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Research Article

Catalytic Studies Featuring Palladium(II) Benzoylthiourea Derivative as Catalyst in Sonogashira Reaction

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Abstract

A benzoylthiourea derivative (**L$_{TU}$**) and its metal complexation of palladium(II) chloride (**ML$_{TU}$**) has been successfully synthesized and characterized via typical spectroscopic and analytical techniques namely IR, ^{1}H and ^{13}C Nuclear Magnetic Resonance, UV-Visible and Gas Chromatography Flame Ionization Detector (GC-FID). The Infrared spectrum for **L$_{TU}$** shows four significant bands of interest namely ν(N-H), ν(C=O), ν(C-N) and ν(C=S) and the values were observed within the range. The ^{1}H NMR spectrum for the compound shows expected protons for N-H at δ_H 10.95 ppm and δ_H 11.15 ppm while the ^{13}C NMR spectrum shows resonances of carbonyl (C=O) carbon and thiones (C=S) at δ_C 168.26 ppm and δ_C 180.56 ppm, respectively. From UV-Vis spectrum, it shows the presence of n-π* and π→π*electronic transitions which are expected to be attributed from the phenyl ring, carbonyl (C=O) and thiones (C=S) chromophores. Complexation of **L$_{TU}$** with palladium(II) chloride was done to afford **ML$_{TU}$** which in turn, was tested as homogeneous catalyst in Sonogashira cross-coupling reaction. The reaction was monitored by GC-FID at 6 hours reaction period. The percentage conversion of 4-bromoacetophenone to the coupled product was 75.73% indicated that **ML$_{TU}$** can act as an ideal potential catalyst in the Sonogashira reaction.

Keywords: Thiourea; Homogeneous Catalysis; Sonogashira reaction

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1. Introduction

Sonogashira cross-coupling reaction of terminal alkynes with aryl halides catalyzed over a Pd(0)/Cu(I) system has become one of the most important and powerful transition-metal-catalyzed transformation of organic synthesis to generate C(sp^2)-C(sp) bond or in other word C≡C bond [1-5]. This reaction has found several commercial applications to be important intermediates in organic synthesis including natural products, molecular electronics, polymer and

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biologically actives molecule for the production of enediyne antibiotics or the contraceptive pill in the pharmaceutical industry [6-11]. Basically, Sonogashira reaction is carried out in an organic solvent such as amine, benzene, toluene, DMA, THF or DMF [12-13].

Based on the literature, *N,N*-dimethylacetamide (DMA) shows an excellent conversion to the product in the catalytic reaction because DMA is soluble in various organic compounds [14]. Palladium catalysts such as $Pd_2(dba)_3$, $Pd(PPh_3)_4$ or $Pd(PPh_3)_2Cl_2$ are expensive and sometimes difficult to handle and recover [15-16]. Besides, the use of phosphine tend to be very sensitive to air and moisture thus required an inert atmosphere conditions to perform as an efficient catalyst, and less useful for industrial scale reactions [17-19]. Thiourea is an organic compound which consists of carbon, nitrogen, sulphur and hydrogen atoms which provide a multitude of bonding possibilities [20-21]. Thus, the versatility and unique properties of thiourea has attracted a great interest to replace the functionality of phosphine as ligand in the catalytic system. Moreover, thioureas are able to coordinate with various transition metal ions as monodentate or bidentate ligands [22].

Inspired by the unique properties of thiourea derivatives in numerous reported applications, as well as the their tendency to form complexation with many metals, thus in this report we focus on the design and synthesis of benzoylthiourea derivative and its metal complex involving palladium acting as homogenous catalyst to be applied in Sonogashira reaction. The role and behavior of this catalyst in the catalytic studies Sonogashira cross-coupling reaction was further investigated.

2. Materials and Methods

2.1. Materials

All chemicals used in this study were commercially available and used as received without any purification step taken. Chemicals namely 4-methylbenzoylchloride, ammonium thiocyanate, phenylacetylene and copper(I) iodide were purchased from MERCK. In addition, benzonitrile and 4-bromoacetophenone were supplied from Sigma Aldrich. Other chemicals used in this study namely palladium(II) chloride and acetonitrile were purchased from R & M Supplier. In addition, acetone was supplied by Fisher Scientific.

The infra-red (IR) spectra were recorded on a Fourier Transform-Infrared Spectrometer, Perkin Elmer Spectrum 100 in the range of 4000-400 cm^{-1} as potassium bromide (KBr) disc. Electronic absorption spectra of the samples were recorded in the range of 200-400 nm using Shimadzu UV-Vis Spectrophotometer 1601 series in 1 cm^3 cuvette. The ^1H (400.11 MHz) and ^{13}C (100.61 MHz) NMR spectra were recorded using Bruker Avance III 400 Spectrometer in $(CD_3)_2SO$ as solvent and internal standard at room temperature in the range between δ_H 0-15 ppm and δ_C 0-200 ppm, respectively.

2.2. Preparation of *N*-Nonyl-*N'*-(4-Methylbenzoyl)Thiourea (L_{TU})

4-methylbenzoylchloride (2 ml, 15 mmol) was added dropwise into a solution of ammonium thiocyanate (1.14 g, 15 mmol) in 30 ml acetone followed by stirring at room temperature for *ca.* 10 minutes. Next, nonylamine (2.74 ml, 15 mmol) was added dropwise to the mixture. The reaction mixture was put at reflux with continuous stirring *ca.* 3 hours and the progress of the reaction was monitored using Thin Layer Chromatography (TLC) (hexane: ethyl acetate: 6:4). When adjudged completion, the reaction mixture was cooled to room temperature before it was then filtered. The off-white precipitate was removed and the filtrate was separated into two parts. The first part was placed in a vial for recrystallisation from acetone while the second part was added to three ice cubes, which was then filtered to obtain white precipitate. The combined white precipitate was then recrystallized from methanol to afford the title compound **L_{TU}** as white crystalline solid with 65% percentage yield.

2.3. Preparation of (Dichloro(*N*-Nonyl-*N'*-(4-Methylbenzoyl)Thiourea-K^1O) Palladium(II) (ML_{TU})

The ligand *N*-nonyl-*N'*-(4-methylbenzoyl) thiourea (**L_{TU}**) (0.1 g, 0.03 mmol) was dissolved in little amount of acetonitrile (MeCN) in a 100 mL three necked round bottom flask. Whilst, cis-bis (benzonitrile) palladium(II) chloride (**M1**) (0.30 g, 0.79 mmol) was also dissolved separately in acetonitrile. Then, the metal salt was added dropwise into the flask containing the ligand solution. The mixture was stirred and put at reflux under nitrogen atmosphere for *ca.* 3 hours. The colour of the reaction mixture changed from dark brown to reddish brown with formation of light brown precipitate. When adjudged completion, the reaction mixture was cooled to room temperature before it was filtered to give light brown solid of the title compound **ML_{TU}**. Scheme 1 shows the preparation of palladium(II) thiourea complex (**ML_{TU}**).

2.4. Homogeneous Catalytic Testing in Sonogashira Reaction

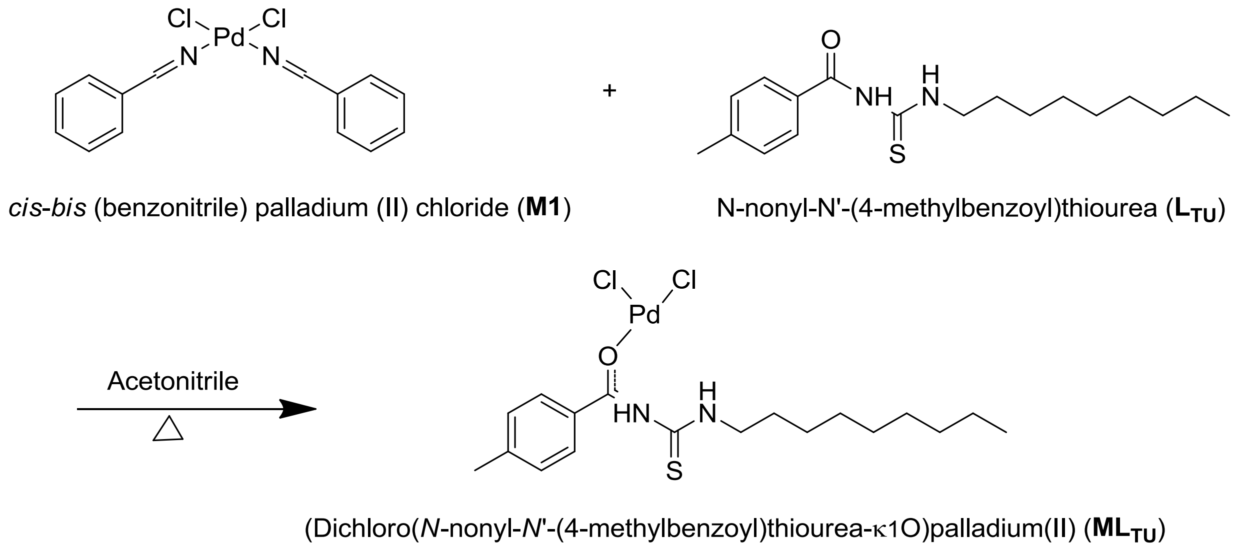
4-bromoacetophenone (1.00 mmol, 0.20 g), phenylacetylene (2.00 mmol, 0.22 ml), triethylamine (5 ml) and equimolar amount of the respective palladium catalyst (**ML_{TU}**) and copper iodide (1 mmol%) was mixed together in Radley's 12-placed reaction carousel whilst purged with nitrogen and heated to 100 °C for 6 hours. The reaction was monitored regularly by GC-FID. The conversion of 4-bromoacetophenone to the product (**C1**) was 75.73%. The synthetic approach for the Sonogashira cross-coupling reaction is illustrated in Scheme 2.

3. Results and Discussion

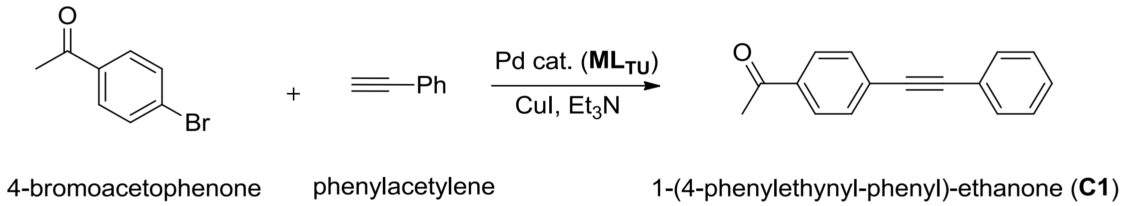
3.1. Infrared Spectroscopy

Infrared spectrum of the synthesized compound (**L_{TU}**) and the metal complex (**ML_{TU}**) have been analyzed in the expected frequency region of the *υ*(N−H), *υ*(C=O), *υ*(C−N), *υ*(C=S) and *υ*(C=N). According to the IR spectrum for the ligand (**L_{TU}**), the stretching vibration for *ν*(C=O) is assigned at 1667 cm^{-1}. However, for the IR spectrum of **ML_{TU}**, the vibration signal has shifted to 1674 cm^{-1} suggesting formation of bonding between the ligand and the metal center at oxygen and proves the formation of the metal-thiourea in this complex [23]. In addition, during complexation process, palladium accepts electron from the oxygen atom from thiourea derivative as palladium is an electropositive atom. Therefore, the bonding between carbon and oxygen atom becomes weak and tend to form a bonding with palladium metals [24]

Besides that, a strong band was observed at 751 cm^{-1} in IR spectrum of free ligand (**L_{TU}**) attributed to *ν*(C=S) stretching vibration. This band is slightly shifted to 747 cm^{-1} in the IR spectrum of **ML_{TU}** indicates that no bond formation occurs between the sulfur atom and palladium metal as predicted. Moreover, there are no reduction in the double bond character in *ν*(C=S) stretching which also proves the sulfur atom did not form any bond with the palladium metal. In addition, there is also a new band observed in the IR spectrum of **ML_{TU}** which is the *ν*(C=N) stretching band. This indicates that there is tautomerisation occurs between the oxygen, carbon and nitrogen atom. Therefore, by comparing the IR spectrum of the metal complex (**ML_{TU}**) and free ligand (**L_{TU}**), it can be



Scheme 1. The preparation of palladium thiourea complex (**ML_{TU}**)



Scheme 2. Synthetic approach for the Sonogashira reaction

concluded that the ligand (**LTU**) only bound to the palladium metal on the oxygen atom. Table 1 below shows the FTIR data for both ligand (**LTU**) and the palladium complex (**MLTU**).

3.2. Nuclear Magnetic Resonance Spectroscopy

^{1}H and ^{13}C NMR were used to resolve the chemical structure of the synthesized ligand (**LTU**) and its metal complex (**MLTU**). The ^{1}H NMR spectra for **LTU** and **MLTU** show the methyl resonance at δ_H 0.86 ppm and δ_H 0.83 ppm respectively as triplet due to coupling with $-CH_2$. For **LTU**, two singlet resonances are observed at δ_H 10.95 ppm and δ_H 11.15 ppm, correspond to one proton in the N−H which is attached to the carbonyl (C=O) group and another proton from N−H which is attached to the thione (C=S) group. These resonances are observed to be deshielded in the spectra due to the interaction of hydrogen bonding between C−O···H−N−C=S. While, in compound **MLTU**, N−H protons appeared at δ_H 11.93 ppm and δ_H 11.19 ppm respectively. The resonance of carbonyl group has been shifted to downfield due to the coordination with the Pd(II) where the reduction in the electronic density around the nitrogen atom has taken place [25].

The ^{13}C NMR spectra for **LTU** and **MLTU** show a resonance of methyl group at δ_C 14.08 ppm and δ_C 14.37 ppm respectively. Furthermore, the aromatic carbon resonances can be found in between δ_C 129.02-145.11 ppm. The carbonyl (C=O) and thione (C=S) carbons of **LTU** and **MLTU** can be clearly observed in the range of δ_C 180.52-176.97 ppm and δ_C 168.26-168.83 ppm, respectively. The shifted of the chemical shift of C=O and C=S are caused by metal-ligand interactions of palladium(II) metal (**MLTU**) and ligand (**LTU**) [26-28]. Table 2 shows the summary data for ^{1}H and ^{13}C NMR data for **LTU** and **MLTU**.

Table 1. The FTIR data for ligand (**LTU**) and palladium complex (**MLTU**)

Compounds	ν(N-H) cm^{-1}	ν(C=O) cm^{-1}	ν(C-N) cm^{-1}	ν(C=S) cm^{-1}	ν(C=N) cm^{-1}
LTU	3248	1667	1378	751	-
Intensity	(m)	(s)	(m)	(s)	
MLTU	3169	1674	1375	747	1561
Intensity	(w)	(s)	(m)	(s)	(s)

Table 2. The summary data for ^{1}H and ^{13}C NMR for **LTU** and **MLTU**

Compounds	^{1}H NMR / δ_H (ppm)	^{13}C NMR / δ_C (ppm)
LTU	(t, $^3J_{HH}$ = 7 Hz, 3H, CH_3), 0.86 (m, 12H, 6 x CH_2), 1.24-1.29 (q, 7 Hz, 2H, CH_2), 1.61 (s, 3H, CH_3), 2.37 (q, $^3J_{HH}$ = 7 Hz, 2H, CH_2), 3.61 (pseudo-d, $^3J_{HH}$ = 8 Hz, 2H, C_6H_4), 7.29-7.31 (pseudo-d, $^3J_{HH}$ = 8 Hz, 2H, C_6H_4), 7.86-7.88 (2 x s, 1H, NH), 10.95, 11.15	(2 x CH_3), 14.37, 21.53 (8 x CH_2), 22.60, 26.89, 28.06, 29.15, 29.18, 29.40, 31.77, 45.16 (C_6H_4), 129.02, 129.39, 129.73, 143.78 (C=S), 168.26 (C=O), 180.56
MLTU	(t, $^3J_{HH}$ = 7 Hz, 3H, CH_3), 0.83 (m, 12H, 6 x CH_2), 1.64-1.73 (q, 7 Hz, 2H, CH_2), 1.49 (s, 3H, CH_3), 2.36 (q, $^3J_{HH}$ = 7 Hz, 2H, CH_2), 3.75 (pseudo-d, $^3J_{HH}$ = 8 Hz, 2H, C_6H_4), 7.23-7.27 (pseudo-d, $^3J_{HH}$ = 8 Hz, 2H, C_6H_4), 7.92-8.06 (2 x s, 1H, NH), 11.19, 11.93	(2 x CH_3), 14.08, 21.71 (8 x CH_2), 22.64, 26.83, 28.93, 29.11, 29.18, 29.36, 31.81, 46.72 (C_6H_4), 129.74, 129.87, 130.19, 145.11 (C=S), 168.83 (C=O), 176.97

3.3 Uv-Vis Analysis

In this study, electronic absorption spectra of **L$_{TU}$** and **ML$_{TU}$** were recorded in methanol with the concentration 10^{-5} M. Table 3 shows the electronic absorption data for the **ML$_{TU}$** and **L$_{TU}$**. Figure 1 shows the UV-Vis spectra for **ML$_{TU}$** and the corresponding ligand **L$_{TU}$**.

It is clearly observed, **L$_{TU}$** and **ML$_{TU}$** show the absorption occurs in the region below than 300 nm. The $\pi\rightarrow\pi^*$ transition band in the both compounds are expected to be attributed from phenyl, carbonyl (−C=O) and thione (−C=S) chromophores which can be observed in the range of 249 to 283 nm. Moreover, $n\rightarrow\pi^*$ transition band may be overlapped with $\pi\rightarrow\pi^*$ due to presence of carbonyl (−C=O) chromophore.

Based on the spectrum in Figure 1, it can be observed that there is a large shift between the metal complex and the ligand. The mixture of $\pi\rightarrow\pi^*$ and n-π^* transitions in the ligand **L$_{TU}$** is red-shifted in the metal complex **ML$_{TU}$** as it can be clearly observed that the wavelength becomes longer in the metal complex. This may be due to the bond formation between ligand **L$_{TU}$** and the palladium metal which increases the extent of conjugation in the metal complex (**ML$_{TU}$**). In the presence of conjugated double bonds, the electronic energy levels of chromophore move close together and the energy required to produce a transition from an occupied electronic energy level to an unoccupied level decreases, and the wavelength becomes longer which also known as bathochromic shift which refer to the electron conjugated π bond in phenyl ring and NH groups [29].

3.4. Catalytic Studies of Homogeneous Sonogashira Reaction

The palladium complex **ML$_{TU}$** that has been prepared in this study was tested as a homogeneous catalyst in Sonogashira reaction between 4-bromoacetophenone and phenylacetylene in the presence of triethylamine as base and solvent. Copper iodide (CuI) was added to the reaction mixture where it acts as co-catalyst and could influence the stability and reactivity of palladium intermediates [15]. The reaction was carried out in a Radleys 12-placed carousel reactor vessel whilst continuously flushed with nitrogen gas. The reactor vessel was then heated at optimum temperature (100 ^{o}C) for *ca.*

Table 3. Electronic absorption data for the **ML$_{TU}$** and **L$_{TU}$**

Compounds	Concentration (M)	Wavelength (Absorbance) λ/nm (ε/M^{-1} cm^{-1})	
L$_{TU}$	4.58 x 10^{-5}	253.40 (12561)	282.60 (7491)
ML$_{TU}$	3.70 x 10^{-5}	272.40 (5401)	282.20 (2089)

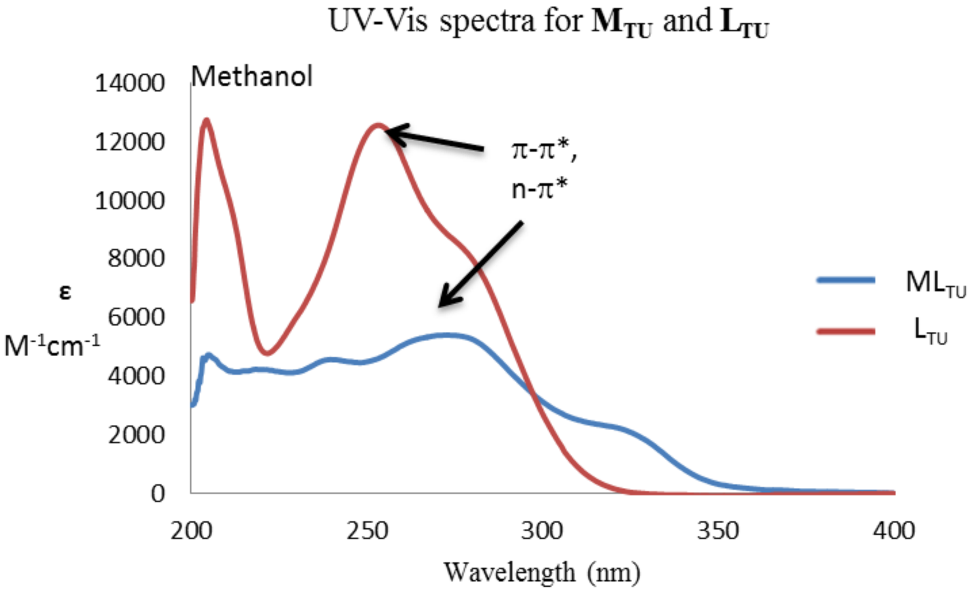


Figure 1. UV-Vis spectra for **L$_{TU}$** and **ML$_{TU}$**

6 hours. The temperature was carefully controlled by a contact thermometer (± 1 °C). The reaction was monitored using Gas Chromatography Flame Ionisation Detector (GC-FID) by determining the percentage conversion of starting material which is 4-bromoacetophenone to the coupled product. Scheme 3 shows the synthetic approach for the Sonogashira reaction.

The reaction of 4-bromoacetophenone using **ML$_{TU}$** as homogeneous catalyst exhibited 75.73% conversion of starting materials into the desired Sonogashira product after 6 hours reaction period. The conversion might not achieve up to 100% which may due to the catalyst system that may be considerably less reactive under Sonogashira conditions [30]. Furthermore, optimization technique for catalytic study in Sonogashira reaction can be done in many different conditions such as different temperature, catalyst loading, solvent used and the presence of nitrogen gas to get a higher conversion which is believed to increase the percentage yield. As a conclusion, these findings indicate that the palladium complex (**ML$_{TU}$**) can act as a potential catalyst in the Sonogashira cross-coupling reaction. Thus, this type of molecular framework bearing thiourea-palladium complexes as catalyst can be further developed in cross-coupling reactions especially in Sonogashira reaction by their electronic and geometric properties. As shown in Table 4, the catalytic data indicate that **ML$_{TU}$** complex can be used as homogenous catalyst in Sonogashira reaction involving 4-bromoacetophenone with phenylacetylene which gave more than 75% conversion after just *ca.* 6 hours of the reaction period.

4. Conclusion

In conclusion, one new benzoylthiourea compound (**L$_{TU}$**) and its metal complex reacted with palladium (II) chloride (**ML$_{TU}$**) were successfully synthesized and characterized via IR, ^{1}H and ^{13}C NMR and UV-Vis spectroscopic and analytical techniques. This type of catalyst featuring benzoylthiourea derivative is believed suitable to act as catalyst as it shows promising result which converted 75.73% 4-bromoacetophenone into the coupled product. In addition, the preparation of thiourea derivatives does not require any special treatment compared to other synthetic methods.

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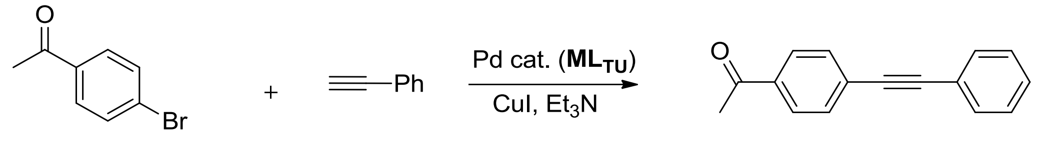
Table 4. The catalytic activity and performance of **ML$_{TU}$**

Complex	Without catalyst	Synthesized **ML$_{TU}$**
Catalyst loading (mmol)	0.00	1.00
Retention time (hours)	24	6
Temperature (^{o}C)	120	100
Conversion of 4-bromoacetophenone (%)	16.95	75.73



Scheme 3. Synthetic approach for the Sonogashira cross-coupling reaction

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