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New non-functionalized and nitrile-functionalized benzimidazolium salts and their silver(I) complexes: Synthesis, crystal structures and antibacterial studies

Rosenani A. Haque [a], Umie F.M. Haziz [a], Amirul Al-Ashraf Abdullah [b,c], Noor Shaheeda [b], Mohd R. Razali [a,*]

[a] School of Chemical Sciences, Universiti Sains Malaysia, 11800, USM, Penang, Malaysia
[b] School of Biological Sciences, Universiti Sains Malaysia, 11800, USM, Penang, Malaysia
[c] Centre for Chemical Biology, University Sains Malaysia, 11900 Penang, Malaysia

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ABSTRACT

Two series of new benzyl substituted benzimidazolium salts, non-functionalized series, 1-(2′/3′/4′-methylbenzyl)-3-(2″-propyl)benzimidazolium bromide/hexafluorophosphate (**1**–**3**·Br/PF_6) and nitrile-functionalized series, 1-(2′/3′/4′-methylbenzonitrile)-3-(2″-propyl)benzimidazolium bromide/hexafluorophosphate (**4**–**6**·Br/PF_6) were successfully synthesized as *N*-heterocyclic carbene (NHC) precursors. Reaction of **1**–**6**·Br with Ag_2O facilitate the *in situ* deprotonation of salt **1**–**6**·Br that afforded the formation of a series of silver(I) complexes, $[Ag(L)_2]\cdot PF_6$ (**7**–**12**), respectively (where L = 2′/3′/4′-methyl/cyano benzyl). Both NHC ligand salts and Ag(I)–NHC complexes have been characterized using ^1H and ^{13}C NMR, FTIR spectroscopy and elemental analysis technique. Molecular structure of ligand salts **1**, **2**, and **4**·PF_6 and complexes **8**, **10** and **11** were established by single crystal X-ray diffraction method. Qualitative antibacterial studies against the Gram-negative bacteria *Escherichia coli* (ATCC 25922) and the Gram-positive bacteria *Staphylococcus aureus* (ATCC 12600), were carried out on all the synthesized ligands salts (**1**–**6**·PF_6) and complexes **7**–**12** using Kirby–Bauer disc diffusion method. All the ligand salts show negative result in this study while the antimicrobial activity of the Ag(I)–NHC complexes were varies with the nature of the ligands.

1. Introduction

N-Heterocyclic carbene (NHC) compounds usually derived from deprotonation of an azolium salt by a strong base [1]. Having the ability to bond with both hard and soft metal, NHCs are known to become more versatile ligands than phosphine [2]. A large number of NHC complexes have been prepared and characterized while their various applications have been discovered.

For all synthesized NHC complexes, the most popular is Ag(I)–NHC. In 1993, the first Ag(I)–NHC complex is successfully synthesized using free carbene method by Arduengo [3]. Ag(I)–NHC complexes have been observed to be very stable to air and moisture, and can be prepared efficiently [4]. Furthermore, their usefulness is often associated with the yield and the cost of their synthesis [5]. Ag(I)–NHC complexes are also famously known because of its several purposes such as carbene transfer agents in transmetallation studies [6–12], catalysis [13–16], nanomaterials [17], and biological activity [18–23].

Silver-base compounds are used as antimicrobials for centuries [24] and after discovery of numerous application of the Ag(I)–NHC complexes, many researchers revealed that silver derivatives of NHCs can be used in medicinal applications [25]. The slow release of silver ions from the Ag(I)–NHC complexes into the infected site could obtain better prevention of infection and promote healing. The inability of some of the current silver antimicrobial agents to kill the pathogens in a sustained period of time became a problem and the slow release ability of the Ag(I)–NHC complexes can be used to solve this problem. [4,24,26,27] With this promising ability, the first Ag(I)–NHC complex that proven in possessing antimicrobial activity against *E. coli*, *Staphylococcus aureus* and *P. aeruginosa* was reported by Youngs and co-workers [19].

In recent years, our group research have interested in the chemistry of metal–NHC complexes due to their diverse applications. Using imidazole and benzimidazole as the main attentions, many metal–NHC complexes such as silver [4,5,28–35], mercury [5,28,33], gold [32], palladium [33], and the new interest, selenium adducts [36] have been studied. These complexes were synthesized differently based on their substituents at 1- and 3-nitrogen

* Corresponding author.

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in imidazolium or benzimidazolium rings and these substituents can make the compound either symmetry, non-symmetry, mono nuclear or dinuclear NHC complexes. These substituents may be functionalized or/and non-functionalized groups such as nitrile-functionalized group [28–30], allylic groups [31], benzylic groups, or common alkyl groups [34,35]. The variety of the metal and substituents used were led to discovery of their potentials either in catalysis, anticancer or antimicrobial studies. Among all, nitrile-functionalized NHC complexes have received great attention because of their structurally divergent motifs and other applications such as catalysis studies [28,37] and as potential anticancer agents. [29,30] The nitrile functionality on these carbene ligands provide an extra space for bonding or bridging to metal centers and this unique ability gave benefit either in coordination or in the formation of supramolecular architectures [29].

As a continuation in our research on silver chemistry of NHC, we present the synthesis, characterization, and crystal structure studies for a new series of non-functionalized and nitrile-functionalized benzimidazolium salts and their respective Ag(I)–NHC complexes. These prepared complexes were then screened for their *in vitro* antimicrobial activity against Gram-positive *Staphylococcus aureus* (*S. aureus*) and Gram negative *Escherichia coli* (*E. coli*).

2. Experimental

2.1. Reagents and instruments

All chemicals and solvents were purchased from commercial sources and were used as received. The starting material, *N*-(2′-propyl)benzimidazole was synthesized according to the literature procedure with slight modifications [38]. The melting point was tested using a Stuart Scientific SMP-1 (UK) instrument. Elemental analysis was carried out on a Perkin Elmer Series II, 2400 microanalyzer. The FT-IR spectra were recorded in potassium bromide disks using a Perkin Elmer 2000 system spectrometer in the range of 4000 cm to 400 cm^{-1}. Nuclear magnetic resonance (NMR) spectra were recorded in d_6-DMSO using Bruker 500-MHz Ascend spectrometers at ambient temperature with TMS as an internal standard. The ^1H and ^{13}C NMR peaks were labeled as singlet (s), doublet (d), triplet (t), and multiplet (m). Chemical shifts were referenced with respect to solvent signals.

2.2. Synthesis of benzimidazolium salts (**1**–**6**)

2.2.1. Synthesis of 1-(2′-methylbenzyl)-3-(2″-propyl)benzimidazolium hexafluorophosphate salt (**1**·PF_6)

In a round bottom flask, 2-methylbenzyl bromide (2.31 g, 12.5 mmol) was added dropwise to *N*-(2′-propyl)benzimidazole (2.00 g, 12.5 mmol) dissolved in 1,4-dioxane (30 mL). The solution mixture was allowed to reflux for 12 h. A white precipitate of **1**·Br that formed in the reaction medium was filtered, washed with fresh 1,4-dioxane (3 × 5 mL) and left for air-dried. Potassium hexafluorophosphate, KPF_6 (0.534 g, 2.90 mmol) dissolved in methanol (20 mL) were added into the round bottom flask containing **1**·Br (0.500 g, 1.45 mmol) while stirring. The mixture was then stirred for 3–4 h at room temperature and then left to stand overnight. The white solid of **1**·PF_6 were filtered, washed with distilled water (3 × 5 mL) and left to dry at ambient temperature. The crystals of **1**·PF_6 suitable for single crystal X-ray diffraction studies was afforded within a week by slow evaporation of methanol from the concentrated solution at room temperature. (Yield: 0.534 g, 89%). MP: 182–186 °C. *Anal.* Calc. of $C_{18}H_{21}F_6N_2P$: C, 52.68; H, 5.12; N, 6.83%; Found: C, 51.91; H, 4.42; N, 6.57%. **IR** (KBr, cm^{-1}): 3113 (Csp^3–H_{arom} stretching); 2922, 2759 (Csp^3–H_{aliph} stretching); 1613, 1558 (C=N stretching) 1487–1315 (C—N stretching); **^1H NMR** (500 MHz, d_6-DMSO) in δ ppm: 1.65–1.66 (6H, d, isoprop CH_3 × 2, J = 7.00 Hz); 2.37 (3H, s, Ar–CH_3 methylbenzyl); 5.07–5.13 (1H, sept, isoprop CH); 5.76 (2H, s, benzylic CH_2), 7.03–7.05 (1H, d, Ar–H, J = 7.50 Hz); 7.17–7.21 (1H, m, Ar–H); 727–7.32 (2H, m, Ar–H); 7.63–7.66 (1H, t, benzimi H, J = 7.75 Hz); 7.68–7.71 (1H, t, benzimi H, J = 7.75 Hz); 7.81–7.82 (1H, d, benzimi H, J = 8.00 Hz); 8.17–8.19 (1H, d, benzimi H, J = 8.00 Hz); 9.89 (1H, s, NC*H*N); **^{13}C NMR** (125 MHz, d_6-DMSO), δ (ppm): 18.8 (Ar–CH_3 methylbenzyl); 21.5 (isoprop CH_3 × 2); 48.4 (isoprop CH); 50.9 (Benzylic CH_2); 113.9, 114.3, 128.6, 130.7, 130.7, 131.4 (Arene C); 126.4, 126.6, 126.8, 127.5, 132.0, 136.2 (benzimi C); 141.3 (N*C*HN).

2.2.2. Synthesis of 1-(3′-methylbenzyl)-3-(2″-propyl)-benzimidazolium hexafluorophosphate salt (**2**·PF_6)

The preparation was similar to that resulting **1**·PF_6, but using 3-methylbenzyl bromide (2.31 g, 12.5 mmol) instead of 2-methylbenzyl bromide. Crystals suitable for single crystal X-ray diffraction studies were grown within a week by slow evaporation of methanol from the concentrated solution of **2**·PF_6 at room temperature. (Yield: 0.568 g, 95%). MP: 142–147 °C. *Anal.* Calc. of $C_{18}H_{21}F_6N_2P$: C, 52.68; H, 5.12; N, 6.83%; Found: C, 53.05; H, 4.51; N, 6.68%. **IR** (KBr, cm^{-1}): 3119, 3021 (Csp^3–H_{arom} stretching); 2979, 2773 (Csp^3–H_{aliph} stretching); 1633, 1558 (C=N stretching); 1480–1323 (C—N stretching); **^1H NMR** (500 MHz, d_6-DMSO) in δ ppm: 1.66–1.68 (6H, d, isoprop CH_3 × 2, J = 6.50 Hz); 2.31 (3H, s, Ar–CH_3 methylbenzyl); 5.05–5.11 (1H, sept, isoprop CH); 5.70 (2H, s, benzylic CH_2), 7.18–7.20 (1H, t, Ar–H, J = 4.00 Hz); 7.29–7.30 (2H, d, Ar–H, J = 4.50 Hz); 7.36 (1H, s, Ar–H); 7.63–7.70 (2H, m, benzimi H,); 7.90–7.92 (1H, d, benzimi H, J = 8.00 Hz); 8.14–8.16 (1H, d, benzimi H, J = 8.50 Hz); 10.01 (1H, s, NC*H*N); **^{13}C NMR** (125 MHz, d_6-DMSO), δ (ppm): 20.9 (Ar–CH_3 methylbenzyl); 21.5 (isoprop CH_3 × 2); 50.0 (isoprop CH); 50.8 (Benzylic CH_2); 113.9, 114.2, 125.1, 131.0, 133.0, 138.3 (Arene C); 126.5, 126.7, 128.6, 128.8, 129.3, 130.7 (benzimi C); 141.0 (N*C*HN).

2.2.3. Synthesis of 1-(4′-methylbenzyl)-3-(2″-propyl)benzimidazolium hexafluorophosphate salt (**3**·PF_6)

The preparation was similar to that resulting **1**·PF_6, but using 4-methylbenzyl bromide (2.31 g, 12.5 mmol) instead of 2-methylbenzyl bromide. A white solid of **3**·PF_6 were filtered, washed with distilled water (3 × 5 mL) and left to dry at ambient temperature. (Yield: 0.511 g, 86%). MP: 140–144 °C *Anal.* Calc. of $C_{18}H_{21}F_6N_2P$: C, 52.68; H, 5.12; N, 6.83%; Found: C, 53.00; H, 4.60; N, 6.76%. **IR** (KBr, cm^{-1}): 3155 (Csp^3–H_{arom} stretching); 2995, 2950 (Csp^3–H_{aliph} stretching); 1615, 1558 (C=N stretching); 1489–1431 (C—N stretching); **^1H NMR** (500 MHz, d_6-DMSO) in δ ppm: 1.64–1.66 (6H, d, isoprop CH_3 × 2, J = 7.00 Hz); 2.27 (3H, s, Ar–CH_3 methylbenzyl); 5.03–5.09 (1H, sept, isoprop CH); 5.68 (2H, s, benzylic CH_2), 7.20–7.22 (2H, d, Ar–H, J = 8.00 Hz); 7.41–7.42 (2H, d, Ar–H, J = 8.00 Hz); 7.61–7.67 (2H, m, benzimi H); 7.88–7.90 (1H, d, benzimi H, J = 8.00 Hz); 8.12–8.13 (1H, d, benzimi H, J = 8.00 Hz); 9.99 (1H, s, NC*H*N); **^{13}C NMR** (125 MHz, d_6-DMSO), δ (ppm): 20.7 (Ar–CH_3 methylbenzyl); 21.5 (isoprop CH_3 × 2,); 49.8 (isoprop CH); 50.7 (Benzylic CH_2); 128.2, 129.5, 138.1 (Arene C); 113.9, 114.2, 126.5, 126.7, 130.7, 131.0 (benzimi C); 140.9 (N*C*HN).

2.2.4. Synthesis of 1-(2′-methylbenzonitrile)-3-(2″-propyl) benzimidazolium hexafluorophosphate salt (**4**·PF_6)

The preparation was similar to that resulting **1**·PF_6, but using 2-(bromomethyl)benzonitrile (2.45 g, 12.5 mmol) instead of 2-methylbenzyl bromide to produce **4**·Br. By the reaction of **4**·Br (0.5 g, 1.40 mmol) and KPF_6 (0.515 g, 2.80 mmol), the obtained **4**·PF_6 were filtered, washed with distilled water (3 × 5 mL) and left to dry at ambient temperature. Crystals suitable for single crystal X-ray diffraction studies were obtained within a week by slow evaporation of the **4**·PF_6 from methanol at room temperature.