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Indole Chemistry

# General, Mild, and Metal-Free Functionalization of Indole and Its Derivatives Through Direct C3-Selenylation

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**Abstract:** A very mild method for the introduction of functionalized alkylselenyl group at C-3 position of the indole ring was developed. The proposed procedure consists of an electrophilic substitution of indole and its derivatives with bis(*O*,*O*-diisopropoxyphosphorothioyl) diselenide and subsequent cleavage of the P–Se bond with tetrabutylammonium fluoride in the presence of various electrophilic reagents. This method can be successfully applied, inter alia, for the preparation of amino acid and glucoside derivatives of 3-selenoindole.

## Introduction

The indole ring is a structural motif that is widely distributed among the naturally occurring and synthetic bioactive compounds.[1] By way of example, indole-based natural anticarcinogens can be isolated from cruciferous vegetables or deep-water plants[2–3] while its derivatives obtained synthetically are commonly used as pharmaceuticals of diverse biological activities. For instance, oxindoles[4] are used as antimicrobial agents, while 2-arylindoles are COX-2 inhibitors, reducing the inflammation and pain.[5] Among them, 3-sulfenylated and 3-selenylated indoles are found to exhibit anticancer and anti-HIV activity.[6–10] This ubiquity of indole across pharmaceuticals and natural products qualifies it as an attractive scaffold for novel drug development.

Various synthetic methods for indole selenylation have been reported. Over the past few years, synthetic methods for the preparation indoyl selenides have been drastically improved, but the reaction of indole with diorganyl diselenide in the basic conditions remains the most common pathway.[11] Other commonly used selenylation methods are electrophilic substitution with organoselenium halides or phthalimides[12–15] and copper-catalyzed reaction with diorganyl diselenides.[16] However, despite of their advantages, this methods have one common drawback: all methods require the usage of diaryl or dialkyl diselenides, and especially the preparation of the latter might be the major challenge of the synthetic procedure. Most of these reported procedures focus on the usage of diaryl diselenides, among which diphenyl diselenide is being the one most commonly used,[17–22] and thus omit the discussion of the difficulties related to the diselenide preparation. An alternative method of the synthesis involves the reaction of indole with in-situ prepared cyanogen triselenide, which is highly toxic. Obtained 3-selenocyanatoindole can be further reduced using $NaBH_4$, finally forming sodium selenolate that can be used in the reaction with electrophiles (eg. alkyl halides) to form indoyl selenoethers.[23] Finally, metal-catalyzed indole and 5-deazapurine selenylation reactions were reported, although harsh conditions of the processes (temperature ≈ 110 °C) limit their application in the synthesis.[24–27]

As stated before, great deal of attention has been lately paid to synthesis of indoyl thio- and selenoethers due to their potent therapeutic value. The most prominent (and well known bioactive) group of indoyl thio- and selenoethers contain aryl substituents on the chalcogen atom, eg. tubulin polymerization inhibitors or PPAR gamma agonists.[28,29] The popularity of these scaffold is due to the simplicity of the synthesis of aryl diselenides, which are used to incorporate thio- and selenoaryl substituent into indole ring.[16] The recently developed anti-HIV agents[10] composed of an indole ring bearing alkylselenyl substituents shows that there is an urgent need to develop a simple and general path for the synthesis of these potentially bioactive compounds.

According to the known metabolic pathway, the selenium incorporation into bioorganic compounds takes place with the participation of the selenophosphate.[30] Inspired by nature, we decided to examine the selenylation efficiency of indoles by selenophosphate analogue, namely, bis(*O*,*O*-diisopropoxyphosphorothioyl) diselenide **1**. In present work we report easy, selective and efficient method for introduction of protected selenole group into indole scaffold. The formed indole *O*,*O*-diisopropoxyphosphorothioylselenyl derivatives possess hydrolyzable Se–P bond, which can be selectively deprotected in the presence of electrophilic substrate. Thus, our synthetic route offers an efficient method to synthesize various alkyl selenoindoles, such as alkyl, aryl or acyl. The most prominent advantage of our method is mild reaction conditions, which allow us to obtain susceptible selenoindole derivatives, such as *Se*-(3-indolyl)-L-selenocysteine, an example of unnatural tryptophan-

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