Full Paper

Applied Organometallic Chemistry

Received: 21 September 2010 Revised: 29 November 2010 Accepted: 29 November 2010 Published online in Wiley Online Library: 4 April 2011

(wileyonlinelibrary.com) DOI 10.1002/aoc.1772

Synthesis, microwave-promoted catalytic activity in Suzuki–Miyaura cross-coupling reactions and antimicrobial properties of novel benzimidazole salts bearing trimethylsilyl group

Ülkü Yılmaz[a], Hasan Küçükbay[a]*, Nihat Şireci[b], Mehmet Akkurt[c], Selami Günal[d], Rıza Durmaz[d] and M. Nawaz Tahir[e]

A mixture of benzimidazole salts (2–7), $Pd(OAc)_2$ and K_2CO_3 in DMF–H_2O catalyzes the Suzuki–Miyaura cross-coupling reactions promoted by microwave irradiation resulting in high yield within a short time. In particular, the yield of the Suzuki–Miyaura reactions with aryl bromides was found to be nearly quantitative. The synthesized benzimidazole salts (2–7) were identified by ^1H-^{13}C, NMR, IR spectroscopic methods and microanalysis. The molecular structure of 1 was determined by X-ray crystallography. The antibacterial and antifungal activities of the novel benzimidazole derivatives (1–7) were also tested against standard strains.

Supporting information may be found in the online version of this article.

Keywords: benzimidazole salt; carbene; palladium catalysis; coupling reaction; Suzuki–Miyaura coupling; microwave; antimicrobial activity.

Introduction

The Suzuki–Miyaura cross-coupling reaction of organoboron compounds and organic halides or pseudohalides can be considered as one of the most efficient methods for the formation of carbon–carbon bonds.[1–3] The Suzuki–Miyaura reaction has become a mainstay of modern synthetic organic chemistry for the preparation of biaryl compounds. A large number of synthetic methods have been developed over the year for the selective construction of carbon–carbon bonds, in particular for the formation of biaryl derivatives.[4–9]

Metal-catalyzed cross-coupling reactions, notably those permitting C–C bond construction, have witnessed a meteoritic development and are now routinely employed as a powerful synthetic tool both in the laboratory and in industry. In this context, palladium is arguably the most studied transition metal, and tertiary phosphines occupy a preponderant place as ancillary ligands. Seriously challenging this situation, the use of N-heterocyclic carbenes (NHCs) as alternative ligands in palladium-catalyzed cross-coupling reactions is rapidly gaining in popularity because of their superior performance compared with the more traditional tertiary phosphanes.[10,11]

Both NHCs and electron-rich alkenes which can be used as NHCs source are highly air- and moisture-sensitive and require handling under strict inert conditions.[12–15] Contrary to cumbersome preparation and isolation of NHCs and electron-rich alkenes, *in situ* preparation of NHCs has more advantages, using a strong base, diazolium salts and a common palladium source such as $PdCl_2$ or $Pd(OAc)_2$, in a number of catalytic synthesis, particularly C–C coupling reactions. Pd(II)–NHC complexes are more attractive as pre-catalysts because of their stability to air, moisture and heating and their excellent long-term storage profile.[7] In particular, $Pd(OAc)_2$–benzimidazole or imidazole ligands could be very effective catalytic systems in these reactions.[16–18]

In the past 10 years, heating and driving chemical reactions by microwave energy has been an increasingly popular theme in the scientific community. The use of metal catalysts in conjunction with microwaves may have significant advantages over traditional heating methods since the inverted temperature gradient under microwave conditions may lead to an increased lifetime of catalyst through elimination of wall effects.[19] Although there are extensive studies on Suzuki-type C–C cross-coupling reaction

* *Correspondence to: Hasan Küçükbay, İnönü University, Faculty of Science and Arts, Department of Chemistry, 44280 Malatya, Turkey. E-mail: hkucukbay@inonu.edu.tr*

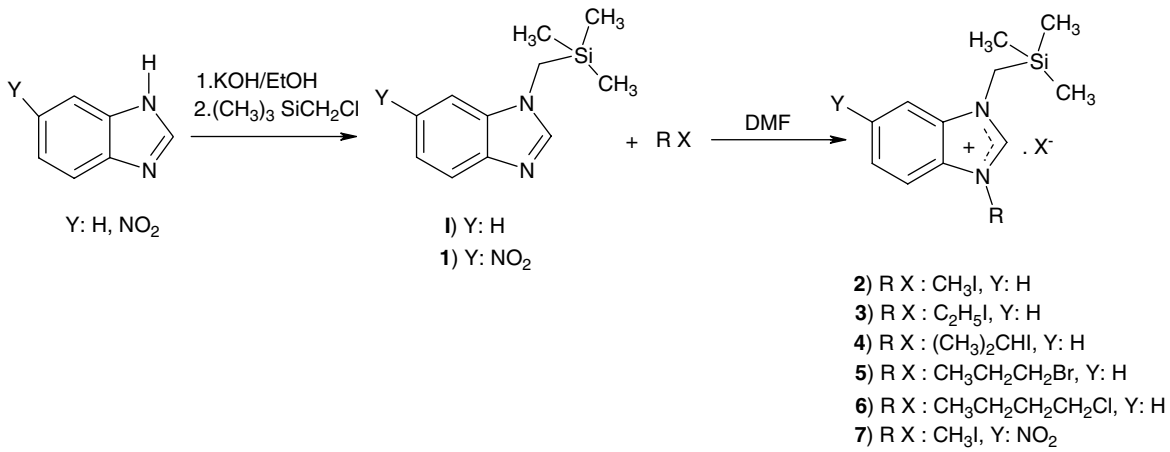
a *İnönü University, Faculty of Science and Arts, Department of Chemistry, 44280 Malatya, Turkey*

b *Adıyaman University, Faculty of Education, 02040 Adıyaman, Turkey*

c *Erciyes University, Faculty of Sciences, Department of Physics, 38039 Kayseri, Turkey*

d *İnönü University, Faculty of Medicine, Department of Microbiology, 44280 Malatya, Turkey*

e *University of Sargodha, Department of Physics, Sargodha, Pakistan*



Scheme 1. Synthesis pathways of the benzimidazole derivatives.

incorporating microwave irradiation with high yield in a short time,[20–27] there is no study on Suzuki–Miyaura cross-coupling reaction including trimethylsilylmethyl-substituted benzimidazole derivatives in the literature. The nature, size and electronic properties of the substituents on the nitrogen atom(s) of the benzimidazole may play a crucial role in tuning the catalytic activity. In order to find a more efficient palladium catalyst, we synthesized a series of new benzimidazole salts, **1**–**7** (Scheme 1), containing trimethylsilylmethyl moiety, and we aimed to investigate the activity of *in-situ* Pd-carbene-based catalytic systems for the Suzuki cross-coupling reactions. Some alkylsilyl substituted benzimidazole derivatives have also been reported to possess important antitumor activity.[28,29] Since benzimidazole compounds have been found to have a broad range of pharmacological activity, many research groups as well as our group have been interested in these types of heterocyclic compounds.[30–40]

Herein, we report on the microwave-assisted catalytic activity of $Pd(OAc)_2$/trimethylsilylmethyl substituted benzimidazole catalytic system in Suzuki cross-coupling reactions. The other aim of this study was to investigate *in vitro* antimicrobial and antifungal activities of the novel trimethylsilylmethyl-substituted benzimidazole derivatives. X-ray structural analysis of compound **1** was also determined to clarify the nitro group position 5 or 6 for the tautomerization of starting 5(6)-nitrobenzimidazole.

Experimental

All preparations were carried out in an atmosphere of purified argon using standard Schlenk techniques. Starting materials and reagents used in reactions were supplied commercially from Aldrich or Merck Chemical Co. Solvents were dried with standard methods and freshly distilled prior to use. All catalytic activity experiments were carried out in a microwave oven system manufactured by Milestone (Milestone Start S Microwave Labstation for Synthesis) under aerobic conditions. ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz) spectra were recorded using a Bruker DPX-300 high-performance digital FT NMR spectrometer. Infrared spectra were recorded as KBr pellets in the range 4000–400 cm^{-1} on a Perkin-Elmer FT-IR spectrophotometer. Elemental analyses were performed by LECO CHNS-932 elemental analyzer. Melting points were recorded using an electrothermal-9200 melting point apparatus, and are uncorrected.

1-Substitutebenzimidazoles, **I** used in this work as starting compounds were prepared according to the literature procedure.[41]

GC-MS Analysis

GC-MS spectra were recorded on an Agilient 6890 N GC and 5973 Mass Selective Detector using with an HP-Innowax column of 60 m length, 0.25 mm diameter and 0.25 µm film thickness. GC-MS parameters for both Suzuki and Heck coupling reactions were as follows: initial temperature 60 °C; initial time, 5 min; temperature ramp 1, 30 °C/min; final temperature, 200 °C; ramp 2, 20 °C/min; final temperature 250 °C; run time 30.17 min; injector port temperature 250 °C; detector temperature 250 °C, injection volume, 1.0 µl; carrier gas, helium; mass range between *m/z* 50 and 550.

1-(Trimethylsilyl)methyl-6-nitrobenzimidazole, ***1***

(Chloromethyl)trimethylsilane (1.8 cm^3, 12.90 mmol) was added to a mixture of 5(6)-nitrobenzimidazole (2.00 g; 12.26 mmol) and KOH (0.70 g, 12.5 mmol) in EtOH (20 cm^3). The mixture was heated under reflux for 4 h, then cooled, and the precipitating potassium chloride was filtered off and washed with a little EtOH. The solvent was then removed from the filtrate *in vacuo*. The residue was washed with water (25 cm^3) twice and crystallized from EtOH–DMF (2 : 1). Yield, 1.96 g, (64%); m.p., 162–163 °C. Anal. found: C, 52.91; H, 5.97; N, 16.74. Calcd for $C_{11}H_{15}N_3O_2Si$: C, 52.99; H, 6.06; N, 16.85. Found: IR: υ(C═N): 1490 cm^{-1}.^{1}H-NMR (DMSO-d_6): δ = 8.54 (s, 1H, N═C*H*–N); 8.17 and 7.85 (m, 3H, Ar–*H*); 4.02 (s, 2H, CH_2Si); 0.01 ppm [s, 9H, Si (CH_3)$_3$]. ^{13}C-NMR (DMSO-d_6): δ = 148.58 (N═*C*H–N); 142.86, 142.54, 139.20, 118.08, 116.12, 111.77 (C_6H_4); 36.25 (N–CH_2–Si); −2.06 ppm (CH_3–Si).

Synthesis of 1-(trimethylsilyl)methyl-3-methylbenzimidazolium iodide, ***2***

A mixture of 1-trimethylsilylmethylbenzimidazole (1.02 g, 5 mmol) and iodomethane (0.40 cm^3, 6.43 mmol) in dimethylformamide (5 ml) was refluxed for 3 h. The mixture was then cooled and the volatiles were removed under vacuum. The residue was crystallized from a dimethylformamide–ethanol (1 : 1). White crystals of the title compound **2** (1.51 g, 87%) were obtained, m.p., 236–237 °C; $\upsilon_{(CN)}$ = 1488 cm^{-1}. Anal. found: C 41.60, H 5.53, N 8.05. Calculated for $C_{12}H_{19}N_2ISi$: C 41.62, H 5.53, N 8.09. ^{1}H NMR (δ, DMSO-d_6): 9.60

(s, 1H, NCHN), 8.13–7.70 (m, 4H, C_6H_4), 4.24 (s, 2H, CH_2Si), 4.11 (s, 3H, CH_3) and 0.12 [s, 9H, $(CH_3)_3Si$]. ^{13}C NMR (δ, DMSO-d_6): 141.9 (NCHN), 132.2, 126.8, 126.6, 114.3 and 113.9 (C_6H_4), 38.3 (CH_2Si), 33.8 (CH_3) and −2.2 [$(CH_3)_3Si$].

Similarly, 1-(trimethylsilyl)methyl-3-ethylbenzimidazolium iodide, **3** was synthesized from 1-(trimethylsilyl)methylbenzimidazole and iodoethane. Yield, 1.46 g (yellow crystals), 81%; m.p., 126–127 °C; $\upsilon_{(CN)} = 1478\ cm^{-1}$. Anal. found: C 43.26, H 5.79, N 7.56. Calcd for $C_{13}H_{21}N_2ISi$: C 43.33, H 5.87, N 7.77. ^1H NMR (δ, DMSO-d_6): 9.70 (s, 1H, NCHN), 8.13 −7.66 (m, 4H, C_6H_4), 4.55 (q, 2H, CH_2 ethyl, $J = 7.2$ Hz), 4.24 (s, 2H, CH_2Si), 1.54 (t, 3H, CH_3 ethyl, $J = 7.2$ Hz) and 0.11 [s, 9H, $(CH_3)_3Si$]. ^{13}C NMR (δ, DMSO-d_6): 141.1 (NCHN), 132.3, 131.2, 126.9, 126.7, 114.5 and 114.0 (C_6H_4), 42.5 (CH_2 ethyl), 38.4 (CH_2Si), 14.9 (CH_3 ethyl) and −2.2 [$(CH_3)_3Si$].

Similarly, 1-(trimethylsilyl)methyl-3-isopropylbenzimidazolium iodide, **4** was synthesized from 1-(trimethylsilyl)methylbenzimidazole and 2-iodopropane. Yield, 1.41 g (yellow crystals), 75%; m.p., 96–98 °C; $\upsilon_{(CN)} = 1486\ cm^{-1}$. Anal. found: C 44.88, H 6.18, N 7.43. Calcd for $C_{14}H_{23}N_2ISi$: C 44.92, H 6.19, N 7.48. ^1H NMR (δ, DMSO-d_6): 9.82 (s, 1H, NCHN), 8.18–7.61 (m, 4H, C_6H_4), 5.10 (sept, 1H, CH isopropyl, $J = 6.6$ Hz), 4.24 (s, 2H, CH_2Si), 1.64 (d, 6H, CH_3 isopropyl, $J = 6.6$ Hz) and 0.10 [s, 9H, $(CH_3)_3Si$]. ^{13}C NMR (δ, DMSO-d_6): 139.9 (NCHN), 132.3, 130.8, 126.8, 126.3, 114.4 and 113.8 (C_6H_4), 50.9 (CH isopropyl), 38.6 (CH_2Si), 22.3 (CH_3 isopropyl) and −2.1 [$(CH_3)_3Si$].

Similarly, 1-(trimethylsilyl)methyl-3-propylbenzimidazolium bromide, **5** was synthesized from 1-(trimethylsilyl)methylbenzimidazole and 1-bromopropane. Yield, 1.44 g (white crystals), 88%; m.p., 86–87 °C; $\upsilon_{(CN)} = 1481\ cm^{-1}$. Anal. found: C 51.35, H 7.08, N 8.49. Calculated for $C_{14}H_{23}N_2BrSi$: C 51.37, H 7.08, N 8.56. ^1H NMR (δ, DMSO-d_6): 9.78 (s, 1H, NCHN), 8.14–7.61 (m, 4H, C_6H_4), 4.51 (t, 2H, CH_2 propyl, $J = 7.2$ Hz), 4.25 (s, 2H, CH_2Si), 1.92 (sextet, 2H, CH_2 propyl, $J = 7.2$ Hz), 0.91 (t, 3H, CH_3 propyl, $J = 7.2$ Hz) and 0.10 [s, 9H, $(CH_3)_3Si$]. ^{13}C NMR (δ, DMSO-d_6): 141.5 (NCHN), 132.3, 131.4, 126.9, 126.7, 114.5 and 114.1 (C_6H_4), 48.4 (CH_2 propyl), 38.4 (CH_2Si), 22.6 (CH_2 propyl), 11.1 (CH_3 propyl) and −2.2 [$(CH_3)_3Si$].

Similarly, 3-^{n}butyl-1-(trimethylsilyl)methylbenzimidazolium chloride, **6** was synthesized from 1-(trimethylsilyl)methylbenzimidazole and 1-chlorobutane. Yield, 1.06 g (white crystals), 71%; m.p., 125–126 °C; $\upsilon_{(CN)} = 1488\ cm^{-1}$. Anal. found: C 60.63, H 8.48, N 9.36. Calcd for $C_{15}H_{25}N_2ClSi$: C 60.68, H 8.49, N 9.43. ^1H NMR (δ, DMSO-d_6): 9.95 (s, 1H, NCHN), 8.15–7.66 (m, 4H, C_6H_4), 4.55 (t, 2H, CH_2 butyl, $J = 7.2$ Hz), 4.26 (s, 2H, CH_2Si), 1.89 (quint, 2H, CH_2 butyl, $J = 7.2$ Hz), 1.31 (sextet, 2H, CH_2 butyl, $J = 7.2$ Hz), 0.92 (t, 3H, CH_3 butyl, $J = 7.2$ Hz) and 0.09 [s, 9H, $(CH_3)_3Si$]. ^{13}C NMR (δ, DMSO-d_6): 141.6 (NCHN), 132.2, 131.4, 126.9, 126.7, 114.5 and 114.1 (C_6H_4), 46.8 (CH_2 butyl), 38.3 (CH_2Si), 31.1 (CH_2 butyl), 19.5 (CH_2 butyl), 13.8 (CH_3 butyl) and −2.2 [$(CH_3)_3Si$].

*Synthesis of 3-methyl-1-(trimethylsilyl)methyl-6-nitrobenzimidazolium iodide, **7***

A mixture of 1-(trimethylsilyl)methyl-6-nitrobenzimidazole (1.1 g, 4.41 mmol) and iodomethane (0.30 ml, 4.80 mmol) in dimethylformamide (5 ml) was refluxed for 3 h. The mixture was then cooled and the volatiles were removed under vacuum. The residue was crystallized from a dimethylformamide–ethanol (1 : 1). Yellow crystals of the title compound **7** (1.54 g, 89%) were obtained, m.p. 206–208 °C; $\upsilon_{(CN)} = 1474\ cm^{-1}$. Anal. found: C 36.72, H 4.63, N 10.61. Calcd for $C_{12}H_{18}N_3O_2ISi$: C 36.84, H 4.64, N 10.74. ^1H NMR (δ, DMSO-d_6): 9.84 (s, 1H, NCHN), 9.19–8.27 (m, 3H, C_6H_3), 4.37 (s, 2H, CH_2Si), 4.15 (s, 3H, CH_3), 0.14 [s, 9H, $(CH_3)_3Si$]. ^{13}C NMR (δ, DMSO-d_6): 146.0 (NCHN), 136.0, 132.0, 121.9, 115.3 and 111.5 (C_6H_3), 38.9 (CH_2Si), 34.4 (CH_3) and −2.4 [$(CH_3)_3Si$].

Single-crystal X-ray Diffraction Analysis of 1-Trimethylsilylmethyl-6-nitrobenzimidazole, 1

The X-ray data were collected on an Bruker X8 Prospector diffractometer at room temperature with an highly sensitive APEX II area detector using an IμS (microfocus source) with multilayer mirrors, that give an intense monochromatic Cu K_α radiation ($\lambda = 1.54178$ Å). An empirical absorption correction was applied using SADABS.[42] The structures were solved by direct methods using the SIR-97 program[43] and refined on F^2 by full matrix least-squares using the SHELXL-97 program.[44] The hydrogen atoms were placed in calculated positions (C–H = 0.95–0.99 Å) and included in the refinement using the riding model, with $U_{iso}(H) = 1.2$ or 1.5 U_{eq} (C). A summary of the crystal data, experimental details and refinement results for **1** is given in Table 1. The hydrogen bond and molecular packing geometry of compound **1** were calculated with PLATON.[45] The graphical representations of the structure were made with ORTEP.[46]

General Procedure for the Suzuki Reactions

$Pd(OAc)_2$ (1 mmol%), benzimidazolium halides (**2**–**7**; 2 mmol%), aryl halide (1 mmol), phenylboronic acid (1.2 mmol), K_2CO_3

Table 1. The crystal data, data collection and refinement values of compound **1**

Crystal data	
$C_{11}H_{15}N_3O_2Si$	$Z = 12$
$M_r = 249.35$	$D_x = 1.298$ mg m^{-3}
Monoclinic, $P2_1/c$	Cu $K\alpha$ radiation
$a = 6.6049$ (2) Å	$\mu = 1.60$ mm^{-1}
$b = 10.0291$ (3) Å	$T = 100$ K
$c = 57.7965$ (15) Å	Crystal shape needle, colorless
$\beta = 91.599$ (1)°	Crystal dimensions: 0.05 × 0.05 × 0.20 mm^3
$V = 3827.02$ (19) Å^3	
Data collection	
Bruker X8 Prospector diffractomer	$\theta_{max} = 62.1°$
ω and ϕ scans	$h = -7 \rightarrow 7$
Absorption correction: multi-scan (based	$k = -11 \rightarrow 11$
on symmetry-related measurements)	$l = -65 \rightarrow 62$
$T_{min} = 0.740$, $T_{max} = 0.740$	
34 644 measured reflections	
5995 independent reflections	
5950 reflections with $I > 2\sigma(I)$	
$R_{int} = 0.043$	
Refinement	
Refinement on F^2	H atoms constrained to parent site
$R[F^2 > 2\sigma(F^2)] = 0.048$	Calculated weights $w = 1/[\sigma^2(F_o^2) + (0.071P)^2 + 3.3398P]$ where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.126$	$(\Delta/\sigma)_{max} < 0.0001$
$S = 1.12$	$\Delta\rho_{max} = 0.81$ e Å^{-1}
5995 reflections	$\Delta\rho_{min} = -0.28$ e Å^{-1}
469 parameters	Extinction correction: none

(2 mmol), water (3 ml) and DMF (3 ml) were added to microwave apparatus and the mixture was heated at 120 °C (300 W) for 10 min. It was carried out ramp time 3 min to reach 120 °C. At the end of the reaction, the mixture was cooled, the product extracted with ethyl acetate–*n*-hexane (1 : 5) and chromatographed on a silica gel column. The purity of coupling products was checked by NMR and GC-MS, and yields are based on aryl halide. The coupling products were confirmed by increasing the peaks on gas chromatograms and mass values from MS spectrums. All coupling products were also isolated and characterized by ^{1}H-NMR or MS before the serial catalytic work up each time.

The Suzuki coupling yields between phenylboronic acid and 4-bromoacetophenone were also determined as a isolated yield for the comparison purposes with the GC-based yields (Table 3 entries, 6–11). The isolated yields were determined as follows: at the end of the Suzuki coupling reaction, the mixture was cooled to room temperature, the contents of the reaction vessel were poured into a separatory funnel. Water (3 ml) and ethyl acetate (5 ml) were added, and the coupling product was extracted and removed. After further extraction of the aqueous phase with ethyl acetate (5 ml) and combining the extracts, the ethyl acetate was removed *in vacuo*, leaving the *p*-acetylbiphenyl product as a pale white solid, which was characterized by comparison of NMR data with that in the literature.

Biological Activity: Methods of Antimicrobial Testing

Antimicrobial activities of the compounds were determined by using agar dilution procedure outlined by the National Committee for Clinical Laboratory standards.[47,48] Minimal inhibitory concentrations for each compound were investigated against standard bacterial strains: *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853 and the yeasts *Candida albicans* and *C. tropicalis* obtained from the Department of Microbiology, Faculty of Medicine, Ege University (Turkey). The stock solutions of the compounds were prepared in dimethylsulfoxide (DMSO), which had no effect on the micro-organisms in the concentrations studied. All of the dilutions were done with distilled water. The concentrations of the tested compounds were 800, 400, 200, 100, 50, 25, 12.5, 6.25 and 3.12 μg ml^{-1}. Ampicilin and fluconazole from FAKO (Istanbul, Turkey) were used as a reference compound for the experimental conditions. A loopful (0.01 ml) of the standardized inoculum of the bacteria and yeasts (10^6 CFUs ml^{-1}) was spread over the surface of agar plates. All of the inoculated plates were incubated at 35 °C and results were evaluated after 16–20 h of incubation for bacteria and 48 h for yeasts. The lowest concentration of the compounds that prevented visible growth was considered to be the minimal inhibitory concentration (MIC).

Results and Discussion

1-(Trimethylsilyl)methyl-6-nitrobenzimidazole, **1**, was synthesized from 5(6)-nitrobenzimidazole and KOH in refluxing EtOH in moderate yield of 64%. The molecular structure of compound **1** was confirmed by single crystal X-ray diffraction to clarify the nitro group position 5 or 6 for the tautomerization of starting 5(6)-nitrobenzimidazole compound. Its molecular structure is depicted in Figure 2.

The compound **1**, $C_{11}H_{15}N_3O_2Si$, crystallizes in the monoclinic P $2_1/c$ space group by three crystallographically independent formula units in the asymmetric cell. Intermolecular C–H···N and C–H···O interactions contribute to the stability of the molecular structure. The $\pi-\pi$ interaction involves the two benzene rings in the same asymmetric unit whose centroids are separated by 3.4157 (11) Å.

In the asymmetric unit of the compound **1** (Fig. 1), the three benzimidazole ring systems A(N1/N2/C1–C7), B(N4/N5/C12–C18) and C(N7/N8/C23–C29) are almost planar, with maximum deviations of −0.022(2) for C6, 0.013(2) for C12 and −0.014(2) for C25. The dihedral angles between them are A/B = 0.68(6)°, A/C = 46.34(6)° and B/C = 46.85(6)°. The silicon atoms have a distorted tetrahedral geometry with angles ranging from 106.02(18) to 113.60(17)°. The crystal data, data collection and refinement values of the compound **1** are given in Table 1.

The crystal structure is stabilized by C–H···N and C–H···O hydrogen-bonding interactions (Fig. 2 and Table 2) and $\pi-\pi$

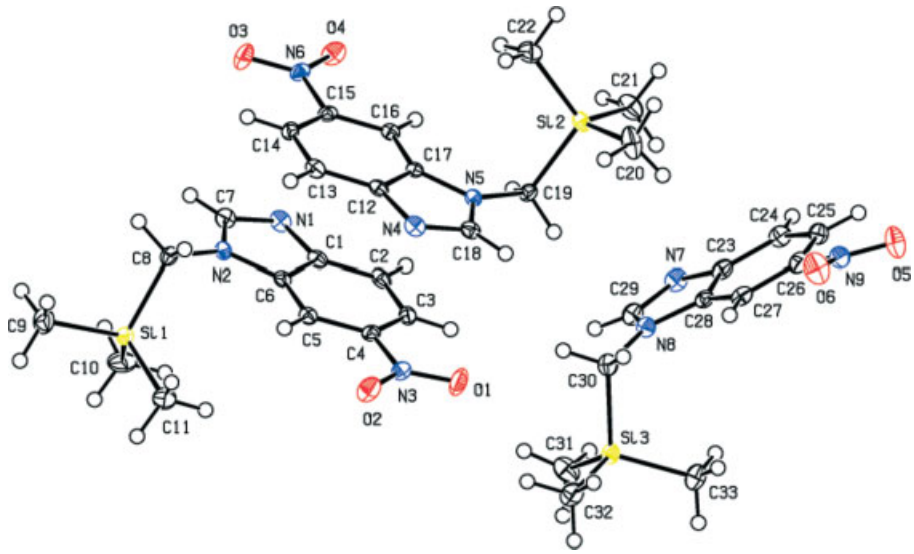


Figure 1. The three independent molecules in the asymmetric unit showing the atom-labeling scheme of **1**. The probability level for the anisotropic displacement parameters is at 50%.

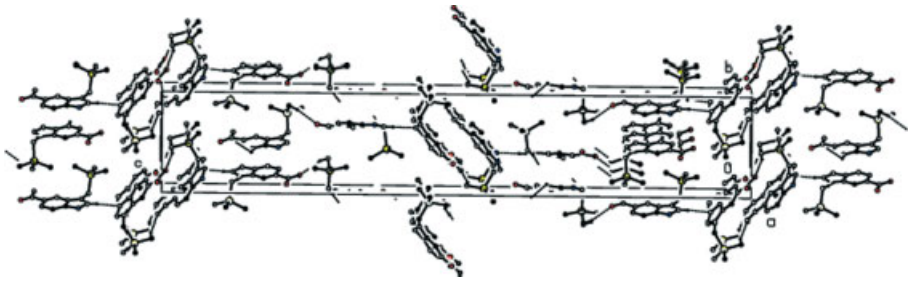


Figure 2. Packing view of the title compound in the unitcell. Hydrogen bonds are indicated as dashed lines.

Table 2. Hydrogen-bond parameters (Å, deg)

	D–H	H···*A*	D···A	*D*–H···*A*
C2–H2···O2^{i}	0.95	2.59	3.174 (3)	120
C8–H8B···N1^{ii}	0.99	2.59	3.525 (2)	157
C10–H10B···O3^{iii}	0.98	2.46	3.324 (3)	147
C18–H18···N7^{ii}	0.95	2.38	3.320 (3)	169
C19–H19A···N4^{i}	0.99	2.61	3.554 (2)	160
C30–H30A···O1	0.99	2.53	3.318 (3)	137
C32–H32B···O1	0.98	2.55	3.361 (3)	140
C33–H33B···O5^{iv}	0.98	2.59	3.523 (3)	158

Symmetry codes: (i) $-1+x, y, z$; (ii) $1+x, y, z$; (iii) $1-x, -1/2+y, 1/2-z$; (iv) $-x, 2-y, -z$.

interactions between the benzene rings of the adjacent molecules in the same asymmetric unit whose centroids are separated by 3.4157(11) Å (Table 2).

Benzimidazolium salts containing trimethylsilyl moiety, **2**–**7**, were prepared by treatment of 1-(trimethylsilyl)methylbenzimidazole or 5-nitro-1-(trimethylsilyl)methylbenzimidazole with appropriate alkyl halides in refluxing DMF with good yields of 71–89%. The synthesis of the benzimidazolium salts **2**–**7** is summarized in Scheme 1. The benzimidazolium salts are air- and moisture-stable both in the solid state and in solution. The eight new benzimidazole derivatives were characterized by ^{1}H NMR, ^{13}C {^{1}H} NMR, IR and elemental analysis techniques which support the proposed structures. The value of $\delta[^{13}C\{^{1}H\}]$, NCHN in benzimidazolium salts is usually around 142 ± 4.[40] For benzimidazolium salts **2**–**7** it was found to be 141.9, 141.1, 139.9, 141.5, 141.6 and 146.0 ppm, respectively. These values are in good agreement with the previously reported results.[27,49] In the ^{1}H NMR spectrum of 1-(trimethylsilyl)methylbenzimidazole,**I** and 1-(trimethylsilyl)methyl-6-nitrobenzimidazole, **1** compounds for NC*H*N proton were observed as singlets at 8.10 and 8.54 ppm, respectively.

The NC*H*N proton signals for the benzimidazolium salts were observed as singlets at 9.60, 9.70, 9.82, 9.78, 9.95 and 9.84 ppm, respectively. As expected, the NC*H*N proton signals were shifted downfield about 1.06–1.85 ppm. These chemical shift values are also typical for NC*H*N protons of benzimidazolium salts for increasing the acidity of the NC*H*N proton.[27,50–52]

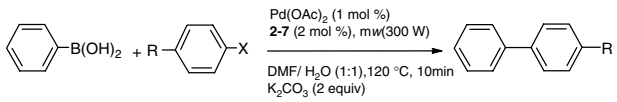
The carbon–nitrogen band frequencies, $\nu_{(C=N)}$ for benzimidazole compounds **I**[41] and **1** were observed at 1489–1490 cm^{-1}, respectively. These bands were observed at 1474–1488 cm^{-1} for the benzimidazolium salts, **2**–**7**. The π-electron delocalization on the imidazolium ring may be responsible for the slight red shift.

The Suzuki–Miyaura Coupling Reactions

The Suzuki–Miyaura reaction is one of the most versatile and utilized reactions for the selective construction of carbon–carbon bonds, in particular for the formation of biaryl and heterobiaryl derivatives.[2,24] The catalytic yield of the coupling is dependent on a variety of parameters such as temperature, solvent, base and nature of catalyst loading. We recently reported the optimum reaction conditions for the Suzuki/Heck coupling reaction, including some benzimidazolium or bis-benzimidazolium salts–$Pd(OAc)_2$ and base as a catalyst system under microwave and conventional heating conditions.[27,53,54] In the present report, a series of aryl chloride and aryl bromide were used for coupling partner with phenylboronic acid. Since relatively less reactive aryl chloride was used, the recently reported optimum parameters were slightly modified for temperature (120 °C/300 W) and reaction time (10 min) after test reactions using phenylboronic acid and 4-bromoacetophenone (Table 3 entries 1–5). Finally, we found that the use of 1% $Pd(OAc)_2$, 2% mol of **2**–**7** and 2% mol K_2CO_3 in DMF–H_2O (1 : 1) at 120 °C/300 W microwave heating led to the best conversation within 10 min.

After having established the optimized coupling reaction conditions, the scope of the reaction and efficiencies of the benzimidazolium salts were evaluated by investigating the coupling of the phenylboronic acid with various *p*-substituted aryl halides. Under the optimized conditions, reaction of *p*-bromoacetophenone, *p*-chloronitrobenzene, *p*-chlorobenzaldehyde and *p*-chlorotoluene with phenylboronic acid gave almost as high a yield using a catalytic system consisting of 2 mol% benzimidazole salts (**2**–**7**), 1 mol% $Pd(OAc)_2$ and 2 equiv. K_2CO_3 in DMF–H_2O (1 : 1) at 120 °C by microwave irradiation (300 W) within 10 min. On the other hand, strong electron donating groups on the aryl chlorides such as *p*-chloroanisole, *p*-chloroaniline and *p*-chlorothioanisole gave a low or moderate yield using the optimized conditions. It is noteworthy that aryl chlorides are arguably the most useful substrates because of their lower cost and the wide range of commercially available compounds.[6] We also tested the catalytic yields using conventional heating system in a preheated oil bath at 10 min at 120 °C, but we obtained only 13% yield using benzimidazole salt, **2**, and *p*-bromoacetophenone in optimized conditions (Table 3, entry 5). Control experiments showed that the Suzuki coupling reaction did not occur in the absence of **2**–**7** in 10 min under microwave heating. The results obtained from optimum conditions for the Suzuki reactions are given in Table 3. Of the seven different aryl halides used in the Suzuki coupling with phenylboronic acid, those with electron-withdrawing substituents were found to give the highest yield (Table 3, entries 6–23). Benzimidazole salt bearing an electron-withdrawing nitro substituent (**7**) was found to be the least effective of the salts examined in Suzuki coupling reactions (Table 3, entries 17, 23, 30, 36, 42 and 48). On the

Table 3. The Suzuki–Miyaura coupling reactions of aryl halides with phenylboronic acid



Entry	R	X	Salt	Yield (%)
1	$COCH_3$	Br	2	69[a]
2	$COCH_3$	Br	2	74[b]
3	$COCH_3$	Br	2	87[c]
4	$COCH_3$	Br	no	nd[d]
5	$COCH_3$	Br	2	13[e]
6	$COCH_3$	Br	2	99 93[f]
7	$COCH_3$	Br	3	99 94[f]
8	$COCH_3$	Br	4	99 93[f]
9	$COCH_3$	Br	5	99 95[f]
10	$COCH_3$	Br	6	99 96[f]
11	$COCH_3$	Br	7	99 94[f]
11	$COCH_3$	Br	7	99
12	NO_2	Cl	2	83
13	NO_2	Cl	3	87
14	NO_2	Cl	4	82
15	NO_2	Cl	5	94
16	NO_2	Cl	6	90
17	NO_2	Cl	7	77
18	CHO	Cl	2	79
19	CHO	Cl	3	82
20	CHO	Cl	4	73
21	CHO	Cl	5	91
22	CHO	Cl	6	80
23	CHO	Cl	7	64
24	CH_3	Cl	2	75
26	CH_3	Cl	3	86
27	CH_3	Cl	4	81
28	CH_3	Cl	5	80
29	CH_3	Cl	6	84
30	CH_3	Cl	7	69
31	OCH_3	Cl	2	57
32	OCH_3	Cl	3	65
33	OCH_3	Cl	4	59
34	OCH_3	Cl	5	70
35	OCH_3	Cl	6	74
36	OCH_3	Cl	7	40
37	NH_2	Cl	2	54
38	NH_2	Cl	3	55
39	NH_2	Cl	4	51
40	NH_2	Cl	5	77
41	NH_2	Cl	6	68
42	NH_2	Cl	7	38
43	SCH_3	Cl	2	56
44	SCH_3	Cl	3	34
45	SCH_3	Cl	4	45
46	SCH_3	Cl	5	44
47	SCH_3	Cl	6	45
48	SCH_3	Cl	7	39

Yields are based on aryl halide. Reactions were monitored by GC-MS. Conditions: temperature ramped to 90 °C (3 min) and held for [a] 5 and [b] 10 min. Temperature ramped to 120 °C (3 min) and held for [c] 5 min. Temperature ramped to 120 °C (3 min) and held for [d] 10 min without salt (**2**). On preheated oil bath, [e] 10 min with thermal heating. [f] Isolated yields. n.d., Not detected.

other hand, benzimidazole salts bearing electron-donating alkyl group are beneficial for better catalytic activity in Suzuki coupling reactions. Similar catalytic results for the Suzuki cross-coupling reactions have also been obtained from $Pd(OAc)_2$ or $PdCl_2$, base and benzimidazole or imidazole catalytic systems which bear different aryl, substituted aryl, alky and substituted alkyl on benzimidazole or imidazole ligands.[8,9,16,17,55]

It is important to note that the endpoint of the all these reactions was clearly observed black particles in the reaction mixture, which probably derived from palladium nanoparticles. As can be seen in Table 3, a high yield of C–C coupling product was obtained from reaction of aryl bromides with phenylboronic acid, as expected.

Antimicrobial Activity

The antimicrobial and antifungal activity results (MIC) are given in Tables 2 and 3, respectively. Tables 4 and 5 also contain results for ampicillin and fluconazole as reference compounds.

Trimethylsilyl substituted benzimidazole derivatives were synthesized and tested against standard strains of Gram-positive (*E. faecalis* and *S. aureus*) and Gram-negative (*E. coli* and *P. aeruginosa*) bacteria and yeasts (*C. albicans* and *C. tropicalis*). As can be seen in Table 4, all tested compounds in this work showed some antibacterial activity against both Gram-positive and Gram-negative bacteria with MICs between 6.25 and 400 μg ml^{-1}. Among the tested compounds **I** showed the highest activity against both Gram-positive and Gram-negative bacteria with MIC value 6.25 μg ml^{-1}. The compounds **2** and **4** also exhibited high

Table 4. The Minimum antibacterial inhibitory concentrations (μg cm^{-3}) of the tested compounds

	Tested microorganisms			
Compound no.	*E. faecalis*	*S. aureus*	*E. coli*	*P. aeruginosa*
Ampicillin	0.78	0.39	3.12	>75
I	6.25	12.5	200	400
1	400	400	800	800
2	50	50	400	400
3	200	200	400	400
4	50	50	400	400
5	200	200	400	400
6	400	400	400	400
7	400	400	800	800

Table 5. The minimum antifungal inhibitory concentrations (μg cm^{-3}) of the tested compounds

	Tested organism	
Compound no.	*C. albicans*	*C. tropicalis*
Fulconazole	1.25	1.25
I	6.25	6.25
1	400	200
2	50	25
3	100	100
4	50	25
5	100	100
6	100	100
7	400	400

activity against Gram-positive bacteria with MIC value 50 μg ml^{-1}. Compound **I** also showed the highest activity against Gram-negative bacteria *E. coli* with MIC value 200 μg ml^{-1}.

As can be seen from Table 5, all compounds were found to be effective against *C. tropicalis*, with a range of MICs between 25 and 50 μg ml^{-1}. Among the tested compounds, **I** also showed the highest antifungal activity against *C. albicans* and *C. tropicalis* with MIC values of 6.25 μg ml^{-1}. Compounds **2** and **4** also exhibited significant antifungal activity against *C. albicans* and *C. tropicalis* with a range of MICs between 25 and 50 μg ml^{-1}. From the data obtained in this work, it is suggested that increased hydrophobic character of the benzimidazole derivatives may play some role in the antimicrobial activities.

Conclusion

We prepared one 1-substituted benzimidazole (**1**) and six benzimidazole salts containing trimethylsilylmethyl substituent (**2**–**7**). The use of the palladium catalyst system including benzimidazolium salts in Suzuki coupling reaction gives better yield under microwave-assisted conditions and short reaction times compared with those given in literature.

The Suzuki coupling reactions were carried out using 300 W power microwave irradiation at 120 °C in 10 min. The precatalysts used in this work were prepared from the corresponding benzimidazole salts (**2**–**7**) directly, thereby avoiding the handling of an isolated highly moisture- and air-sensitive carbene. It can be concluded that Suzuki reaction may be accelerated by microwave irradiation even using aryl chlorides particularly bearing electron-withdrawing substituents. To confirm position of NO_2 group in compound **1**, crystal structural analysis was also performed and the position of NO_2 was determined as the **6** position of the benzimidazole ring. Compounds **I** and **2**–**4** were found to be effective in inhibiting the growth of Gram-positive bacteria (*E. faecalis* and *S. aureus*) and yeast-like fungi (*C. albicans* and *C. tropicalis*)

Supporting Information

Supporting information can be found in the online version of this article. CCDC holds the supplementary crystallographic data 794 108. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax (+44) 1223-336-033; or email deposit@ccdc.cam.ac.uk.

Acknowledgment

We thank Dr Holger Ott (Bruker AXS GmbH, Karlsruhe, Germany) for the data collection. We wish to thank İnönü University Research Fund (BAPB-2010/124) for financial support of this study.

References

[1] A. Suzuki, *Pure Appl. Chem.* **1985**, *57*, 1749.
[2] N. Miyaura, A Suzuki, *Chem. Rev.* **1995**, *95*, 2457.
[3] F. Alonso, I. P. Beletskaya, M. Yus, *Tetrahedron* **2008**, *64*, 3047.
[4] L. Yin, J. Liebscher, *Chem. Rev.* **2007**, *107*, 133.
[5] A. Tudose, L. Delaude, B. Andre, A. Demonceau, *Tetrahedron Lett.* **2006**, *47*, 8529.
[6] L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem. Int. Ed.* **2009**, *48*, 9792.
[7] E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *Angew. Chem. Int. Ed.* **2007**, *46*, 2768.
[8] C. S. Linninger, E. Herdtweck, S. D. Hoffmann, W. A. Herrmann, *J. Mol. Struct.* **2008**, *890*, 192.
[9] R. Singh, M. S. Viciu, N. Kramareva, O. Navarro, S. P. Nolan, *Org. Lett.* **2005**, *7*, 1829.
[10] N. Marion, S. P. Nolan, *Accounts Chem. Res.* **2008**, *41*, 1440.
[11] F. E. Hahn, M. C. Jahnke, T. Pape, *Organometallics* **2006**, *25*, 5927.
[12] E. Çetinkaya, P. B. Hitchock, H. Küçükbay, M. F. Lappert, S. Al-Juaid, *J. Organomet. Chem.* **1994**, *481*, 89.
[13] H. Küçükbay, B. Çetinkaya, S. Guesmi, P. H. Dixneuf, *Organometallics* **1996**, *5*, 2434.
[14] B. Çetinkaya, E. Çetinkaya, J. A. Chamizo, P. H. Hitchcock, H. A. Jasim, H. Küçükbay, M. F. Lappert, *J. Chem. Soc., Perkin Trans. 1* **1998**, 2047.
[15] H. Küçükbay, E. Çetinkaya, B. Çetinkaya and M. F. Lappert, *Synth. Commun.* **1997**, *27*, 4059.
[16] Y. Gök, N. Gürbüz, Y. Özdemir, B. Çetinkaya, E. Çetinkaya, *Appl. Organomet. Chem.* **2005**, *19*, 870.
[17] S. Demir, I. Özdemir, B. Çetinkaya, *Appl. Organomet. Chem.* **2006**, *20*, 254.
[18] İ. Özdemir, M. Yiğit, E. Çetinkaya, B. Çetinkaya, *Appl. Organomet. Chem.* **2006**, *20*, 187.
[19] C. O. Kappe, *Angew. Chem. Int. Ed.* **2004**, *43*, 6250.
[20] H. Prokopvova, J. Ramirez, E. Fernandez, C.O. Kappe, *Tetrahedron Lett.* **2008**, *49*, 4831.
[21] T. N. Glasnov, S. Findenig, C.O. Kappe, *Chem. Eur. J.* **2009**, *15*, 1001.
[22] N. E. Leadbeater, M. Marco, *Org.Lett.* **2002**, *4*, 2973.
[23] K. B. Avery, W. G. Devine, C. M. Kormos, N. E. Leadbeater, *Tetrahedron Lett.* **2009**, *50*, 2851.
[24] F. Chanthavong, N. E. Leadbeater, *Tetrahedron Lett.* **2006**, *47*, 1909.
[25] R. K. Arvela, N. E. Leadbeater, *Org. Lett.* **2005**, *7*, 2101.
[26] P. Appukkuttan, E. Van der Eycken, *Eur. J. Org. Chem.* **2008**, 1133.
[27] Ü. Yılmaz, N. Şireci, S. Deniz, H. Küçükbay, *Appl. Organomet. Chem.* **2006**, *20*, 254.
[28] E. Lukevics, P. Arsenyan, I. Shestakova, I. Domracheva, A. Nesterova, O. Pudova, *Eur. J. Med. Chem.* **2001**, *36*, 507.
[29] L. Ignatovich, V. Muravenko, I. Shestakova, I. Domrachova, J. Popelis, E. Lukevics, *Appl. Organomet. Chem.* **2010**, *24*, 158.
[30] A.K. Singh, J.W. Lown, *Anti-Cancer Drug Des.* **2000**, *15*, 265.
[31] S-T. Huang, I-J. Hsei, C. Chen, *Bioorg. Med. Chem.* **2006**, *14*, 6106.
[32] P.R. Turner, W. A. Denny, *Mutation Res.* **1996**, *355*, 141.
[33] S.A. Galal, K.H. Hegab, A.S. Kassab, M.L. Rodriguez, S. M. Kerwin, A-M. A. El-Khamry, H.I. E. Divani, *Eur. J. Med. Chem.* **2009**, *44*, 1500.
[34] E. Carlsson, P. Lindberg, S. Unge, *Chem. Britain* **2002**, *5*, 42.
[35] S.K. Kotovskaya, Z.M. Basakova, V.N. Charushin, O.N. Chupakhin, E. F. Belanov, N.I. Bormotov, S.M. Balakhnin, O.A. Serova, *Pharm. Chem. J.* **2005**, *39*, 574.
[36] B. Çetinkaya, E. Çetinkaya, H. Küçükbay, R. Durmaz, *Arzneim. Forsch/Drug Res.* **1996**, *46*, 1154.
[37] B. Çetinkaya, E. Çetinkaya, H. Küçükbay, R. Durmaz, *Arzneim. Forsch/Drug Res.* **1996**, *46*, 821.
[38] H. Küçükbay, E. Çetinkaya, R. Durmaz, *Arzneim. Forsch/Drug Res.* **1995**, *45*, 1331.
[39] H. Küçükbay, B. Durmaz, *Arzneim. Forsch/Drug Res.* **1997**, *47*, 667.
[40] H. Küçükbay, R. Durmaz, N. Okuyucu, S. Günal, C. Kazaz, *Arzneim. Forsch/Drug Res.* **2004**, *54*, 64.
[41] N. Şireci, H. Küçükbay, M. Akkurt, Ş. P. Yalçın, M. N. Tahir, H. Ott, *J. Coord. Chem.* **2010**, *63*, 3218.
[42] SADABS: G. M. Sheldrick, 2008/1, Göttingen, **2008**.
[43] SIR97: A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori, R. Spagna, *J. Appl. Cryst.* **1999**, *32*, 115.
[44] SHELX: G. M. Sheldrick. *Acta Crystallogr.* **2008**, *A64*, 112.
[45] PLATON: A. L. Spek, *J. Appl. Crystallogr.* **2003**, *36*, 7.
[46] ORTEP-3: L. J. Farrugia, *J. Appl. Crystallogr.* **1997**, *30*, 565.
[47] National Committee for Clinical Laboratory Standards (NCCLS), Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, Approved Standard M7-A2, NCCLS Villanova, PA, **1997**.
[48] NCCLS, Reference method for broth dilution antifungal susceptibility testing of yeasts. Proposed Standard. Document M27-P. NCCLS, Villanova, PA, **1992**.
[49] I. Özdemir, Y. Gök, N. Gürbüz, E. Çetinkaya, B. Çetinkaya, *Synth. Commun.* **2004**, *34*, 4135.

[50] M. Akkurt, S. Türktekin, H. Küçükbay, Ü. Yılmaz, O. Büyükgüngör, *Acta Cryst. E.* **2005**, *61*, o166.
[51] H. Küçükbay, R. Durmaz, M. Güven, S. Günal, *Arzneim.-Forsch./Drug Res.* **2001**, *51*, 420.
[52] M. Akkurt, S.Ö. Yıldırım, H. Küçükbay, Ü. Yılmaz, O. Büyükgüngör, *Acta Cryst. E.* **2005**, *61*, o301.
[53] N. Şireci, Ü. Yılmaz, H. Küçükbay, *Asian J. Chem.* **2010**, *22*, 7153.
[54] H. Küçükbay, N. Şireci, Ü. Yılmaz, M. Akkurt, Ş.P. Yalçın, M.N. Tahir, H. Ott, *Appl. Organomet. Chem.* **2011**, *25*, DOI 10.1002/aoc.175.
[55] W. Huang, J. Guo, Y. Xiao, M. Zhu, G. Zou, J. Tang, *Tetrahedron* **2005**, *61*, 9783.