Ionic-Liquid Mediated Facile Synthesis Of *N*-Phenyl Rhodanines from Arylisothiocyanate and Thioglycolic Acid

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I. INTRODUCTION

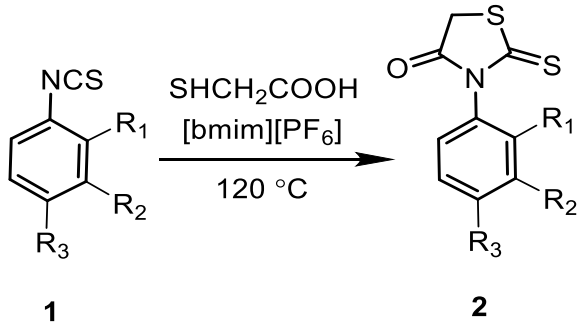
The development of efficient synthetic methodologies for the preparation of heterocyclic compounds has attracted a significant interest in the fields of organic chemistry and materials science [1]. Rhodanine is a well-known five-membered heterocyclic motif associated with thiazole nucleus as a parent framework including thioxo and carbonyl group are present at 2- and 4-position of the ring respectively. Rhodanine has remarkable importance due to its structural diversity and biological activities, making them valuable candidates for novel therapeutic agents against medicinal chemistry. Additionally, these entities are recognized as advantageous frameworks in pharmacological investigations and are routinely employed as agents exhibiting antibacterial [2], antifungal [3], antidiabetic [4], anti-inflammatory [5], antiviral [6], antitumor [7], antitubercular [8], anti-HIV [9], and antioxidant [10]. To date, only four drugs; pioglitazone, ciglitazone, troglitazone, and rosiglitazone containing rhodanine motif are well known for the type-2 diabetes. The pioglitazone drug consists the core structure of rhodanine which has been used as oral medication of type-2 diabetes to increase the body's sensitivity to insulin. The mechanism of action of pioglitazone, predominantly mediated by the activation of the peroxisome proliferator-activated receptor-gamma (PPAR-gamma), a nuclear receptor that is found in adipocytes, skeletal muscle, and hepatic tissues. However, the drugs troglitazone and rosiglitazone are withdrawn from the market due to their high risk of life-threatening liver injury effect, and risks of heart attack respec tively. On the other hand, ciglitazone is also known as rhodanine containing drug which could not approved for clinical used due to its severe liver toxicity. Therefore, designing of such rhodanine derivatives is highly desirable. Among these compounds, *N*-phenyl rhodanines are of particular importance due to their diverse applications, including their roles as pharmaceuticals, agrochemicals, and in the development of functional materials [11]. Traditional synthetic routes to *N*-phenyl rhodanines often involve multi-step processes with low yield and requirement of harsh reaction conditions.

In recent years, the utilization of ionic liquids as catalysts as well as solvent has emerged as a promising strategy to enhance reaction efficiency and selectivity [12]. The synthesis of *N*-phenyl rhodanines using ionic liquid represents a significant advancement in the field, offering a more efficient and environmentally friendly alternative to traditional methods. This innovative approach not only enhances yield but also aligns with the growing emphasis on sustainable practices in chemical synthesis. Moreover, the integration of ionic liquids in this synthesis aligns with the principles of green chemistry, promoting safer and more sustainable chemical processes. Such method exemplifies the shift towards eco-friendly alternatives in organic synthesis, addressing both efficiency and environmental concerns. Green chemistry initiatives are crucial for minimizing the environmental impact of chemical processes, emphasizing the importance of sustainable methods in organic synthesis. The continued exploration of green chemistry principles is essential for advancing sustainable practices in the chemical industry and mitigating the adverse environmental effects of traditional synthesis methods. This approach not only facilitates the synthesis of *N*-

phenyl rhodanines but also underscores the importance of green chemistry in promoting environmentally friendly practices in organic synthesis. The findings reinforce the need for ongoing research into green chemistry methodologies, which are vital for fostering innovation and sustainability in the chemical industry. The use of ionic liquids in the synthesis of *N*-phenyl rhodanines exemplifies the potential for innovative methods to support sustainable development goals in the chemical sector. This synthesis approach not only improves efficiency but also contributes to the broader goals of sustainability within the chemical industry, aligning with the principles of green chemistry. This synthesis method not only exemplifies the practical application of green chemistry principles but also highlights the ongoing need for innovation in sustainable chemical processes. The challenges associated with traditional synthesis methods often necessitate innovative solutions, making the exploration of alternative approaches essential for the advancement of sustainable chemical practices [13]. This exploration underscores the critical need for adopting greener methodologies that align with sustainability goals in the chemical industry, particularly in the synthesis of complex organic compounds. The transition towards greener methodologies is not only beneficial for environmental protection but also essential for fostering innovation and efficiency in chemical synthesis.

II. RESULTS AND DISCUSSION

In continuous of our previous work to synthesis the bioactive heterocyclic compounds [14-16], we started our experiment with phenylisothiocynate (1), and thioglycoric acid. It was observed that the cyclization reaction involving phenylisothiacynate and thioglycoric acid proceed effectively in ionic liquid, specifically 1-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF_6], resulting in the formation of the corresponding *N*-phenyl rhodanine. The yield of requisite 2a increased with the increase of the temperature at 120 °C. Mainly, two ionic liquids viz [bmim][PF_6] and [bmim][BF_4], were studied for cyclization reaction of thiazolidin-4 ones. Notably, [bmim][PF_6] afforded good result presumably due to its hydrophobic activation activity. It was assumed that water generated in situ in the condensation process exhibits miscibility with the hydrophilic ionic liquid [bmim][BF_4], thereby inhibiting the reaction from proceeding to completion. In contrast, the hydrophobic characteristics of [bmim][PF_6] would establish a micro environment that facilitates the equilibrium by expelling water from the ionic liquid phase, thereby culminating in an enhanced conversion rate. In the course of our investigation to study the effect of the solvent for one-pot reaction, we found that the reaction



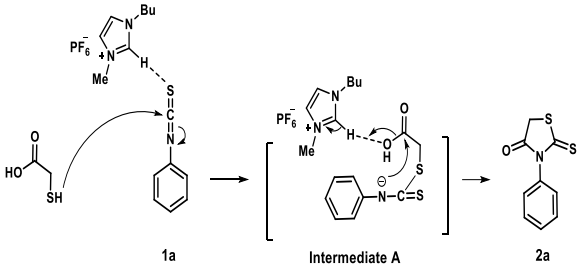
1 **2**

Entry	R_1	R_2	R_3	Time (h)	Yield[b] (%)
2a	H	H	H	6	76
2b	H	H	F	6	80
2c	Cl	H	H	6	88
2d	H	Cl	H	6	79
2e	H	H	Me	15	56
2f	Me	H	H	24	61
2g	H	Me	Me	15	63
2h	H	H	OMe	24	71
2i	H	H	t-butyl	12	69
2j	H	H	CN	12	74
2k	H	H	NO_2	12	74
2l	H	CF_3	H	12	76

Scheme 1. Synthesis of *N*-phenyl-rhodanine

did not proceed with acetonitrile, dimethylformamide, dichloromethane, and diphenyl ether. Compared with dichloromethane, ethanol, and tetrahydrofuran in ionic liquids demonstrated a remarkable increase in the reactivity with reduce in reaction time and a significant increase in outcome yield. To our delight, without use of solvent gave the similar results. Therefore, it is not a solvent of choice for sustainable chemistry. However, [bmim][PF_6] is non-volatile and easy to handle, therein acting as a benign and efficient medium. Encouraged by the results obtained above, we extended this process to various aldehyde and amine substrates to gain more insight into this reaction

(Scheme 1). It turned out that in [bmim][PF_6], various phenylisothiocynate reacted smoothly with thioglycoric acid and afforded the corresponding *N*-phenyl rhodanine (2a-l) in good to excellent yields.



Scheme 2. Plausible reaction mechanism

The plausible mechanism is represented in Scheme 2. The ionic liquid can activate the isothiocynate moiety followed by nucleophilic attack of sulphur atom of thioglycoric acid, thus forming the imine intermediate (A). Then, the nitrogen atom of intermediate A performed the intramolecular attack on the COOH group of thioglycoric acid to produce *N*-phenyl rhodamine.

In conclusion, the ionic-liquid-mediated synthesis of *N*-phenyl rhodanines from arylisothiocyanates and thioglycolic acid represents a significant advancement in organic chemistry, particularly in the realm of sustainable practices. This innovative approach addresses the limitations of traditional synthesis methods, which often involve cumbersome multi-step processes and harsh reaction conditions, by enhancing both reaction efficiency and product purity.

III. EXPERIMENT SECTION

An equimolar mixture of phenylthiocynate 1 (25 mmol) and thioglycoric acid (25 mmol) was dissolved in an ionic liquid [Bmin)[PF_6] (4 g), and the solution was stirred for 1 h at 120 °C. Thereafter, the reaction content was allowed to stir at 120 °C for 1 h. The progress of the reaction was monitored by thin-layer chromatography (TLC). The solid product was extracted by solvent extraction using ethyl acetate (25x2) and washed with 10% sodium bicarbonate (25x3). Evaporated organic solvent under vacuum and crude solid product was purified by column chromatography using eluent 5 to 15% ethyl acetate in petroleum ether to obtained pure *N*-phenyl rhodanine (2).

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