76. Found: C, 25.31; H, 1.76; N, 6.03; S, 6.68.

1,1’,1’’-Tris[4-(dimethylamino)imidazole-2,4,5-triyl)pyridinium] tris(tetraphenylborate) (17)

A solution of *N*-tosyl-2,4,5-tribromoimidazole (**14**) (4.59 g, 10.0 mmol) and 4-(dimethylamino)pyridine (**1**) (3.66 g, 30.0 mmol) in 200 mL of 1,2-dichlorobenzene was heated for 1 h at 140°C. After cooling, a mixture of 50 mL of petroleum ether and 50 mL of ethyl acetate was added, whereupon a grey solid precipitated. The solvent was distilled off and the residue was dissolved in ethanol. Then, a solution of sodium tetraphenylborate (5.13 g, 15.0 mmol) in ethanol was added. The resulting precipitate was filtered off and recrystallized from chloroform. The salt was obtained as a yellowish solid, mp 190 °C. ^{1}H NMR (DMSO-d_6): δ = 8.88 (d, ^3J = 7.8 Hz, 2H; 2′-H, 6′-H), 8.30 (d, ^3J = 7.8 Hz, 4H; 2′′-H, 6′′-H), 6.73 – 7.24 (m, 66H; 3′-H, 5′-H, 3′′-H, 5′′-H, 3′′′-H, 5′′′-H, BPh_4), 3.25 (s, 6H; Me′′, Me′′′), 3.22 (s, 12H; Me′) ppm; NH was not detectable; ^{13}C NMR (DMSO-d_6): δ = 155.7 (C-4′, C-4′′, C-4′′′), 141.1 (C-2′, C-2 ′′, C-2′′′, C-6′, C-6′′, C-6′′′), 135.4 (C-2, C-6 of BPh_4), 125.3 (C-3, C-4, C-5 of BPh_4), 121.5 (C-1 of BPh_4), 107.8 (C-3′, C-3′′. C-3′′′, C-5′, C-5′′, C-5′′′) ppm; the resonance frequencies of NMe_2 groups are overlapped by the solvent´s resonance frequencies. The signals of C-2, C-4, and C-5 were not detected; IR (KBr): 3425, 3053, 1647, 1571, 1424, 1401, 1211, 735, 706 cm^{-1}. No satisfactory elemental analysis was obtained.

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