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N-Phenyl-substituted carbene precursors and their silver complexes: synthesis, characterization and antimicrobial activities

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A series of unsymmetrically substituted *N*-heterocyclic carbene (NHC) precursors (1a–e) were synthesized from the reaction of *N*-phenylbenzimidazole with various alkyl halides. These compounds were used to synthesize NHC–silver(I) complexes (2a–e). The five new 1-phenyl-3-alkylbenzimidazolium salts (1a–e) and their NHC–silver complexes (2a–e) were characterized by the ^{1}H NMR, ^{13}C NMR and FT-IR spectroscopic methods and elemental analysis techniques. Also, the two NHC–silver complexes 2b and 2c were characterized by single-crystal X-ray crystallography, which confirmed the linear C—Ag—Cl arrangements. The antibacterial activities of the NHC precursor and NHC–silver complexes were tested against three Gram-positive bacterial strains (*Bacillus subtilis*, *Listeria monocytogenes* and *Staphylococcus aureus*) and three Gram-negative bacterial strains (*Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*) using the microdilution broth method. The NHC–silver complexes showed higher antibacterial activity than the NHC precursors. In addition, silver complexes 2a–d showed high antibacterial activity against the Gram-positive bacteria *L. monocytogenes* and *S. aureus* compared to the standard, tetracycline. Copyright © 2014 John Wiley & Sons, Ltd.

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Keywords: *N*-heterocyclic carbene; benzimidazolium salt; silver complex; antimicrobial activity; X-ray diffraction

Introduction

N-Heterocyclic carbenes (NHCs) are stable singlet carbenes that can act as excellent donor ligands towards 52 elements, except Sc, Tc and Cd, in the periodic table.[1] Since the first report by Öfele in 1968, and the first isolation by Arduengo in 1991, NHCs have attracted much attention.[2–10] NHC–metal complexes have higher stability towards oxygen, heat and moisture than phosphine metal-based complexes, which makes them quite attractive as phosphine substitutes.[11] NHCs are most frequently prepared via deprotonation of the corresponding azolium salts such as benzimidazolium, tetrazolium, triazolium and imidazolium, and have been extensively used as organocatalysts and ancillary ligands in transition metal-catalysed reactions.[12–17] Using these ligands, their metal complexes have shown high catalytic activity in metathesis, the creation of furan, polymerization, hydrosilylation, hydrogenation and coupling reactions.[18–33]

Recently, NHC–silver complexes have attracted particular interest because of their wide use as ligand transfer agents to group 8–10 metals, catalysis, nanomaterials and for their different biological activity as antimitochondrial, antimicrobial and anticancer agents.[1,34–50] Thus NHC–silver complexes have had a significant role in the rapid development of NHC–metal complexes. One important reason for this is that NHC–silver complexes are easily synthesized by three different methods: (i) reaction of azolium salts with silver bases such as Ag_2CO_3, AgOAc and Ag_2O; (ii) reaction of free NHC–carbene salts; and (iii) reaction of azolium salts with silver salts under basic phase transfer conditions.[46,51,52] Among these approaches, route (i) is more convenient and the most frequently used.

In this study, a new series of phenyl-substituted NHC precursors and their NHC–silver complexes were synthesized and characterized by elemental analysis, FT-IR, NMR and X-ray diffraction (for **2b** and **2c**) methods. The antibacterial activities of the NHC precursors and NHC–silver complexes were tested against three Gram-positive bacterial strains – *Bacillus subtilis*, *Listeria monocytogenes*, *Staphylococcus aureus* – and three Gram-negative bacterial strains – *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* – by using the microdilution broth method.

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Experimental

General Considerations

All reactions for the preparation of *N*-phenyl-substituted benzimidazolium salts (**1a–e**) and their NHC–silver complexes (**2a–e**) were carried out under argon in flame-dried glassware using standard Schlenk techniques. Solvents were purified and degassed by standard procedures. Chemicals were purchased from Aldrich and Merck. All ^{1}H and ^{13}C NMR were performed in $CDCl_3$ and DMSO. The ^{1}H and ^{13}C NMR spectra were recorded using a Bruker AC300P FT spectrometer operating at 300.13 MHz (^{1}H) and 75.47 MHz (^{13}C). Chemical shifts (δ) are given in ppm relative to tetramethylsilane as an internal reference. Coupling constants (J) are given in hertz (Hz). ^{1}H NMR signals are labelled as singlet (s), doublet (d), triplet (t) or multiplet (m). FT-IR spectra were recorded on a Mattson 1000 spectrophotometer, with wavenumbers in cm^{-1}. Melting points were measured in glass capillary tubes with an Electrothermal 9200 melting point apparatus. Elemental analyses were performed using TUBITAK Microlab.

X-ray diffraction data for **2b** and **2c** were collected on a Bruker Kappa APEXII CCD diffractometer with Mo-K_α ($\lambda = 0.71073$ Å) radiation at room temperature. Lattice parameters were obtained by least-squares fit to the optimized setting angles of the collected reflections by means of APEX2.[53] Multi-scan numerical absorption correction with SADABS was employed.[54] The molecular structures of **2b** and **2c** were solved by direct methods using the SHELXS-97 program[55] and refined by full-matrix least-squares on F^2 using SHELXL-97.[55]

For **2b** and **2c**, all H atoms were placed geometrically and treated as riding with C—H = 0.93 Å (aromatic), 0.96 Å (methyl), 0.97 Å (methylene), with $U_{iso}(H) = 1.2U_{eq}$(methylene, methine) or $U_{iso}(H) = 1.5U_{eq}$(methyl). Details of the crystallographic data and structure refinement for **2b** and **2c** are listed in Table 1.

Table 1. Crystallographic data and structure refinement for **2b** and **2c**

Compound	**2b**	**2c**
Empirical formula	$C_{25}H_{26}AgClN_2$	$C_{23}H_{22}AgClN_2O_3$
Formula weight	497.80	517.75
Crystal system	Triclinic	Triclinic
Space group	$P\bar{1}$	$P\bar{1}$
Cell parameters (Å, °)		
a	9.3934 (2)	9.3399 (3)
b	9.9077 (2)	10.4602 (3)
c	12.5491 (3)	12.3177 (3)
α	74.355 (1)	67.483 (1)
β	81.372 (1)	79.146 (1)
γ	85.213 (1)	77.227 (1)
Volume (Å^3), *Z*	1110.78 (4), 2	1076.96 (5), 2
Absorption coefficient (mm^{-1})	1.041	1.087
Crystal size (mm^3)	0.20 × 0.22 × 0.30	0.25 × 0.16 × 0.14
D_x ($Mg\,m^{-3}$)	1.488	1.597
F(000)	508	524
θ range (°)	2.1–28.0	2.3–28.3
Number of measured reflections	17 832	19 380
Number of unique reflections	5 233	5 322
Number of reflections with $I > 2\sigma(I)$	4 394	4 189
Number of refined parameters	268	274
Goodness of fit on F^2	1.03	1.03
$R[F^2 > 2\sigma(F^2)]$, wR_2	0.029, 0.075	0.033, 0.071
Residual density (e Å^{-3})	−0.54, 0.42	−0.39, 0.50
CCDC No.	891 112	891 111

Synthesis

General preparation of 1-phenyl-3-alkylbenzimidazolium salts, ***1***

To a solution of 1-phenylbenzimidazole (1.0 mmol) in DMF (4 ml), alkyl halides (1.0 mmol) were added slowly at room temperature and the resulting mixture was stirred at 80 °C for 12 h. Diethyl ether (15 ml) was added to obtain a crystalline solid which was filtered off. The solid was washed with diethyl ether (2 × 15 ml) and dried under vacuum. The crude product was recrystallized from ethyl alcohol/diethyl ether at room temperature. The crystallized compounds were obtained as white, white, cream, white and cream solids for NHC ligand precursors (**1a–e**), respectively.

1-Phenyl-3-(2,4,6-trimethylbenzyl)benzimidazolium chloride, ***1a***. Yield 86%; m. p. 197–198 °C; $\nu_{(CN)}$: 1548.74 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$); δ: 2.31 [s, 3 H, $NCH_2C_6H_2(CH_3)_3$-4]; 2.39 [s, 6 H, $NCH_2C_6H_2(CH_3)_3$-2,6]; 6.23 [s, 2 H, $NCH_2C_6H_2(CH_3)_3$-2,4,6]; 6.93 [s, 2 H, $NCH_2C_6H_2(CH_3)_3$-2,4,6]; 7.16–7.87 (m, 9 H, C_6H_4 and C_6H_5); 11.72 (s, 1 H, NC*H*N). ^{13}C NMR (75.47 MHz, $CDCl_3$); δ: 20.5 [$NCH_2C_6H_2(CH_3)_3$-2,6]; 21.1 [$NCH_2C_6H_2(CH_3)_3$-4]; 48.2 [$NCH_2C_6H_2(CH_3)_3$-2,4,6]; 113.5, 114.3, 127.4 and 131.5 ($C_6H_4N_2$); 124.9, 130.1, 130.8 and 132.9 (NC_6H_5); 125.6, 128.5, 138.1 and 139.5 [$NCH_2C_6H_2(CH_3)_3$]; 143.4 (NCHN). Anal. Calcd for $C_{23}H_{23}N_2Cl$: C, 76.12; H, 6.39; N, 7.72. Found: C, 76.23; H, 6.28; N, 7.69%.

1-Phenyl-3-(2,3,4,5,6-pentamethylbenzyl)benzimidazolium chloride, ***1b***. Yield 83%, m.p. 215–216 °C. $\nu_{(CN)}$ = 1547.88 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$); δ: 2.23 [s, 3 H, $NCH_2C_6(CH_3)_5$-4]; 2.27 [s, 6 H, $NCH_2C_6(CH_3)_5$-2,6]; 2.37 [s, 6 H, $NCH_2C_6(CH_3)_5$-3,5]; 6.26 [s, 2 H, $NCH_2C_6(CH_3)_5$-2,3,4,5,6]; 7.48–7.88 (m, 9 H, C_6H_4 and C_6H_5); 11.38 (s, 1 H, NC*H*N). ^{13}C NMR (75.47 MHz, $CDCl_3$); δ: 16.9 [$NCH_2C_6(CH_3)_5$-2,6]; 17.2 [$NCH_2C_6(CH_3)_5$-4,]; 17.3 [$NCH_2C_6(CH_3)_5$-3,5]; 49.4 [$NCH_2C_6(CH_3)_5$-2,3,4,5,6]; 113.4, 114.5, 125.0 and 131.7 ($C_6H_4N_2$); 125.8, 130.7, 131.5 and 135.6 (NC_6H_5); 127.4, 133.0, 133.7 and 137.0 [$NCH_2C_6(CH_3)_5$]; 142.9 (NCHN). Anal. Calcd for $C_{25}H_{27}N_2Cl$: C, 76.80; H, 6.96; N, 7.17. Found: C, 76.69; H, 7.05; N, 7.13%.

1-Phenyl-3-(3,4,5-trimethoxybenzyl)benzimidazolium chloride, ***1c***. Yield 88%, m.p. 226–227 °C. $\nu_{(CN)}$ = 1591.58 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$); δ: 3.46 [s, 6 H, $NCH_2C_6H_2(OCH_3)_3$-3,5]; 3.56 [s, 3 H, $NCH_2C_6H_2(OCH_3)_3$-4]; 6.65 [s, 2 H, $NCH_2C_6H_2(OCH_3)_3$-3,4,5]; 6.92 (s, 2 H, $NCH_2C_6H_2(OCH_3)_3$-3,4,5]; 7.31–7.65 (m, 11 H, C_6H_4 and C_6H_5); 10.21 (s, 1 H, NC*H*N). ^{13}C NMR (75.47 MHz, $CDCl_3$); δ: 53.7 [$NCH_2C_6H_2(OCH_3)_3$-3,5]; 58.7 [$NCH_2C_6H_2(OCH_3)_3$-4]; 63.4 [$NCH_2C_6H_2(OCH_3)_3$-3,4,5]; 108.8, 116.1, 133.3 and 134.2, ($C_6H_4N_2$); 130.2, 131.7, 132.9 and 133.6 (NC_6H_5); 127.3, 134,9, 135.2 and 139.9 [$NCH_2C_6H_2(OCH_3)_3$]; 155.6 (NCHN). Anal. Calcd for $C_{23}H_{23}N_2O_3Cl$: C, 67.23; H, 5.64; N, 6.82. Found: C, 67.35; H, 5.51; N, 6.79%.

1-Phenyl-3-naphthalenomethylbenzimidazolium chloride, ***1d***. Yield 82%, m.p. 220–221 °C. $\nu_{(CN)}$ = 1595.98 cm^{-1}.^{1}H NMR (300.13 MHz, $CDCl_3$); δ: 6.65 (s, 2 H, $NCH_2C_{10}H_7$); 7.28–7.89 (m, 16 H, C_6H_4, C_6H_5 and $NCH_2C_{10}H_7$); 11.70 (s, 1 H, NC*H*N). ^{13}C NMR (75.47 MHz, $CDCl_3$); δ: 49.6 ($NCH_2C_{10}H_7$); 122.8, 124.9, 125.4, 126.5, 127.7, 128.1, 128.4, 129.1, 130.2, 130.7, 130.9, 131.3, 131.7, 133.0 and 133.9 ($C_6H_4N_2$, NC_6H_5 and $NCH_2C_{10}H_7$); 143.4 (NCHN). Anal. Calcd for $C_{24}H_{19}N_2Cl$: C, 77.72; H, 5.16; N, 7.55. Found: C, 77.81; H, 5.09; N, 7.50%.

1-Phenyl-3-(2-morpholinoethyl)benzimidazolium chloride, ***1e***. Yield 80%, m.p. 148–150 °C. $\nu_{(CN)}$ = 1552.82 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$); δ: 2.27 [t, *J*: 5.5 Hz, 2 H, $NCH_2CH_2NC_4H_8O$]; 3.04 [t, *J*: 4.6 Hz, 4 H, $NCH_2CH_2N(CH_2CH_2)_2O$]; 3.63 (t, *J*: 5.8 Hz, 2 H, $NCH_2CH_2NC_4H_8O$); 5.09 [t, *J*: 4.8 Hz, 4 H, $NCH_2CH_2N(CH_2CH_2)_2O$]; 7.34–7.92 (m, 9 H, C_6H_4 and C_6H_5); 11.42 (s, 1 H, NCHN). ^{13}C NMR (75.47 MHz, $CDCl_3$); δ: 44.7 [$NCH_2CH_2N(CH_2CH_2)_2O$]; 56.6 [$NCH_2CH_2N(CH_2CH_2)_2O$]; 53.6 [$NCH_2CH_2N(CH_2CH_2)_2O$]; 66.9 [$NCH_2CH_2N(CH_2CH_2)_2O$]; 110.5, 113.7, 130.1 and 131.1 (C_6H_4); 124.8, 127.5, 130.8 and 131.5 (C_6H_5); 143.4 (NCHN). Anal. Calcd for $C_{19}H_{22}N_3OCl$: C, 66.37; H, 6.45; N, 12.22. Found: C, 66.29; H, 6.51; N, 12.27%.

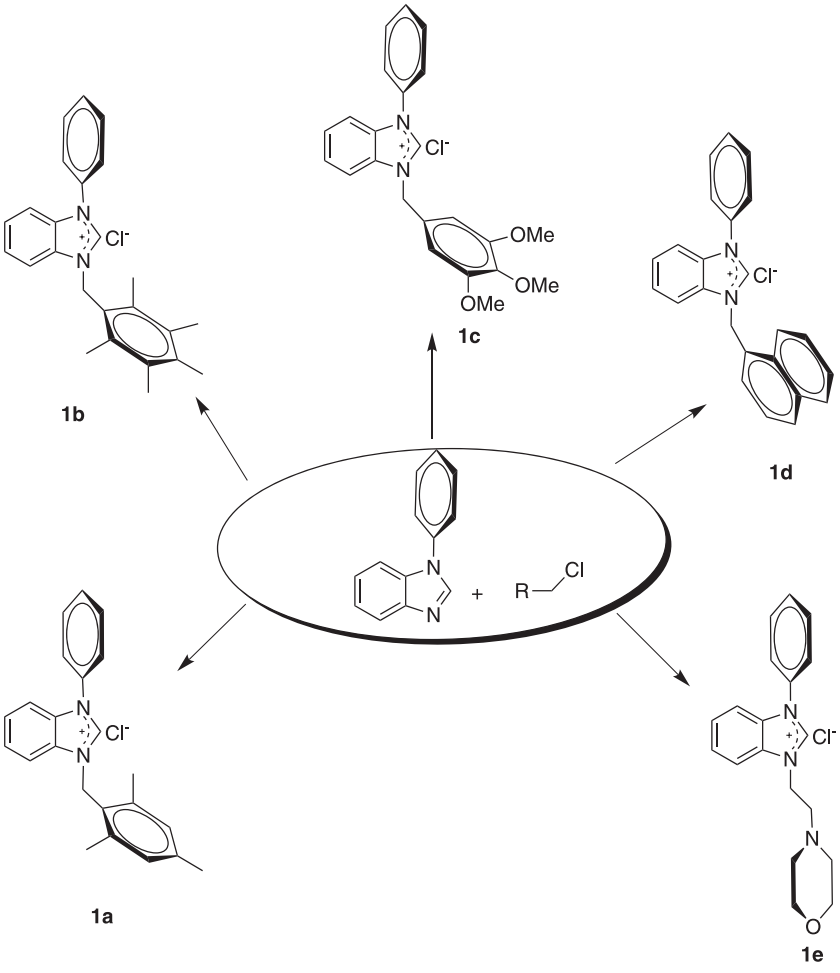
*General preparation of N-*phenyl-substituted NHC–silver complexes, **2**

A solution of benzimidazolium salt (1.0 mmol), silver oxide (0.5 mmol) and activated 4 molecular sieves in dichloromethane (30 ml) was stirred at room temperature for 10 h in the dark. The reaction mixture was filtered through celite and the solvent removed under reduced pressure. The crude product was recrystallized from dichloromethane–dimethyl ether at room temperature. The crystallized compounds were obtained as very light pink, white, white, very light cream and cream solid crystals for NHC–silver complexes (**2a–e**), respectively.

[1-Phenyl-3-(2,4,6-trimethylbenzyl)benzimidazol-2-ylidene]chlorosilver(I), ***2a***. Yield 71%, m.p. 244–245 °C. $\nu_{(CN)}$ = 1595.81 cm^{-1}. ^1H NMR (300.13 MHz, DMSO); δ: 1.65 [s, 3 H, $NCH_2C_6H_2(CH_3)_3$-4]; 2.52 [s, 6 H, $NCH_2C_6H_2(CH_3)_3$-2,6]; 5.55 [s, 2 H, $NCH_2C_6H_2(CH_3)_3$-2,4,6]; 6.71 [s, 2 H, $NCH_2C_6H_2(CH_3)_3$-2,4,6]; 7.45–8.26 (m, 9 H, C_6H_4 and C_6H_5). ^{13}C NMR (75.47 MHz, DMSO); δ: 20.4 [$NCH_2C_6H_2(CH_3)_3$-2,6]; 21.1 [$NCH_2C_6H_2(CH_3)_3$-4]; 55.3 [$NCH_2C_6H_2(CH_3)_3$-2,4,6]; 112.8, 125.0, 128.2 and 130.4 [$C_6H_4N_2$]; 125.5, 129.8, 134.1 and 135.2 [NC_6H_5]; 126.7, 134.3, 137.9 and 138.5 [$NCH_2C_6H_2(CH_3)_3$]; the carbenic carbon was not detected. Anal. Calcd for $C_{23}H_{22}N_2AgCl$: C, 58.81; H, 4.72; N, 5.96. Found: C, 58.90; H, 4.63; N, 5.88%.

[1-Phenyl-3-(2,3,4,5,6-pentamethylbenzyl)benzimidazol-2-ylidene]chlorosilver (I), ***2b***. Yield 75%, m.p. 263–264 °C. $\nu_{(CN)}$ = 1593.44 cm^{-1}. ^1H NMR (300.13 MHz, DMSO); δ: 1.94 [s, 3 H, $NCH_2C_6(CH_3)_5$-4]; 2.17 [s, 12 H, $NCH_2C_6(CH_3)_5$-2,3,5,6]; 5.62 [s, 2 H, $NCH_2C_6(CH_3)_5$-2,3,4,5,6]; 7.47–8.20 (m, 9 H, C_6H_4 and C_6H_5). ^{13}C NMR (75.47 MHz, DMSO); δ: 17.3 [$NCH_2C_6(CH_3)_5$-2,3,5,6]; 17.5 [$NCH_2C_6(CH_3)_5$-4]; 54.5 [$NCH_2C_6(CH_3)_5$-2,3,4,5,6]; 112.4, 112.7, 125.5 and 130.4 [$C_6H_4N_2$]; 126.6, 129.8, 130.3 and 133.4 [NC_6H_5]; 127.3, 133.5, 134.2 and 135.1 [$NCH_2C_6(CH_3)_5$]; the carbenic carbon was not detected. Anal. Calcd for $C_{25}H_{26}N_2AgCl$: C, 60.32; H, 5.26; N, 5.63. Found: C, 60.19; H, 5.34; N, 5.69%.

[1-Phenyl-3-(3,4,5-trimethoxybenzyl)benzimidazol-2-ylidene]chlorosilver(I), ***2c***. Yield 73%, m.p. 267–269 °C. $\nu_{(CN)}$ = 1594.06 cm^{-1}.^1H NMR (300.13 MHz, DMSO); δ: 3.61 [s, 6 H, $NCH_2C_6H_2(OCH_3)_3$-3,5]; 3.65 [s, 3 H, $NCH_2C_6H_2(OCH_3)_3$-4]; 5.67 [s, 2 H, $NCH_2C_6H_2(OCH_3)_3$-3,4,5]; 6.97 [s, 2 H, $NCH_2C_6H_2(OCH_3)_3$-3,4,5]; 7.24–8.00 (m, 9 H, C_6H_4 and C_6H_5). ^{13}C NMR (75.47 MHz, DMSO); δ: 52.6 [$NCH_2C_6H_2(OCH_3)_3$-3,5]; 56.4 [$NCH_2C_6H_2(OCH_3)_3$-4]; 60.5 [$NCH_2C_6H_2(OCH_3)_3$-3,4,5]; 106.1, 112.6, 131.8 and 134.2 ($C_6H_4N_2$); 125.4, 126.5, 130.5 and 133.7 (NC_6H_5); 113.1, 137.8, 138.1 and 153.5 [$NCH_2C_6H_2(OCH_3)_3$]; the carbenic carbon was not detected. Anal. Calcd for $C_{23}H_{22}N_2O_3AgCl$: C, 53.35; H, 4.28; N, 5.41. Found: C, 53.24; H, 4.37; N, 5.43 %.



Scheme 1. Synthesis of *N*-phenyl-substituted benzimidazolium salts as NHC precursors.

[1-Phenyl-3-naphthalenomethylbenzimidazol-2-ylidene] chlorosilver(I), ***2d***. Yield 79%, m.p. 226–227 °C. $\nu_{(CN)}$ = 1594.13 cm^{-1}.^1H NMR (300.13 MHz, DMSO); δ: 6.28 (s, 2 H, $NCH_2C_{10}H_7$); 7.07–7.76 (m, 16 H, C_6H_4, C_6H_5 and $NCH_2C_{10}H_7$). ^{13}C NMR (75.47 MHz, DMSO); δ: 50.3 ($NCH_2C_{10}H_7$); 123.6, 125.5, 126.0, 126.8, 127.3, 129.3, 129.9, 130.4, 130.7, 131.9, 133.8, 134.1, 134.3 and 138.1 ($C_6H_4N_2$, NC_6H_5 and $NCH_2C_{10}H_7$); the carbenic carbon was not detected. Anal. Calcd for $C_{24}H_{18}N_2AgCl$: C, 60.34; H, 3.80; N, 5.86. Found: C, 60.45; H, 3.69; N, 5.77%.

[1-Phenyl-3-(2-morpholinoethyl)benzimidazol-2-ylidene] chlorosilver(I), ***2e***. Yield 80%, m.p. 134–135 °C. $\nu_{(CN)}$ = 1594.48 cm^{-1}. ^1H NMR (300.13 MHz, DMSO); δ: 2.44 [t, *J*: 5.0 Hz, 4 H, $NCH_2CH_2N(CH_2CH_2)_2O$]); 2.52 [t, *J*: 5.9 Hz, 2 H, $NCH_2CH_2N(CH_2CH_2)_2O$]; 2.79 [t, 2 H, *J*: 5.8 Hz, $NCH_2CH_2N(CH_2CH_2)_2O$]; 4.63 [t, *J*: 5.3 Hz, 4 H, $NCH_2CH_2N(CH_2CH_2)_2O$]; 7.46–7.96 (m, 9 H, C_6H_4 and C_6H_5). ^{13}C NMR (75.47 MHz, DMSO); δ: 46.7 [$NCH_2CH_2N(CH_2CH_2)_2O$]; 58.2 [$NCH_2CH_2N(CH_2CH_2)_2O$]; 54.0 [$NCH_2CH_2N(CH_2CH_2)_2O$]; 66.6 [$NCH_2CH_2N(CH_2CH_2)_2O$]; 112.5, 124.9, 129.8 and 133.8 (C_6H_4); 125.2, 126.6, 130.6, 130.3 and

138.2 (C_6H_5); 188.7 (2-$C_{carbene}$). Anal. Calcd for $C_{19}H_{21}N_3OAgCl$: C, 50.63; H, 4.70; N, 9.32. Found: C, 50.51; H, 4.79; N, 9.35%.

Antibacterial Activity

The antibacterial activities of the synthesized compounds were tested against *B. subtilis* (ATCC 6633), *E. coli* (ATCC 25922), *K. pneumoniae* (FMC 5), *L. monocytogenes* (1/2B), *Ps. aeruginosa* (ATCC 27853) and *S. aureus* (ATCC 25923). Antibacterial activity was evaluated by determining the minimum inhibitory concentration (MIC) using the microdilution broth method with some modification, according to Ávila *et al.*[56] The compounds were dissolved in dimethyl sulfoxide (DMSO) to obtain a stock solution of 3200 $\mu g\,l^{-1}$ concentration. This solution was then added to the first two wells on a micro-titre plate and twofold dilutions were made in Mueller Hinton broth (Oxoid, Basingstoke, UK) from well two. The final concentration range was from 25 to 3200 $\mu g\,l^{-1}$. One sample (100 μl) of each diluted solution and the samples for both growth and sterility controls (containing sterile culture medium and DMSO, and no antimicrobial agents) were distributed in a 96-well plate. Suspensions of bacteria were prepared to contain approximately 10^5 cfu ml^{-1} and applied to microtitration plates and incubated at 37 °C for 24 h. Bacterial growth was detected by the addition of a solution (2.5 mg ml^{-1}) of 2,3,5-triphenyl tetrazolium chloride (TTC) in 96% EtOH. The MIC values ($\mu g\,ml^{-1}$) of the tested substances, i.e. the lowest concentration at which no growth occurred, were determined by the TTC colorimetric reaction from yellow (absence of growth) to purple. All experiments were performed in duplicate. DMSO was found to have no effect on the microorganisms for all the concentrations tested (data not shown). Tetracycline (Sigma T3258-T6) was used as positive control to assess the MIC values of the reference strains.

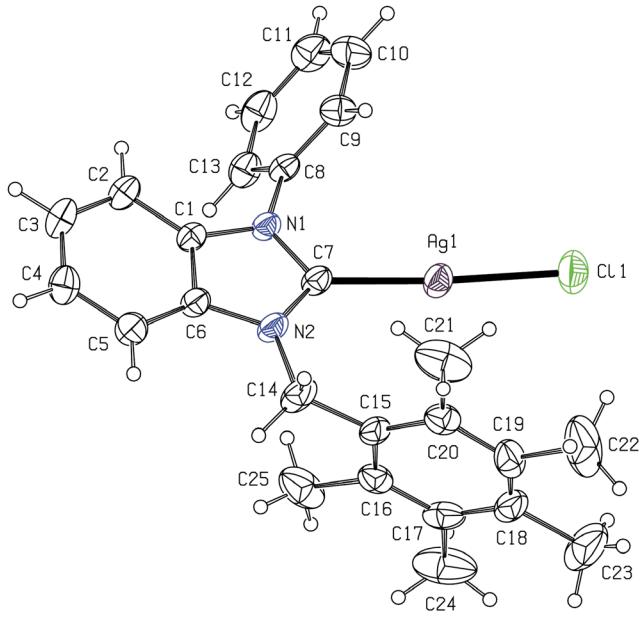
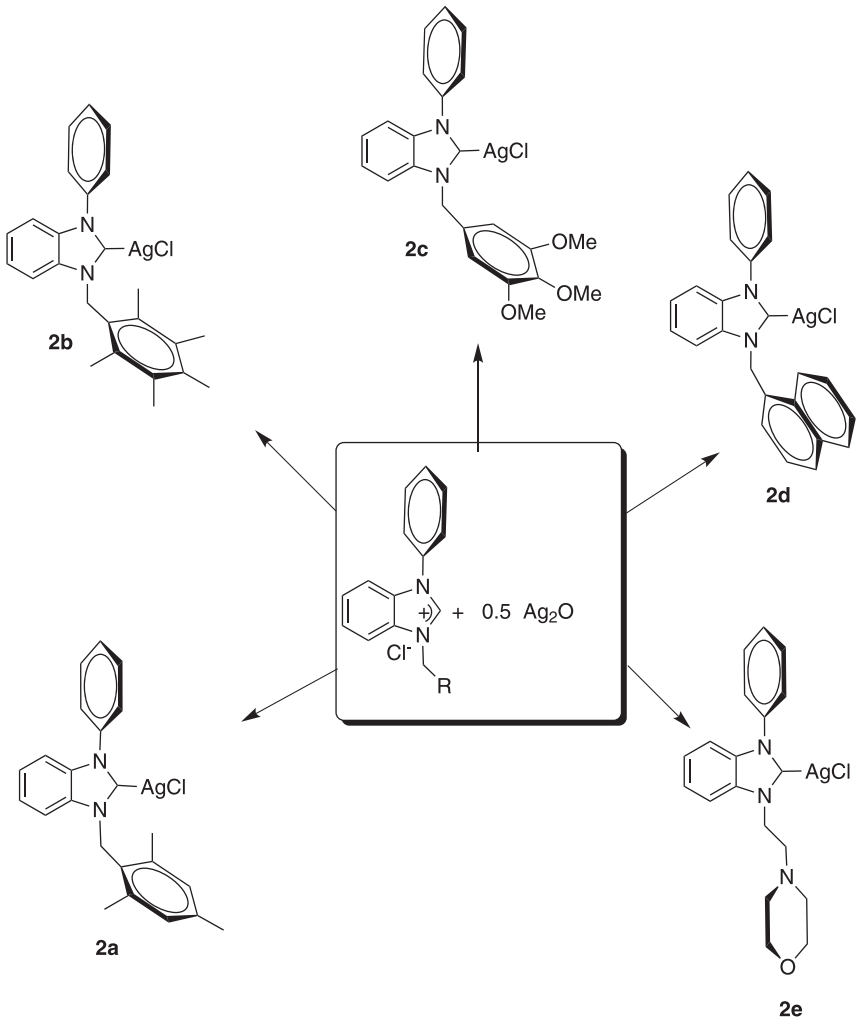


Figure 1. Molecular structure of **2b** with displacement ellipsoids drawn at the 30% probability level.



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

Results and Discussion

Synthesis of *N*-Heterocyclic Carbene Precursors and Silver Complexes

The synthetic routes for phenyl-substituted *N*-heterocyclic carbene precursors and their corresponding silver complexes described in this study are given in Schemes 1 and 2, respectively. The 1-phenyl-3-alkylbenzimidazolium salts (**1a–e**) as *N*-phenyl-substituted NHC-precursors were obtained by quaternization *N*-phenylbenzimidazole with various alkyl halides in DMF (Scheme 1). The obtained salts were stable to air and moisture both in the solid state and in solution. The structures of **1a–e** were established by spectroscopic data and elemental analysis. The ^{1}H NMR spectra of the benzimidazolium salts further

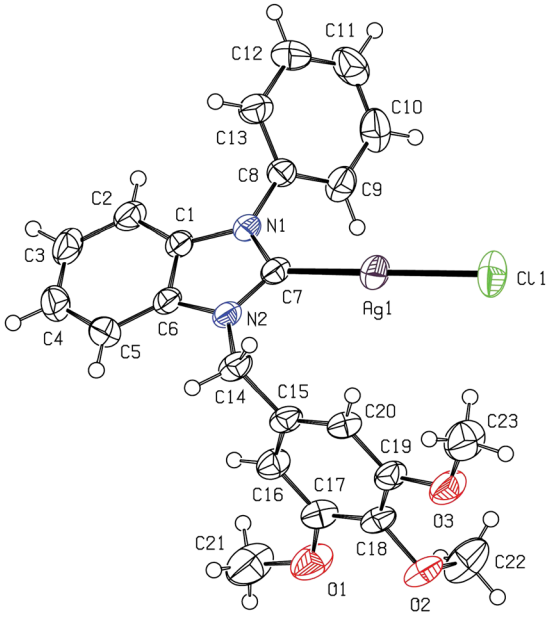


Figure 2. Molecular structure of **2c** with displacement ellipsoids drawn at the 50% probability level.

supported the assigned structures; the resonance for C(2)—H was observed as sharp singlets at 11.72, 11.38, 10.21, 11.70 and 11.42 ppm for **1a–e**, respectively. ^{13}C NMR chemical shifts were consistent with the proposed structures; the imino carbons are typical singlets in the ^{1}H-decoupled mode at 143.4, 142.9, 155.6, 143.4 and 143.4 ppm for benzimidazolium salts (**1a–e**), respectively. The FT-IR data clearly indicate the presence of —C=N—with bands ascribed to ν(C= N) being observed at 1548.7, 1590.2, 1591.6, 1596.0 and 1593.36 cm^{-1} for benzimidazolium salts (**1a–e**), respectively.

The NHC–silver complexes (**2a–e**) were synthesized by treatment of 1-phenyl-3-alkylbenzimidazolium salts with 0.5 equiv. Ag_2O in dichloromethane (Scheme 2). The reaction mixture was stirred for 10 h at room temperature to afford the NHC–silver complexes. NHC–silver complexes (**2a–e**) were soluble in halogenated solvents and insoluble in non-polar solvents. The NHC–silver complexes were characterized by spectroscopic methods (^{1}H NMR, ^{13}C NMR and FT-IR) and elemental analysis. Furthermore, the solid-state structures of **2b** and **2c** were analysed by single-crystal X-ray diffraction. ^{1}H NMR and ^{13}C NMR spectra were consistent with the proposed formulae. The absence of a downfield NC*H*N signal for silver complexes (**2a–e**) in the ^{1}H NMR spectra indicated a successful complex formation. Also in the ^{13}C NMR, the carbene carbon resonance observed in **1e** at

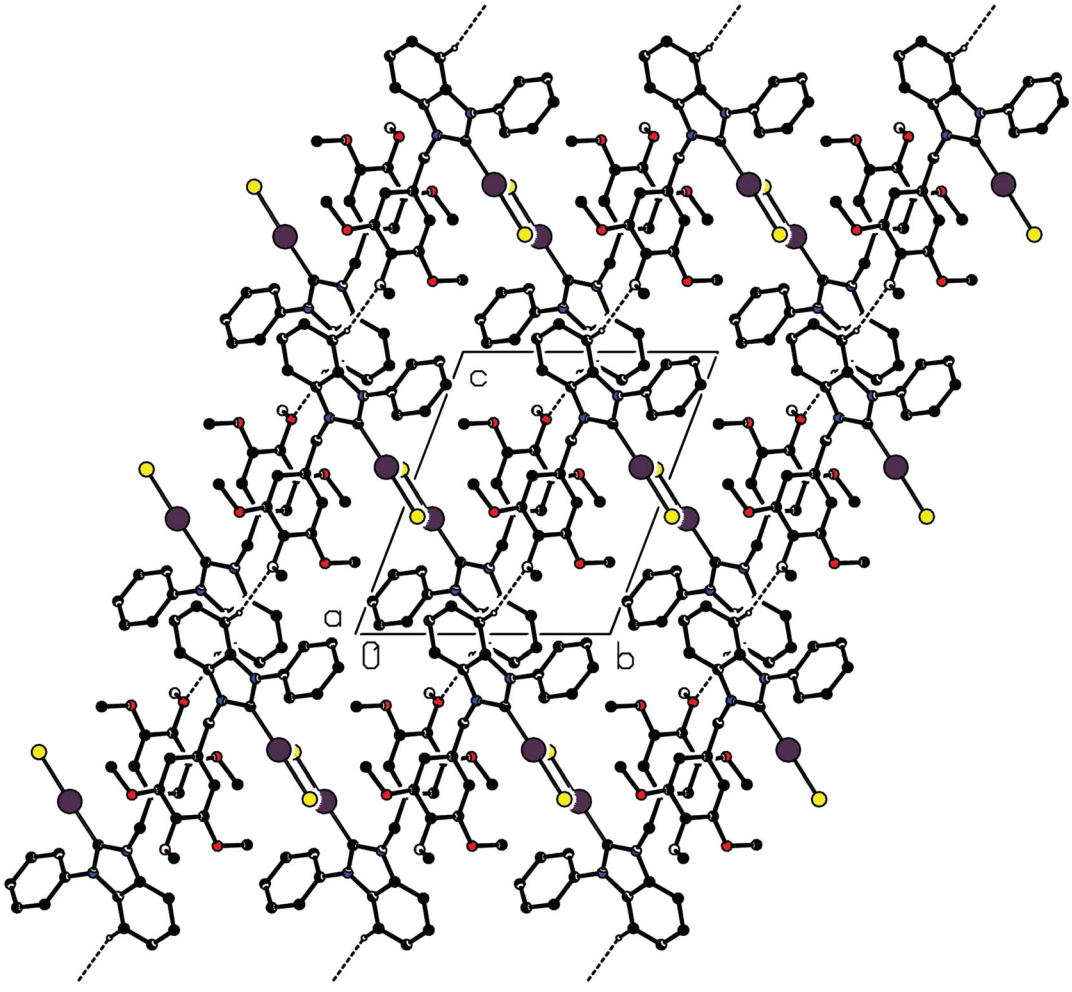


Figure 3. View of the hydrogen bonding and packing of **2c** down the *a*-axis. All hydrogen atoms not involved in hydrogen bonding are omitted for clarity.

Table 2. Hydrogen bond parameters for **2b** and **2c**[a]

	D—H (Å)	H···*A* (Å)	D···A (Å)	*D*—H···*A* (°)
For **2b**				
C9—H9···Cg2^{i}	0.93	2.81	3.638(3)	150
C14—H14B···Cg4^{ii}	0.97	2.81	3.620(3)	142
Symmetry codes: (i) $1-x, -y, 1-z$; (ii) $1-x, -y, -z$				
For **2c**				
C2—H2···O2^{i}	0.93	2.41	3.259(3)	151
C22—H22B···Cg2^{ii}	0.96	2.88	3.601(3)	133
Cg1···Cg2^{iii}			3.7093(14)	0
Cg2···Cg2^{iv}			3.7089(15)	0
Symmetry codes: (i) $x, y, -1+z$; (ii) $-x, 1-y, 1-z$; (iii) $1-x, 1-y, -z$; (iv) $1-x, 1-y, -z$				

[a]Cg1 and Cg2 are the centroids of the N1/N2/C1/C6/C7 and C1–C6 rings, respectively.

143.4 ppm was shifted downfield in **2e**, at 188.7 ppm, which is characteristic for carbene metal complexes,[57] further demonstrating the formation of expected NHC–silver complex. However, in the other complexes, resonances for carbene carbons were not detected, which has also been mentioned in the literature and is likely due to the fluxional behaviour of NHC complexes.[20,49–52] The FT-IR data for NHC–silver complexes exhibited a characteristic ν(C=N) band at 1595.81, 1593.44, 1594.06, 1594.13 and 1594.48 for **2a–e**, respectively.

Benzimidazolium salts at 48 h and silver complexes at 24 h were obtained by Liu *et al.*[57] In our study, compounds were achieved in reduced times (for benzimidazolium salts at 12 h and for NHC–silver complexes at 10 h) and greater yields.

Structural Discussion

Suitable crystals for X-ray crystallography to determine the molecular structure of **2b** and **2c** were obtained in a saturated dichloromethane solution with slow infusion of diethyl ether. The molecular structures of **2b** and **2c** are shown in Figs. 1 and 2; Figs. 1–3 were drawn using the PLATON program[58]

In **2b** and **2c**, the benzimidazole groups are almost planar, with maximum deviations of 0.062(2) Å for C1 and −0.017(2) Å for N1, respectively. The terminal phenyl and benzene rings (which form dihedral angles of 88.88(13)° for **2b** and 76.32(14)° for **2c**) make dihedral angles of 63.48(10)° and 85.74(11)° for **2b** and 55.23 (11)° and 74.89(11)° for **2c**, with respect to the central benzimidazole ring system. The Ag—C and Ag—Cl single-bond lengths are, respectively, 2.091(2) and 2.3301(8) Å for **2b** and 2.092(2) and 2.3602(7) Å for **2c**. The C—Ag–Cl bond angle is 176.28(6)° for **2b** and 167.60(6)° for **2c**. The bond lengths and angles of **2b** and **2c** are in agreement with those reported for similar compounds.[7a, 31]

In **2b**, C—H···π interactions contribute to the stabilization of the crystal structure (Table 2) and lead to a 3D supramolecular architecture (see supporting information). In **2c**, molecules are linked by C—H···O hydrogen bonds forming C(11) motifs[59,60] as chains parallel to the *c*-axis. Furthermore, a C—H···π interaction and π–π stacking interactions (Table 2) help to stabilize the 3D crystal packing of **2c**. Figure 3 shows a view of the crystal packing for **2c**.

Antibacterial Evaluation

All the NHC precursors and NHC–silver complexes were screened for antibacterial activities *in vitro* against three Gram-positive bacterial strains – *B. subtilis*, *L. monocytogenes*, *S. aureus* – and three Gram-negative bacterial strains – *E. coli, K. pneumoniae*, *P. aeruginosa* – using the microdilution broth method. Tetracycline was used as a positive control to assess the MIC values of the strains. The MICs (the lowest concentrations of compounds that completely inhibited bacteria growth) of the NHC–precursors and NHC–silver complexes against the six bacteria are presented in Table 3. A smaller MIC value corresponds to higher activity. It can be seen from Table 3 that many of these NHC precursors and NHC–silver complexes were effective against the six bacteria used in the biological experiments. **1a** exhibited high antibacterial activity against *P. aeruginosa* and *B. subtilis*, with an MIC as low as 50 μg ml^{-1} among the synthesized NHC precursors. Similarly, **1b** exhibited high

Table 3. MIC values of the synthesized NHC precursors (**1a–1e**) and NHC–silver complexes (**2a–2e**) against six bacteria

Compound	MIC (μg ml^{-1})					
	Gram-negative			Gram-positive		
	E. coli	*K. pneumoniae*	*P. aeruginosa*	*B. subtilis*	*L. monocytogenes*	*S. aureus*
1a	400	200	50	50	200	400
1b	400	400	100	50	200	400
1c	1600	3200	800	800	800	3200
1d	400	200	100	100	100	400
1e	3200	200	3200	100	>3200	200
2a	50	50	50	50	<50	50
2b	50	25	25	50	<50	100
2c	100	50	50	100	<50	100
2d	100	50	50	50	50	100
2e	100	100	100	100	100	200
Tetracycline	<7.8	<7.8	15.6	<7.8	62.5	125

antibacterial activity against *B. subtilis*, with an MIC as low as 50 μg ml^{-1}. **1e** was effective against *K. pneumoniae*, *B. subtilis* and *S. aureus*. However, **1e**, which contained the alkyl group, exhibited low antibacterial activities against the other three bacteria (*E. coli*, *P. aeruginosa* and *L. monocytogenes*). **1c**, which contained three methoxy groups on the benzyl ring, had a lower antibacterial effect against tested bacteria with 800 μg ml^{-1} and above. The similar MIC values obtained for **1a** and **1b** may be considered to be due to methyl substitution on the benzyl ring. As shown in Table 3, the new NHC–silver complexes showed effective activities against Gram-positive and Gram-negative bacteria with regard to MIC values, between 25 and 200 μg ml^{-1}. According to the results, **2a** and **2b** showed greater antibacterial activities against the tested bacteria than the other synthesized silver complexes. The best antibacterial activity was observed for complex **2b** against Gram-negative *K. pneumoniae* and *P. aeruginosa* (25 μg ml^{-1}). That also may be considered to be due to methyl substituted on the benzyl ring. The presence of electron-donating or electron-withdrawing substituents may be essential for antibacterial activity. The silver complexes had stronger antibacterial effects than the synthesized NHC precursors. Carbene precursor and silver complex (**1e** and **2e**) containing the morpholino group showed the lowest antibacterial activities. Other compounds, except for **1e** and **2e**, comprise aromatic substituents. The different activities on both Gram-positive and Gram-negative bacteria may be directly related to lipophilicity of the substituents of the tested benzimidazolium salts and NHC–silver complexes. Thus benzimidazolium precursors bearing 2,4,6-trimethylbenzyl and 2,3,4,5,6-pentamethylbenzyl groups were more active than the other salts. For the NHC–silver complexes, those with 2,4,6-trimethylbenzyl, 2,3,4,5,6-pentamethylbenzyl and naphthalenomethyl groups were more active.

Conclusions

Five new phenyl-substituted NHC-precursors (**1a–e**) and their NHC–silver complexes (**2a–e**) were synthesized and their structures were confirmed by ^{1}H NMR, ^{13}C NMR, FT-IR, elemental analysis and X-ray diffraction (for **2b** and **2c**). The *in vitro* antibacterial activities of the synthesized compounds were studied against three Gram-positive (*B. subtilis*, *L. monocytogenes*, *S. aureus*) bacterial strains and three Gram-negative (*E. coli*, *K. pneumoniae*, *P. aeruginosa*) bacterial strains to show their inhibitory effect. Almost all the silver complexes showed high antibacterial activity compared to the carbene precursors against both Gram-positive and Gram-negative strains. The silver complexes **2a–d** showed high antibacterial activity against the Gram-positive bacteria *L. monocytogenes* and *S. aureus* compared to tetracycline as the antibacterial standard drug. Further studies with a wider spectrum of electron-withdrawing or electron-donating substituents are necessary to provide a basis for the structure optimization of this class of silver complexes in order to search for more active compounds.

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