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Novel benzimidazolium salts and their silver complexes: Synthesis and antibacterial properties

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ABSTRACT

A series of unsymmetrical *N*,*N*-disubstituted benzimidazolium salts were synthesized as *N*-heterocyclic carbene (NHC) precursors. These compounds were used to synthesize of *N*-heterocyclic carbene silver(I) complexes. New compounds were characterized by NMR and IR spectroscopies and elemental analyses. The antibacterial activity of all the compounds was tested against Gram (+)/(−) and fungal strains using the agar dilution procedure.

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Since the first isolation of a stable, free N-heterocyclic carbene (NHC) by Arduengo in 1991 [1], NHCs had become crucial ligands in organometallic chemistry and homogeneous catalysis [2–4]. The NHC–metal complexes are remarkably stable toward heat, air, and moisture, and many organic reactions using metal–NHC complexes as catalysts have been investigated, such as olefin metathesis [5,6], C–C [7,8], and C–N [9] bond formation reactions. Later discoveries revealed that silver and gold derivatives of NHCs can be used in medicinal applications. NHC complexes of silver have become common-place in the organometallic literature. One reason for this is that NHC silver cpmplexes are easily prepared by a one-pot reaction of an azolium salt with Ag_2O, which can be easily derived. Another reason for this is that carbene silver complexes can be used as carbene transfer reagent for synthesis of Ni, Pd, Pt, Cu, Au, Rh, Ir, and Ru carbene complexes, such a route affords a convenient method for the preparation of these carbene metal complexes [10,11]. In addition, a new discovery shows that silver carbene complexes have shown interesting biological activity as antimicrobial and anticancer agents [12,13]. The achievement such as their synthetic routes, structural features and applications of Ag–NHC complexes has been summarized by Youngs and coworkers [14,15] and Lin et al. [16,17], respectively. The first use of silver NHCs as antimicrobial agents was reported by Youngs and coworkers in 2004 [12].

Silver has a long standing use as an antimicrobial agent, particularly in modern medicine for the prevention and treatment of bacterial infections associated with severe burn wounds [18]. This is evidenced by the use of silver sulfadiazine (Silvadine) in burn wards worldwide since 1968 [19,20]. High antimicrobial activity and minimal side effects of silver sulfadiazine have made it a very convenient therapy for treatment of infections in burns over the past four decades [21–24].

In recent years, considerable attention has been given to the synthesis of benzimidazole derivatives because of their various pharmacological activities such as antitumour, anti-ulcer, antibacterial, and antifungal properties [25–32]. Although there are different antibacterial and antifungal drugs used in the treatment of bacterial and fungal infections, some of them have undesirable side effects [33]. Therefore, many clinically effective antibacterial and antifungal drugs have become less effective due to the development of resistance to these drugs. Since benzimidazole compounds have been found to have a broad range of pharmacological activity, many research groups have been interested in this type of heterocyclic compound [25–32].

In the light of the general importance of these compounds, we wish to report the synthesis and characterization of benzimidazolium salts and their silver complexes. The Ag(I) complexes and the metal-free ligands were screened for their ability to inhibit the growth of a number of Gram-positive and Gram-negative and fungi strains.

The reaction of *N*-butylbenzimidazole with aryl halides to prepare the benzimidazolium salts was found to be very good yields in DMF at 80 °C for 12 h (Scheme 1) [34].

The salts are air- and moisture-stable both in the solid state and in solution. The ^{1}H NMR spectra of the benzimidazolium salts **1a–1e** exhibit the signal for the NCHN proton in the range of δ 11.10–11.83 ppm. These values are typical for NCHN protons of benzimidazolium salts [35,36]. The ^{13}C NMR spectra of **1a–1e** exhibit the NCN resonances between δ 143.5 and 144.0 ppm, which are also typical values previously

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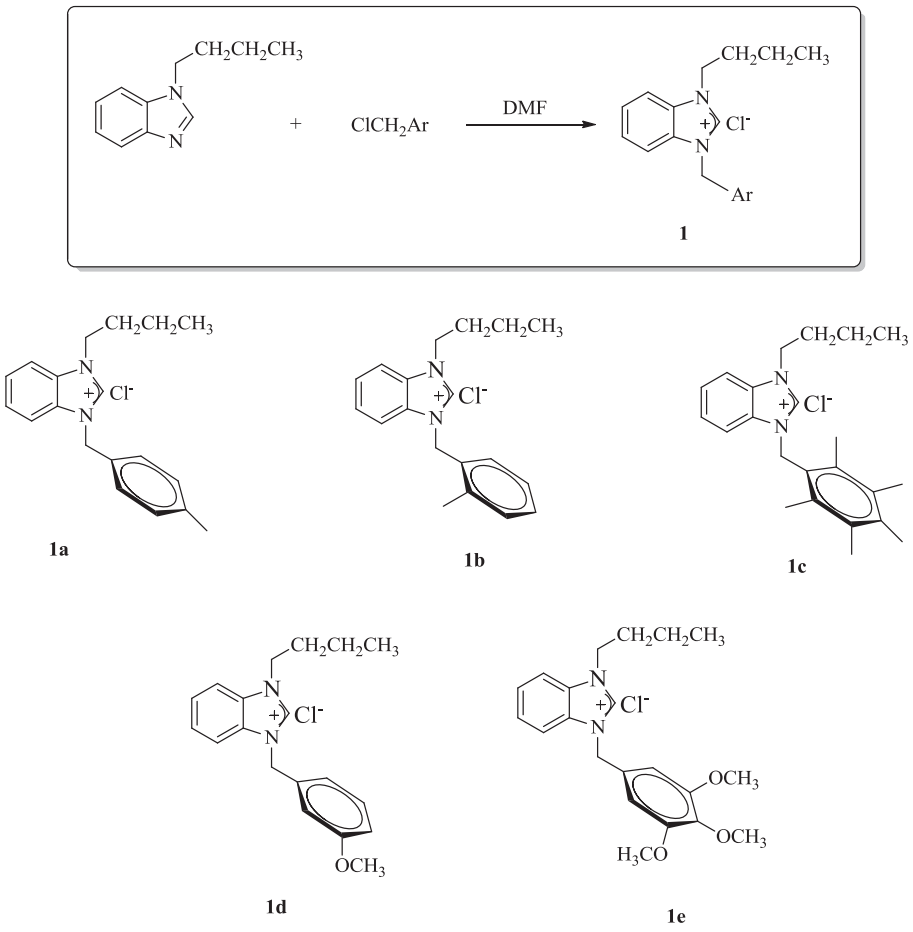


Scheme 1. Synthesis of benzimidazolium salts (**1a**–**1e**).

reported for benzimidazolium salts [37,38]. IR data for benzimidazolium salts clearly indicate the presence of the –C═N–group with a υ(C═N) vibration between 1442 and 1465 cm^{-1}. The NMR and IR values are similar to those found for other 1,3-dialkylbenzimidazolium salts.

Synthesis of the Ag(I) complexes were conducted in the absence of light and all complexes were stored in the dark. The reaction of the benzimidazolium salt with 2 equiv. Ag_2O in dichloromethane resulted in the silver–NHC complex as a crystalline solid (Scheme 2) [39].

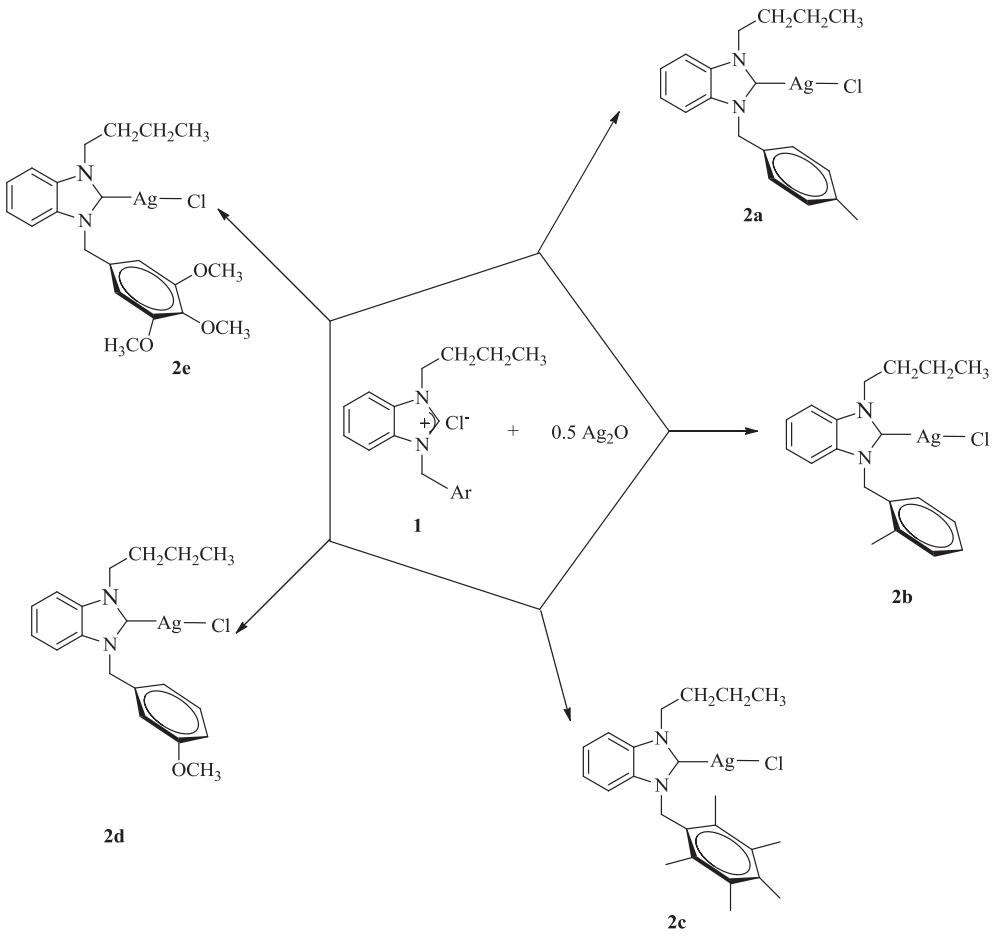
The benzimidazolium salts and silver–NHC complexes were characterized by analytical and spectroscopic techniques [34,39]. The FT-IR spectroscopy, ^{1}H- and ^{13}C NMR spectroscopy, and elemental analysis data of the title compound confirm the proposed structure.

The silver complexes are stable in the air and toward the moisture with good solubility in polar solvents. The successful formation of silver carbene complexes was indicated by the absence of a peak of NC*H*N proton region of δ 11.10–11.83 ppm in their ^{1}H NMR spectra further suggested full conversion to silver (I) NHC complexes.

Nolan et al. have recently reported the synthesis of a series of mono-carbene silver halides [R_2NHC]-AgCl and have demonstrated the influence of halide ions and the solvent on the structural formulas of Ag(I)–NHCs [40]. Similar results have been communicated by Lee et al. [41]. Ion-pair complexes have been obtained in the reaction of *N*,*N*-dimethylimidazoliumiodide with Ag_2O in DCM [42]. Fluxional behavior between [R_2NHC]-AgX and $[(R_2NHC)_2\text{-}Ag]^+[AgX_2]^-$ species was observed in solution for most of the complexes [43]. Mechanism of formation of silver *N*-Heterocyclic carbenes was reported by Peris and coworkers in 2007 [44]. According to these results, the monomeric compound NHC-Ag-X, in which the two ligands adopt a linear disposition, seems to be the most favorable species in CH_2Cl_2 solution.

It is well known that silver ions and silver based compounds are highly toxic to microorganisms [45,46] showing strong biocidal effects. Therefore as an advancement of our previous studies, we have now prepared a series of Ag(I) complexes of NHC and investigated their antimicrobial activity. Antimicrobial activity was observed for all compounds against the both gram(+)/(−) bacterials and fungal strains using the agar dilution procedure recommended by the Clinical and Laboratory Standards Institute [47–49]. The solvent used to prepare the stock solutions (DMSO) played no role in growth inhibition on the same bacteria strains. The antimicrobial activities of the NHC precursors (**1a**–**1e**) and their corresponding silver complexes (**2a**–**2e**) are summarized in Table 1.

As shown table, antimicrobial activity was observed in silver–NHC complexes (**2a–2e**) tested against bacteria and fungi at 100–25 μg/mL concentrations. NHC precursors (**1a–1e**) are less active than corresponding silver complexes against all bacteria strains. Same activity was observed for compounds **1b** with **1c** and **2c** with **2e** against all bacteria strains. Compound **2a** was found effective in inhibiting the growth of all bacterial strains with MICs values between 25 and 50 μg/mL. Especially these compounds are more effective against fungi strains (Table 1). On comparison with the benzimidazolium salts, the silver complexes have shown enhanced activity. The complexes exhibited enhanced antibacterial activity, which is due to the synergistic effect that increases the lipophilicity of the complexes. Because microorganism cell is surrounded by a lipid membrane. Although the cytotoxic effects of silver against Gram-positive and Gram-negative bacteria have long been established, the mechanisms of action are not completely understood. Sporadic studies of the cell toxicity mechanisms of silver suggest that silver ions kill organisms through a variety of ways.



Scheme 2. Synthesis of silver–NHC complexes (**2a**–**2e**).

In conclusion, a series of novel unsymmetrically substituted *N*-heterocyclic carbene precursors and their silver complexes were synthesized and characterized by ^{1}H NMR, ^{13}C NMR, IR and elemental analyses. New silver complexes shown high antibacterial activity compared with the precursors against gram(+)/(−) and fungi strains. More studies are now in progress including a larger collection of bacteria of different species in order to determine if the antimicrobial activity is species dependent and its possible application in different fields. New biological active Pt or Au NHC complexes will be prepared with an aim to develop robust cancer chemotherapeutic agents. Furthermore we will test the properties of both transmetallation reaction and catalysis of silver complexes described in this work.

Table 1
Minimal inhibitory concentrations (lg/mL) of compounds.

Compound	*E. coli*	*S. aureus*	*E. faecalis*	*P. aerug*	*C. albicans*	*C. tropicalis*
1a	200	200	200	200	100	100
1b	400	400	200	200	100	100
1c	400	400	200	200	100	100
1d	400	400	200	200	200	200
1e	800	800	400	400	200	200
2a	50	50	50	50	25	25
2b	100	100	100	50	50	50
2c	100	100	100	100	50	50
2d	100	100	50	50	25	25
2e	100	100	100	100	50	50
Amp.[a]	3.12	3.12	1.56	–	–	–
Cip.[a]	1.56	0.39	0.78	3.12	–	–
Fluc.[a]	–	–	–	–	3.12	3.12

[a] Amp.: Ampicillin, Cip.: Ciprofloxacin, Fluc.: Fluconazole.

Acknowledgments

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[34] All reactions carried out under argon in flame-dried glassware using standard Schlenk techniques. Chemicals were obtained from Sigma Aldrich and Fluka. Melting points were determined in glass capillaries under air with an Electrothermal-9200 melting point apparatus. FT-IR spectra were recorded as KBr pellets in the range 400–4000 cm^{-1} with a ATI UNICAM 1000 spectrometer. ^{1}H and ^{13}C-NMR spectra were recorded with a Varian AS 400 Merkur spectrometer operating at 400 MHz (^{1}H), 100 MHz (^{13}C) in $CDCl_3$ with tetramethylsilane as an internal reference. Coupling constants (*J*values) are given in hertz. NMR multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, quint. = quintet, sex = sextet and m = multiplet signal. Synthesis of benzimidazolium salts (**1a**–**1e**) (Scheme 1). To a solution of 1-butylbenzimidazole (10 mmol) in DMF (10 ml) was added slowly aryl halides (10 mmol) at 25 °C and the resulting mixture was stirred at 80 °C for 12 h. Diethylether (15 ml) was added to obtain a white crystalline solid which was filtered off. The solid was washed with diethylether (3×15 ml), dried under vacuum. The crude product was recrystallized from EtOH–Et_2O at room temperature. *1-butyl-3-(4-methylbenzyl)benzimidazolium chloride* (**1a**)*:* ^{1}H NMR ($CDCl_3$): 0.97 (t, *J* = 7.3 Hz, 3H, $NCH_2CH_2CH_2CH_3$), 1.44 (sex., *J* = 7.5 Hz, 2H, $NCH_2CH_2CH_2CH_3$), 2.03 (quint., *J* = 7.5 Hz, 2H, $NCH_2CH_2CH_2CH_3$), 2.89 (s, 3H, $CH_2C_6H_4$-4-CH_3), 4.60 (t, 2H, *J* = 7.3 Hz, $NCH_2CH_2CH_2CH_3$), 5.80 (s, 2H, $CH_2C_6H_4$-4-CH_3), 7.12–7.39 (m, 8H, C_6H_4 and $CH_2C_6H_4$-4-CH_3), 11.80 (s, 1H, NCHN). $^{13}C\{1H\}$ NMR ($CDCl_3$): 13.5, 19.9, 21.2 ($NCH_2CH_2CH_2CH_3$, $NCH_2CH_2CH_2CH_3$ and $NCH_2CH_2CH_2CH_3$), 31.3 (C_6H_4-4-CH_3), 47.6 ($NCH_2CH_2CH_2CH_3$), 51.4 ($CH_2C_6H_4$-4-CH_3), 111.4, 112.1, 124.1, 124.2, 127.2, 129.7, 129.8, 131.7, 138.4, 138.5 (C_6H_4 and $CH_2C_6H_4$-4-CH_3), 143.5 (NCHN). M.p.: 195–196 °C, $\nu_{(CN)} = 1465\ cm^{-1}$. Anal. Calc. for $C_{19}H_{23}N_2Cl$: C, 72.48; H, 7.36; N: 8.90. Found: C, 72.44; H, 7.35; N: 8.87%. Yield 90% (0.283 g). *1-butyl-3-(2-methylbenzyl)benzimidazolium chloride* (**1b**)*:* ^{1}H NMR ($CDCl_3$): 0.99 (t, *J* = 7.3 Hz, 3H, $NCH_2CH_2CH_2CH_3$), 1.45 (sex., *J* = 7.8 Hz, 2H, $NCH_2CH_2CH_2CH_3$), 2.06 (quint., *J* = 7.5 Hz, 2H, $NCH_2CH_2CH_2CH_3$), 2.41 (s, 3H, $CH_2C_6H_4$-2-CH_3), 4.66 (t, 2H, *J* = 7.3 Hz, $NCH_2CH_2CH_2CH_3$), 5.93 (s, 2H, $CH_2C_6H_4$-2-CH_3), 7.10–7.73 (m, 8H, C_6H_4 and $CH_2C_6H_4$-2-CH_3); 11.65 (s, 1H, NCHN). $^{13}C\{1H\}$ NMR ($CDCl_3$): 13.5, 19.5, 19.8 ($NCH_2CH_2CH_2CH_3$, $NCH_2CH_2CH_2CH_3$ and $NCH_2CH_2CH_2CH_3$), 31.4 (C_6H_4-2-CH_3), 47.6 ($NCH_2CH_2CH_2CH_3$), 50.2 ($CH_2C_6H_4$-2-CH_3), 113.0, 114.0, 126.8, 127.0, 127.1, 128.2, 129.2, 130.7, 131.3, 131.4, 131.6, 136.6 (C_6H_4 and $CH_2C_6H_4$-2-CH_3), 144.0 (NCHN). M.p.: 190–191 °C, $\nu_{(CN)} = 1449\ cm^{-1}$. Anal. Calc. for $C_{19}H_{23}N_2Cl$: C, 72.48; H, 7.36; N, 8.90. Found: C, 72.44; H, 7.35; N, 8.87%. Yield 85 % (0.267 g). *1-butyl-3-(2,3,4,5,6-pentamethylbenzyl)benzimidazolium chloride* (**1c**)*:* ^{1}H NMR ($CDCl_3$): 0.96 (t, *J* = 7.3 Hz, 3H, $NCH_2CH_2CH_2CH_3$), 1.42 (sex., *J* = 7.5 Hz, 2H, $NCH_2CH_2CH_2CH_3$), 1.98 (quint., *J* = 7.5 Hz, 2H, $NCH_2CH_2CH_2CH_3$), 2.23, 2.27and 2.28 (s, 15H, $CH_2C_6(CH_3)_5$-2,3,4,5,6), 4.69 (t, 2H, *J* = 7.3 Hz, $NCH_2CH_2CH_2CH_3$) 5.89 (s, 2H, $CH_2C_6(CH_3)_5$- 2,3,4,5,6), 7.23–7.70 (m, 4H,C_6H_4), 11.10 (s, 1H, NCHN). $^{13}C\{1H\}$ NMR ($CDCl_3$): 16.9, 17.3, 19.8 ($C_6(CH_3)_5$-2,3,4,5,6), 13.52, 31.4, 47.5 ($NCH_2CH_2CH_2CH_3$, $NCH_2CH_2CH_2CH_3$ and $NCH_2CH_2CH_2CH_3$), 48.4 ($NCH_2CH_2CH_2CH_3$), 58.1($CH_2C_6(CH_3)_5$-2,3,4,5,6), 111.4, 112.1, 124.1, 124.3, 127.2, 129.7, 129.8, 131.7, 138.4,138.5 (C_6H_4 and $CH_2C_6(CH_3)_5$-2,3,4,5,6), 143.5 (NCHN). M.p.: 217–218 °C,$\nu_{(CN)} = 1459\ cm^{-1}$. Anal. Calc. for $C_{23}H_{31}N_2Cl$: C, 74.47; H, 8.42; N, 7.55. Found: C, 74.45; H, 8.39; N: 7.53%. Yield 95 % (0.333 g). *1-butyl-3-(3-methoxybenzyl)benzimidazolium chloride* (**1d**)*:* ^{1}H NMR ($CDCl_3$): 0.97 (t, *J* = 7.3 Hz, 3H, $NCH_2CH_2CH_2CH_3$), 1.45 (sex., *J* = 7.5 Hz, 2H, $NCH_2CH_2CH_2CH_3$), 2.03 (quint., *J* = 7.5 Hz, 2H, $NCH_2CH_2CH_2CH_3$), 3.70 (s, 3H, $CH_2C_6H_4$-3-OCH_3), 4.61 (t, 2H, *J* = 7.3 Hz, $NCH_2CH_2CH_2CH_3$), 5.85 (s, 2H, $CH_2C_6H_4$-3-OCH_3), 7.24-7.70 (m, 8H, C_6H_4 and $CH_2C_6H_4$-3-OCH_3), 11.65 (s, 1H, NCHN). $^{13}C\{1H\}$ NMR ($CDCl_3$): 13.5, 19.8 and 31.3 ($NCH_2CH_2CH_2CH_3$, $NCH_2CH_2CH_2CH_3$ and $NCH_2CH_2CH_2CH_3$), 47.5 ($NCH_2CH_2CH_2CH_3$), 51.3 ($CH_2C_6H_4$-3-OCH_3), 55.6 ($CH_2C_6H_4$-3-OCH_3), 112.9, 113.8, 113.9, 114.8, 120.4, 127.0, 127.1, 130.3, 131.3, 131.4, 134.4, 160.2 (C_6H_4 and $CH_2C_6H_4$- 3-OCH_3); 143.6 (NCHN). M.p.:191–192 °C, $\nu_{(CN)} = 1442\ cm^{-1}$. Anal. Calc. for $C_{19}H_{23}N_2OCl$: C, 68.97; H, 7.01; N, 8.47. Found: C, 68.93; H, 6.97; N, 8.51%. Yield 82 % (0.271 g). *1-butyl-3-(3,4,5-trimethoxybenzyl) benzimidazolium chloride* (**1e**)*:* ^{1}H NMR ($CDCl_3$): 0.97 (t, *J* = 7.3 Hz, 3H, $NCH_2CH_2CH_2CH_3$), 1.44 (sex., *J* = 7.5 Hz, 2H, $NCH_2CH_2CH_2CH_3$), 2.04 (quint., *J* = 7.8 Hz, 2H, $NCH_2CH_2CH_2CH_3$), 3.79 and 3.81 (s, 9H, $CH_2C_6H_2$-3,4,5-(OCH_3)$_3$), 5.29 (t, *J* = 7.5 Hz, 2H, $NCH_2CH_2CH_2CH_3$), 5.85 (s, 2H, $CH_2C_6H_2$-3,4,5-(OCH_3)$_3$), 7.28–7.75 (m, 6H, C_6H_4 and $CH_2C_6H_2$-3,4,5-(OCH_3)$_3$), 11.83 (s, 1H, NCHN). $^{13}C\{1H\}$ NMR ($CDCl_3$): 13.4, 19.8, 31.2 ($NCH_2CH_2CH_2CH_3$, $NCH_2CH_2CH_2CH_3$ and $NCH_2CH_2CH_2CH_3$), 47.5 ($NCH_2CH_2CH_2CH_3$), 51.6 ($CH_2C_6H_2$-3,4,5-(OCH_3)$_3$), 56.6 and 60.8 ($CH_2C_6H_2$-3,4,5-(OCH_3)$_3$), 106.1, 113.0, 113.8, 127.0, 127.1, 128.5, 131.2, 131.4, 138.5, 153.8 (C_6H_4 and $CH_2C_6H_2$-3,4,5-(OCH_3)$_3$), 143.6 (NCHN). M.p.: 194–195 °C, $\nu_{(CN)} = 1443\ cm^{-1}$. Anal. Calc. for $C_{21}H_{27}N_2O_3Cl$: C, 64.52; H, 6.96; N, 7.17. Found C, 64.48; H, 7.01; N, 7.20%. Yield 89 % (0.347

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5.81 %. Yield 81 % (0.386 g). Chloro[1-(butyl)-3-(3-methoxylbenzyl) benzimidazolylidene]silver(I), (2d) 1H NMR (CDCl3): 1.01 (t, J = 7.6 Hz, 3H, NCH2CH2CH2CH3), 1.45 (sex., 2H, J = 7.5 Hz NCH2CH2CH2CH3), 1.92 (quint., 2H, J = 7.8 Hz, NCH2CH2CH2CH3), 3.78 (s, 3H, CH2C6H4-3-OCH3), 4.45 (t, 2H, J = 7.3 Hz, NCH2CH2CH2CH3), 5.63 (s, 2H, CH2C6H4–3-OCH3), 6.78–7.42 (m, 8H, C6H4 and CH2C6H4-3-OCH3). 13C{1H} NMR (CDCl3): 13.5, 20.1 and 32.4 (NCH2CH2CH2CH3, NCH2CH2CH2CH3 and NCH2CH2CH2CH3), 49.6 (NCH2CH2CH2CH3), 53.3 (CH2C6H4-3-OCH3), 55.3 (C6H4-3-OCH3), 111.5, 112.2, 112.9, 113.6, 113.8, 113.9, 119.3, 124.3, 130.2, 133.8, 136.4 and 160.0 (C6H4 and CH2C6H4-3-OCH3). M.p.:225–228 °C, ν(CN) = 1455 cm^{-1}. Anal. Calc. for C19H22N2OAgCl: C, 52.14; H, 5.07; N, 6.40. Found C, 52.09; H, 5.10; N, 6.37 %. Yield 57 % (0.248 g). Chloro[1-(butyl)-3-(3,4,5-trimethoxylbenzyl) benzimidazolylidene]silver(I), (2e) 1H NMR (CDCl3): 0.97 (t, J = 7.3 Hz, 3H, NCH2CH2CH2CH3), 1.42 (sex., J = 7.2 Hz, 2H, NCH2CH2CH2CH3), 1.92 (quint., J = 7.3 Hz, 2H, NCH2CH2CH2CH3), 3.81 and 3.82(s, 9H, CH2C6H2-3,4,5-(OCH3) 3), 4.45 (t, J = 7.2 Hz, 2H, NCH2CH2CH2CH3), 5.55 (s, 2H, CH2C6H2-3,4,5-(OCH3)3), 7.28–7.49 (m, 6H, C6H4 and CH2C6H2-3,4,5-(OCH3)3). 13C{1H} NMR (CDCl3): 13.7, 20.2 and 32.3 (NCH2CH2CH2CH3, NCH2CH2CH2CH3 and NCH2CH2CH2CH3), 49.59 (NCH2CH2CH2CH3), 53.5 (CH2C6H2-3,4,5-(OCH3)3), 56.3 and 60.9 (C6H2-3,4,5,-(OCH3)3), 104.6, 111.6, 112.0, 124.3, 124.4, 130.6, 133.7, 133.8, 138.2, and 153.7 (C6H4 and CH2C6H2–3,4,5-(OCH3)3). M.p.: 204–205 °C, ν(CN) = 1478 cm^{-1}. Anal. Calc. for C21H26N2O3AgCl: C, 50.67; H, 5.26; N, 5.63. Found C, 50.69; H, 5.20; N, 5.65 %. Yield 80 % (0.397 g).

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