

Research Article

One-Pot Multicomponent Synthesis of Thiourea Derivatives in Cyclotriphosphazenes Moieties

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In this study, hexasubstituted thiourea was carried out via reaction of isothiocyanato cyclophosphazene intermediates with a series of aromatics amines and amino acids in a one-pot reaction system. The reaction was not as straightforward as typical thiourea synthesis. Six unexpected thiourea derivatives **3a–f** were formed in the presence of cyclotriphosphazene moieties in good yields (53–82%). The structures of **3a–f** were characterized by elemental analysis and FTIR, ¹H, ¹³C, and ³¹P NMR spectroscopies. The occurrence of reverse thioureas formation in a one-pot reaction system is discussed. The possible binding interaction of the synthesised thiourea **3a–b** in comparison to the predicted phenyl thiourea **5a–b** and the targeted **4a** with enzyme enoyl ACP reductase (FabI) is also discussed. Molecular docking of the targeted hexasubstituted thiourea **4a** is able to give higher binding affinity of -7.5 kcal/mol compared to **5a–b** (-5.9 kcal/mol and -6.3 kcal/mol) and thiourea **3a–b** (-4.5 kcal/mol and -4.7 Kcal/mol).

1. Introduction

Thiourea is widely studied and claimed to be used in many applications such as herbicides, pharmaceutical agents, pesticides, rodenticides, vulcanization accelerator, and scaffolds in organic synthesis [1]. In the synthesis of thiourea, isothiocyanate is formed as a reactive intermediate and easily converted to other side product during isolation [2]. Many studies reported on the direct reaction of isothiocyanate intermediate with amines after isolation of KCl to produce thiourea in good purity [3].

Several studies reported on monosubstituted thiourea which consists of one thiourea moiety either as a ligand bearing aromatic, halogen, or alkyl substituents [4] or as a complex compound coordinated with heavy metal center [5]. Multisubstituted thioureas have gained more interest among researchers due to the increase of their pharmaceutical properties. Our recent studies on thiourea reported that compounds that consist of more than one thiourea moiety possess better antimicrobial activities [6–8]. It was

due to the presence of more active sites of thiourea moieties containing C=S, C=O, and N-H groups, which are easily protonated under acidic condition and interacted with the carboxyl and phosphate groups of the bacterial surfaces, thus enhancing the biological activities [7]. Various methods have been reported to make this versatile group of thiourea derivatives easily accessible with excellent yields [2, 9–12].

Hexakisphosphazenes bearing thioureas moieties have been reported from the stepwise reaction of the isolated isothiocyanate intermediates with a series of aliphatic amines via P-Cl substitution of hexachlorocyclotriphosphazene [13]. Hexachlorocyclotriphosphazene, a cyclic inorganic compound with alternating phosphorus and nitrogen atoms, has sparked great interest among researchers for an excellent candidate in constructing hexasubstituted molecules [14, 15]. The substitution of P-Cl bonds with various types of nucleophiles allowed the construction of phosphazenes-based ligands with different types of physical and chemical properties [16]. A wide range of hexasubstituted phosphazene derivatives with