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# Synthesis and structure of some azolium salts

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**Abstract**

The reactions between benzimidazole, imidazole, or 1,2,4-triazole with either benzyl chloride or isopropyl bromide yielded 6 azolium salts, namely 1,3-dibenzylimidazolium chloride (**M1**), 1,3-dibenzylbenzimidazolium chloride (**M2**), 1,3-dibenzyl-1,2,4-triazolium chloride (**M3**), 1,3-diisopropylimidazolium bromide (**M4**), 1,3-diisopropylbenzimidazolium bromide (**M5**), and 1,3-diisopropyl-1,2,4-triazolium bromide (**M6**). These salts can be further used as the starting compounds for the synthesis of complexes based on *N*-heterocyclic carbenes for various applications. The structures of **M1**÷**M6** have been unambiguously determined by means of IR and $^1$H NMR spectroscopic methods.

**Keywords.** *N*-heterocyclic carbenes, azoles, azolium salts.

## 1. INTRODUCTION

In the past few years, transition metal complexes of *N*-heterocyclic carbene ligands (NHCs) have found vast application in molecular catalysis, material science, and medicine [1, 2]. Recently, researchers have also coupled their photo emissivity with anti-cancer activity and demonstrated their potential use towards lifesaving chemo-theranostic treatment [3]. In particular, palladium(II) complexes bearing carbine ligands derived from imidazolium precursors have been successfully developed as highly active precatalysts for C-C coupling reactions such as Mizoroki – Heck and Suzuki – Miyaura cross-coupling as well as CO-olefin copolymerization [4, 5].

Among many ways to synthesize NHC complexes, *in-situ* deprotonation of azolium salts with a basic metal precursor is one of the most widely used method due to its simplicity and efficiency [6, 7]. In this article, we describe the synthesis and structural characterization of some azolium salts that may be used as precursors for the synthesis of NHC complexes.

## 2. EXPERIMENTAL

### 2-1. Synthesis of the azolium salts

*Synthesis of 1,3-dibenzylimidazolium chloride* (**M1**): A 5 M aqueous solution of NaOH (2.0 mL, 10 mmol) was added to a suspension of imidazole (680 mg, 10 mmol) in $CH_3CN$ (10.0 mL). The resulting mixture was stirred at RT for 30 minutes to give a clear solution. To the obtained solution was added benzyl chloride (1.20 mL, 10 mmol). The reaction mixture was held at reflux for 1 day. Another portion of benzyl chloride (1.5 mL, 14 mmol) was added to the reaction mixture and the mixture was stirred under reflux for a further day. After removing the volatiles under reduced pressure, $CHCl_3$ (30 mL) was added to the residue and the resulting suspension was filtered over celite. The remaining solid was washed with $CHCl_3$ (3 × 10 mL), and the solvent of the filtrate was removed *in vacuo* under reduced pressure to give a spongy solid, which upon washing with ethyl acetate (2 x 10 ml) afforded the desired azolium salt as a white powder. Yielded: 2.28 g (80 %).

*Synthesis of 1,3-dibenzylbenzimidazolium chloride* (**M2**): **M2** was prepared starting from benzimidazole (1.18 g, 10 mmol) and 2.7 mL benzyl chloride (24 mmol) following the procedure used for the preparation of **M1**. Yielded: 2.51 g (75 %).

*Synthesis of 1,3-dibenzyl-1,2,4-triazolium chloride* (**M3**): **M3** was prepared starting from 1,2,4-triazole (690 mg, 10 mmol) and benzyl chloride (2.5 mL, 22 mmol) following the procedure used for the preparation of **M1**. Yielded: 2.23 g (78 %).

*Synthesis of 1,3-diisopropylimidazolium* bromide (**M4**): A mixture of imidazole (680 mg, 10 mmol) and $K_2CO_3$ (760 mg, 11 mmol) was suspended in acetonitrile (8 mL) and stirred at ambient temperature for 1 h. To the suspension was added isopropyl bromide (2.1 mL, 20 mmol). The reaction mixture was stirred under reflux conditions for 24

hours followed by the addition of the second portion of isopropyl bromide (3.3 mL, 30 mmol). The reaction mixture was stirred under reflux for an additional 48 h. After removing the volatiles under reduced pressured, $CHCl_3$ (20 mL) was added to the residue and the resulting suspension was filtered over celite. The remaining solid was washed with $CHCl_3$ (3×10 mL), and the solvent of the filtrate was removed under reduced pressure to give a spongy solid, which upon washing with ethyl acetate afforded the desired product as a white powder. Yielded: 2.23 g (85 %).

*Synthesis of 1,3-diisopropylbenzimidazolium* bromide (**M5**): **M5** was prepared starting from benzimidazole (1.18 g, 10 mmol) and isopropyl bromide (5.4 mL, 50 mmol) following the procedure used for the preparation of **M4**. Yielded: 2.21 g (78 %).

*Synthesis of 1,3-diisopropyl-1,2,4-triazolium* bromide (**M6**): **M6** was prepared starting from 1,2,4-triazole (0.69 g, 10 mmol) and isopropyl bromide (3.3 mL, 30 mmol) following the procedure used for the preparation of **M4**. Yielded: 1.76 g (75 %).

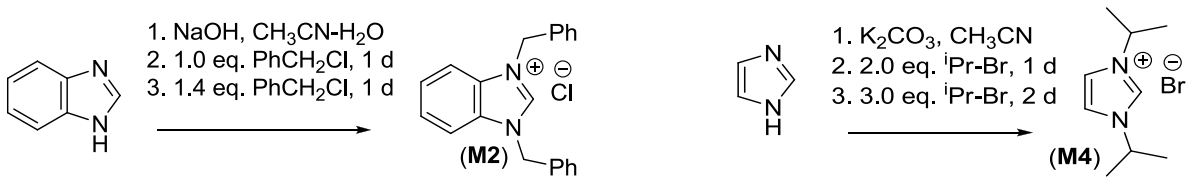
### 2.2. Instrumentation

Analytical thin-layer chromatography was performed with commercial glass plates coated with 0.25 mm silica gel (Merck, Kieselgel 60 F254). The studied compounds were visualized under UV-light at 254 nm. The IR spectra were recorded on an IMPACK-410 NICOLET spectrometer in KBr discs in the range 400-4000 $cm^{-1}$ at Faculty of Chemistry, Hanoi National University of Education. The $^1H$ NMR spectra were recorded on a Bruker AVANCE III 500 MHz, all at 298-300 K, with TMS as the internal standard at Faculty of Chemistry - VNU University of Science.

## 3. RESULTS AND DISCUSSION

Normally, azolium salts are prepared by alkylation of azoles with alkyl halide [8]. According to this method, 1,3-dibenzylazolium chloride (**M1**÷**M3**) and 1,3-diisopropylazolium bromide (**M4**÷**M6**) were synthesized by alkylating three azoles, benzimidazole, imidazole, and 1,2,4-triazole, with 75÷85 % isolated yields. Table 1 summarizes the results of some selected experiments. Scheme 1 shows the synthetic procedure of **M2** and **M4** as two typical examples.

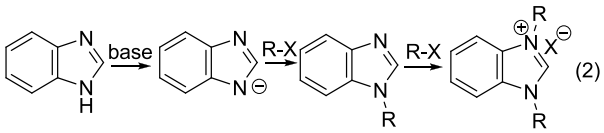
The synthetic procedure of **M1**÷**M6** undergoes three stages as shown in the diagram (2) for **M2** and **M4**.




*Scheme 1*: Synthesis of 1,3-dibenzylazolium chloride (**M2**) and 1,3-diisopropylazolium bromide (**M4**)

*Table 1*: Some selected experiments of producing **M1**÷**M6**

| Compound | Molar ratio of azole:R-X | Solvent (*v/v*) | Base | Temp. ($^oC$) | Time (h) | Yield (%) |
|---|---|---|---|---|---|---|
| **M1** | 1:2.4 | acetonitrile-water (5:1) | NaOH | 85÷90 | 30 | 50 |
| | 1:2.4 | acetonitrile-water (5:1) | NaOH | 85÷90 | 50 | 80 |
| **M2** | 1:2.4 | acetonitrile-water (5:1) | NaOH | 85÷90 | 50 | 75 |
| **M3** | 1:2.2 | acetonitrile-water (5:1) | NaOH | 85÷90 | 50 | 78 |
| **M4** | 1:3.0 | acetonitrile-water (5:1) | NaOH | 85÷90 | 50 | 20 |
| | 1:5.0 | acetonitrile | NaOH | 85÷90 | 72 | 25 |
| | 1:5.0 | acetonitrile | $K_2CO_3$ | 85÷90 | 48 | 60 |
| | 1:5.0 | acetonitrile | $K_2CO_3$ | 85÷90 | 72 | 85 |
| **M5** | 1:5.0 | acetonitrile | $K_2CO_3$ | 85÷90 | 72 | 78 |
| **M6** | 1:3.0 | acetonitrile | $K_2CO_3$ | 85÷90 | 72 | 75 |




The first step involves the deprotonation of benzimidazole with a strong or moderate base such as NaOH or $K_2CO_3$, respectively. This can be achieved easily at room temperature. The deprotonated benzimidazole is then sufficiently nucleophilic to attack the primary carbon of the alkyl halide to generate the corresponding benzimidazolium salt. Prolonging the reaction time and increasing the temperature are necessary to improve the efficiency of this step. Subsequently, in our next experiments (table 1), we conducted all reactions at 85÷90 $^oC$ in extended times (30÷72 hours). Additionally, the alkyl halides were also used in excess compared with the reaction molar ratio of azole:alkyl halides (1:2). Nevertheless, the alkyl halides should not be too excessively used in the synthesis of **M3** and **M6** in order to prevent creating the undesired 1,2,4-triankyl-1,2,4-triazolium.

In the reactions of benzyl chloride with azoles, using a mixture of polar solvents ($CH_3CN$ and $H_2O$) and a strong base such as NaOH gave 1,3-dibenzylazolium chloride salts (**M1**÷**M3**) with high isolated yields (75÷80 %). However, the conversion decreased in the case of isopropyl bromide when a strong base such as NaOH was used. The decreased yield in the *N*-alkylation of the azoles with secondary alkyl halides was due to the tendency of the latter to undergo elimination reaction in the presence of a strong base. Therefore, we carried out the reaction of azoles with excess isopropyl bromide in the presence of $K_2CO_3$ as a relatively weak base for 3 days. To our pleasure, the alkylation furnished 1,3-diisopropylazolium bromide salts (**M4**÷**M6**) as a white powder in much better yields (75÷85 %) (table 1, entries 4, 5, and 6).

Generally, the reaction yields in the synthesis of benzimidazolium salts are lower than those of imidazolium salts. An obvious reason is the presence of the fused electron-withdrawing phenyl ring that reduces the reactivity of benzimidazole.

The purity of the synthesized compounds **M1**÷**M6** was examined preliminary by thin layer chromatography. The results showed that they have adequate purity for further characterization with spectroscopic methods. Several physical properties of **M1**÷**M6** are listed in table 2. The data reveal that **M1**÷**M6** are well soluble in both normal organic solvents such as chloroform, acetonitrile, alcohols, DMSO, and water, but only slightly soluble in acetone. Almost all of the azolium salts are white solids, except for **M3** which has an orange color.

*Table 2:* Form, color and solubility of **M1**÷**M6**

| Comp. | Form | Color | Solubility (at 30 $^oC$) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | water | ethanol | acetone | chloroform | acetonitrile | DMSO |
| **M1** | powder | white | soluble | soluble | slightly soluble | soluble | soluble | soluble |
| **M2** | needles | white | lightly soluble | soluble | slightly soluble | soluble | soluble | soluble |
| **M3** | needles | orange | soluble | soluble | slightly soluble | soluble | soluble | soluble |
| **M4** | needles | white | soluble | soluble | slightly soluble | soluble | soluble | soluble |
| **M5** | needles | white | soluble | soluble | slightly soluble | soluble | soluble | soluble |
| **M6** | needles | white | soluble | soluble | lightly soluble | soluble | soluble | soluble |

The structures of **M1**÷**M6** were elucidated by IR and $^1H$ NMR spectroscopic methods. Main bands in the IR spectra are listed in table 3. The IR spectrum of **M2** is shown in figure 1 as an illustrative example.

*Table 3*: Main bands in IR spectra of **M1**÷**M6**, $cm^{-1}$

| Compound | $\nu_{OH}$ | $\nu_{CH\ aromatic}$ | $\nu_{CH\ aliphatic}$ | $\nu_{(C=C,\ C=N)}$ | $\delta_{CH\ aliphatic}$ | $\nu_{(C-C,\ C-N)}$ | $\delta_{CH\ aliphatic}$ |
|---|---|---|---|---|---|---|---|
| **M1** | 3395 | 3059 | 2986; 2846 | 1659; 1558; 1498 | 1450; 1357 | 1204; 1149; 1080 | 822; 717 |
| **M2** | 3429; 3364 | 3100; 3036 | 2951; 2850 | 1608; 1555; 1454 | 1423; 1373 | 1335; 1280; 1184 | 822; 760 |
| **M3** | 3472; 3391 | 3051 | 2980 | 1624; 1566; 1450 | 1435; 1350 | 1203; 1141; 1076 | 818; 721 |
| **M4** | 3445 | 3062 | 2940; 2800 | 1585; 1454 | 1408; 1340 | 1246; 1130 | 880 |
| **M5** | 3464 | 3070 | 2978 | 1628; 1555; 1462 | 1381; 1331 | 1281; 1184; 1146 | 856; 763 |
| **M6** | 3499 | 3100; 3040 | 2982; 2850 | 1635; 1566; 1516 | 1416 | 1300; 1234; 1184 | 891 |

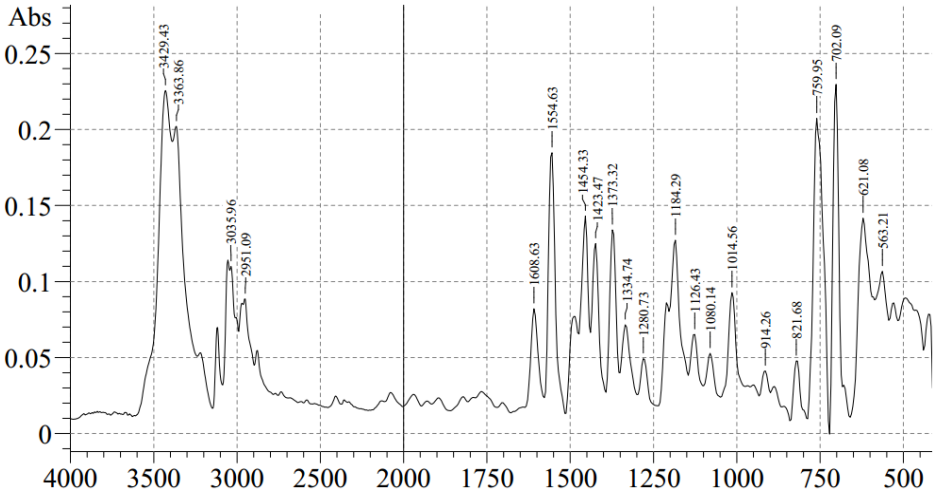



*Figure 1*: IR spectrum of **M2**

The IR spectra of **M1**÷**M6** show characteristic bands for the present functional groups in the azolium salts. For example, in the IR spectrum of **M2** (Fig. 1), those bands at around 1555÷1609 $cm^{-1}$ are characteristic for the (C=C and C=N) vibriations that prove the presence of the benzimidazole frame in **M2**. The presence of benzyl group is characterized by the characteristic absorption pattern of aliphatic $\nu_{CH}$ at 2850÷2951 $cm^{-1}$. In addition, the spectrum shows two intense bands at 3429÷3364 $cm^{-1}$, corresponding to the asymmetric and symmetric stretching vibrations of the O-H group in crystallized water. In the IR spectra of the other salts, similar signals characteristic for water were also observed. This may be because in the process of crystallization, the crystallized azolium salts absorbed water from the solution. Table 3 shows that the IR spectra of **M1**÷**M6** are only slightly changed when the alkyl groups are changed from benzyl to isopropyl or to anion $Cl^-$ to $Br^-$.

The assignment of the $^1$H NMR signals is based on their chemical shifts (δ), intensities, spin - spin splitting patterns, and splitting constants (*J*). The analyzed $^1$H NMR spectra of **M3** and **M4** are shown in figure 2 as representative examples.

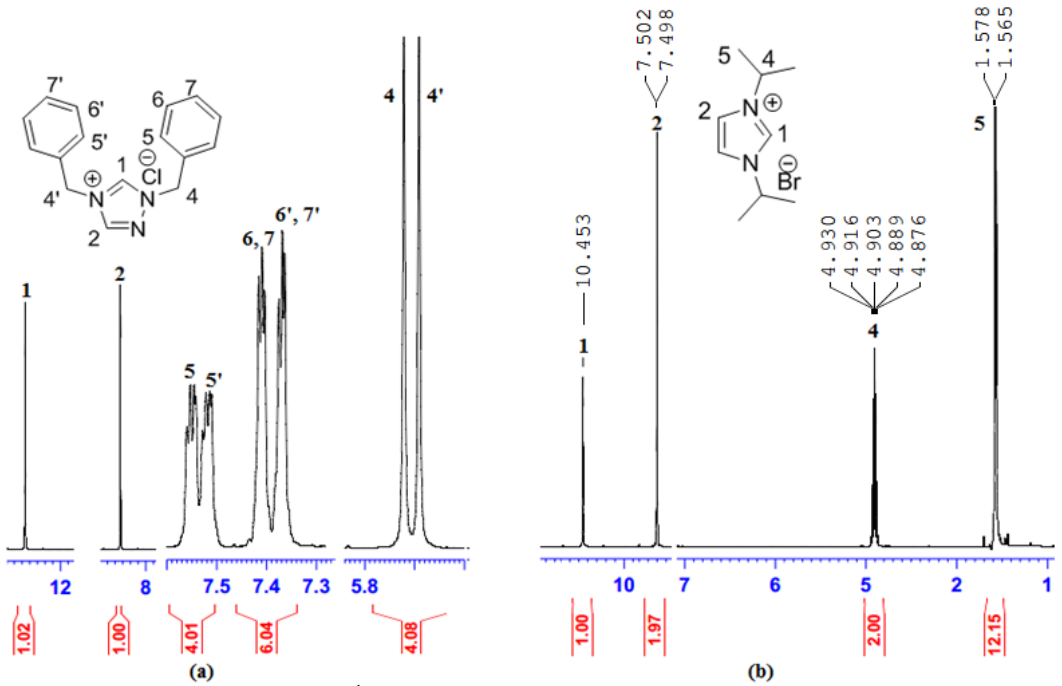



*Figure 2*: $^1$H NMR spectra of **M3** (**a**) and **M4** (**b**)

For example, in $^1$H NMR spectrum of **M4** (figure 2b), the two protons H5 give rise to a doublet centered at 1.57 ppm with $^3J$ = 7.5 Hz, the two protons H4 give rise to a multiplet centered at 4.90

ppm. These indicate that the two isopropyl groups in **M4** are equivalent. Two singlets at 10.45 ppm and 7.50 ppm are assigned for the two protons H1 and H2, respectively. Similarly, all signals in the spectra of **M1** ÷ **M6** are unambiguously assigned. The results are listed in table 4.

*Table 4:* $^1$H NMR signals in **M1**÷**M6**, δ (ppm), *J* (Hz)

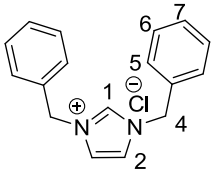
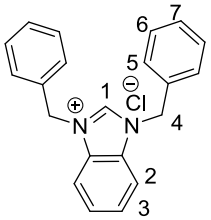
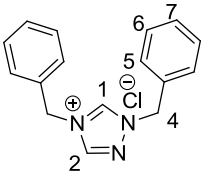
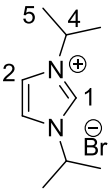
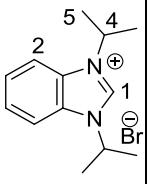
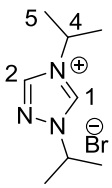
| Comp. (Solvent) | **M1** | **M2** | **M3** | **M4** | **M5** | **M6** |
|---|---|---|---|---|---|---|
| |  ($D_2O$) |  ($(CD_3)_2SO$) |  ($CDCl_3$) |  ($CDCl_3$) |  ($CDCl_3$) |  ($(CD_3)_2SO$) |
| H1 | 8.74 s | 10.39 s | 12.46 s | 10.45 s | 11.37 s | 10.23 s |
| H2 | 7.29-7.37 ov | 8.00 dd $^3J$ 7.0 $^4J$ 3.0 | 8.33 s | 7.50 s | 7.76 dd $^3J$ 6.5 $^4J$ 3.0 | 9.36 s |
| H3 | - | 7.63 dd $^3J$ 7.0 $^4J$ 3.0 | - | - | 7.61 dd $^3J$ 6.5 $^4J$ 3.0 | - |
| H4 | 5.27 s | 5.84 s | 5.72 / 5.69 s | 4.90 m | 5.18 m | 4.78 / 4.72 m |
| H5 | 7.29-7.37 ov | 7.56 d $^3J$ 7.5 | 7.57 / 7.52 dd $^3J$ 7.0 $^4J$ 2.0 | 1.57 d $^3J$ 7.5 | 1.84 d $^3J$ 6.5 | 1.54 / 1.52 d $^3J$ 6.5 |
| H6 | 7.29-7.37 ov | 7.43 t $^3J$ 7.5 | 7.40-7.42 ov | - | - | - |
| H7 | 7.29-7.37 ov | 7.39 t $^3J$ 7.5 | 7.36-7.38 ov | - | - | - |

Table 4 shows signals of all protons in **M1**÷**M6**. Particularly, the resonance of the proton H1 in **M1**÷**M6** is shifted downfield in comparison with that in the corresponding azoles [9], indicating the formation of the azolium salts. Besides, the equivalence of protons groups in **M1**, **M2** and **M4**, **M6** shows that the positive charge is relieved on the imidazole or the benzimidazole framework.

Basing on the results above, we have determined the structures of all synthesized azolium salts (**M1**÷ **M6**) as shown in table 4.

## 4. CONCLUSION

In conclusion, six azolium salts including 1,3-dibenzylimidazolium chloride (**M1**), 1,3-dibenzylbenzimidazolium chloride (**M2**), 1,3-dibenzyl-1,2,4-triazolium chloride (**M3**), 1,3-diisopropylimidazolium bromide (**M4**), 1,3-diisopropylbenzimidazolium bromide (**M5**) and 1,3-diisopropyl-1,2,4-triazolium bromide (**M6**) have been successfully synthesized with good isolated yields. From the reactions between benzimidazole, imidazole, or 1,2,4-triazole with benzyl chloride in the presence of a strong base (NaOH) for 2 days, the azolium salts **M1**÷**M3** were obtained. Under similar conditions but with isopropyl bromide and in the presence of a medium base ($K_2CO_3$) for 3 days at 85÷90 $^o$C, the other azolium salts **M4**÷**M6** were successfully synthesized. These salts can be used as the starting materials for our next study of producing complexes based on *N*-heterocyclic carbenes. The structures of **M1**÷**M6** were clarified by means of IR and $^1$H NMR spectroscopic methods.

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## REFERENCES

1. Garrison J. C., Youngs W. J. *Ag(I) N-Heterocyclic Carbene Complexes: Synthesis, Structure, and Application,* Chem. Rev., **105**, 4001-4005 (2005).
2. Herrmann W. A., Köcher C. *N-Heterocyclic Carbenes,* Angew. Chem. Int. Ed. Engl, **36**, 2162 (1997).
3. Hackenberg F., Müller-Bunz H., Smith R., Streciwilk W., Zhu X., Tacke M. *Novel ruthenium(II) and gold(I) NHC complexes: Synthesis, characterization, and evaluation of their anticancer properties,* Organometallics, **32**, 5551-5560 (2013).
4. Böhm V. P. W., Weskamp T., Gstöttmayr C. W. K., Herrmann W. A. *Nickel-catalyzed cross-coupling of aryl chlorides with aryl grignard reagents,* Angew

Chem., Int. Ed., **39**, 1602 (2000).

5. Wang X., Liu S., Jin D. X. *Preparation, structure, and olefin polymerization behavior of functionalized Nickel(II) N-heterocyclic carbene complexes*, Organometallics, **23**, 6002 (2004).
6. Hahn F. E., Jahnke M. C. *Heterocyclic carbenes: Synthesis and coordination chemistry*, Angew. Chem., Int. Ed., **47**, 3122-3172 (2008).
7. Crabtree R. *The Organometallic chemistry of the transition metals*, 4th Ed., Wiley-Interscience (2005).
8. Fremont de P., Marion N., Nolan S. P. *Carbenes: Synthesis, properties, and organometallic chemistry*, Coord. Chem. Rev., **253**, 862-892 (2009).
9. Tran Thi Da, Nguyen Huu Dinh. *Complex - Synthesis method and structural study*, Vietnam Education Publishing House (2007).

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