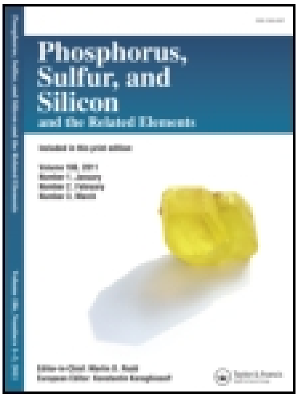

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A CONVENIENT SYNTHESIS OF 2-AMINO-1,3-SELENAZOLES USING IONIC LIQUID AND MICROWAVE IRRADIATION

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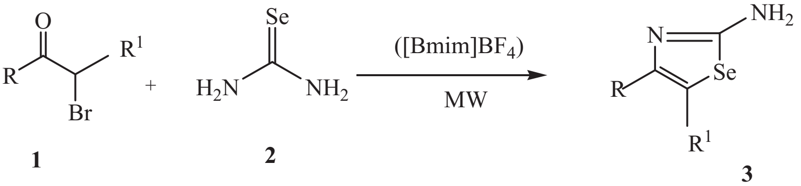
GRAPHICAL ABSTRACT



Abstract *A simple and environmentally benign synthesis of 2-amino-1,3-selenazoles by microwave irradiation using 1-butyl-3-methylimidazolium tetrafluoroborate ([Bmim]BF$_4$) ionic liquid (IL) is described. Acyl halides, phenacyl halides, and α-bromo-β-keto esters easily undergo condensation with selenourea in ([Bmim]BF$_4$) by microwave irradiation to afford the desired products of good purity in excellent yields. The ionic liquid can be easily recovered and reused at least 10 times without losing its activity. The duration of the reaction ranges from 4–6 min.*

Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.*

Keywords [Bmim]BF$_4$; microwave irradiation; selenazoles; selenourea

INTRODUCTION

Selenium, an essential biological trace element, is an integral part of several enzymes, and its use as a nutritional supplement has been popularized recently due to its potential role as an antioxidant in low concentrations and as an anticancer agent in high concentrations.[1] It has also been observed that a number of diseases result from selenium deficiency.[2] The pharmacological properties and therapeutic applications of substituted selenazoles made us enthusiastic about synthesizing a series of 2-amino-1,3-selenazole derivatives using microwave irradiation. The methodology is of particular interest for us, as the ionic liquid (IL) used acts as a solvent and catalyst in the present investigation.

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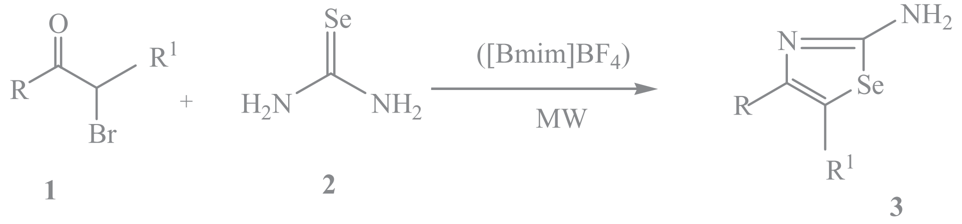
Room temperature ILs have been the subject of considerable interest as new, nonvolatile, and environmentally friendly alternatives to conventional organic solvents. They contain large organic cations and a variety of anions.[3–6] Ionic liquids are compatible with several organic transformations,[7–9] and they readily immobilize several catalysts in their native form[10,11] or supported catalysts.[12] They have been found to alter the outcome of chemical reactions in a dramatic fashion,[13] thus forming a new paradigm in organic synthesis. ILs have also been used in the synthesis of heterocycles such as isoxazoles.[14]

RESULTS AND DISCUSSION

A good number of methods for the synthesis of selenazoles have been reported using starting materials such as selenourea and aracylbromides.[15] Some of the reported methods of the synthesis of selenazoles describe the use of cyanomethyl-1-piperidinoseleno carboimidate hydrochloride,[16] selenourea,[17] 1,4-benzenedicarboselenamide,[18] or selenocarboxylic amides[19] as starting materials. The other procedures mainly start with selenazadienes,[20] phenylselenourea,[21] lithium hexamethyldisilazide (LHMDS),[22] selenoamides,[23] or selenoformamide.[24,25]

However, some of the reported methods require a prolonged reaction time and use of toxic solvents. The increasing attention during the last two decades for environmental protection has led both modern academic and industrial groups to develop green chemical processes with maximum yield and minimum cost. Moreover, selenourea is air- and light-sensitive,[26] and there is a need to develop a mild and eco-friendly methodology for synthesizing this high value compound. As a part of our program, which aimed at the development of synthetic methedologies[27] by eliminating flammable, toxic, or carcinogenic organic solvents, we employed 1-butyl-3-methylimidazolium tetrafluoroborate ([Bmim]BF_4) ionic liquid as a green chemical solvent. The IL plays the dual role of solvent and catalyst. The rapid use of microwave activation as a nonconventional energy source in organic chemistry has also helped us in devising the above synthetic route. Numerous organic reactions such as acylation and alkylation reactions, aromatic and nucleophilic substitutions, condensations, cycloadditions, protection and deprotection reactions, esterifications and transesterifications, heterocyclizations, rearrangements, organometallic reactions, oxidations, and reductions assisted by microwave heating have been widely described.[28] A synthetic strategy using [Bmim]BF_4 ionic liquid and microwave irradiation collectively was found to be a successful and efficient method for the synthesis of 2-amino-1,3-selenazoles. In general, the reaction was carried out by keeping the mixture of α-bromocarbonyl compound, selenourea, and [Bmim]BF_4 in a microwave oven for few minutes. Selenazoles were obtained in quantitative yields. The yields of selenazoles produced from aromatic α-bromoketones (phenacyl bromides) were comparatively higher than those obtained from aliphatic α-bromoketones. Similarly a better yield was observed when α-bromoethylacetoacetate reacted with selenourea. These reactions proceed smoothly without the formation of byproducts or rearranged products.

The compounds **3a–3j** (Scheme 1) registered an IR absorption band for N-H stretching in the range of 3446–3360 cm^{-1}. The ^1H NMR signal for the characteristic proton at position 4 for these selenazoles was observed in the region of δ 7.11–7.55. ^{13}C NMR signals for the three carbon atoms of the selenazole framework are observed in the regions of δ 108–115 for C_4, δ 140–150 for C_5, and δ 155–165 for C_2 carbons, respectively. All the final compounds were characterized by elemental analysis, IR, ^1H NMR, ^{13}C NMR, and mass spectrometry. The data of some of the known compounds were compared with the reported data.[29,30]



1 2 3

	R	R^1
3(a)	C_6H_5	H
(b)	4-CH_3-C_6H_4	H
(c)	4-$CH_3OC_6H_4$	H
(d)	4-Cl-C_6H_4	H
(e)	4-Br-C_6H_4	H
(f)	4-I-C_6H_4	H
(g)	4-NO_2-C_6H_4	H
(h)	$(CH)_3C$	H
(i)	C_6H_5	C_6H_5
(j)	CH_3	$COOC_2H_5$

Scheme 1 Synthesis of 2-amino-1,3-selenazoles by starting from α-bromocarbonyl compounds and selenourea using [Bmim]BF$_4$ ionic liquid and microwave irradiation.

The catalyst was easily recovered by washing the reaction mixture with distilled water and was directly reused for the next turn after evaporation of water under reduced pressure. The recycled catalyst was reused 10 times to catalyze the model reaction affording the corresponding selenazoles in good yields. When ([Bmim]BF$_4$) IL was reused 11 times or more, the yields were decreased by 15–20% (Table 1).

Table 1 Synthesis of 2-amino-1,3-selenazoles by starting from α-bromocarbonyl compounds and selenourea

Product[a]	R	R^1	Time (min)	Yield (%)[b]	Mp (°C)
3a	C_6H_5	H	4	95	130–132
3b	4-CH_3- C_6H_4	H	5	96	165–167
3c	4-$CH_3OC_6H_4$	H	6	96	172–173
3d	4-Cl- C_6H_4	H	4	97	156–158
3e	4-Br- C_6H_4	H	4	95	130–132
3f	4-I- C_6H_4	H	6	95	188–190
3g	4-NO_2- C_6H_4	H	6	98	248–250
3h	$(CH_3)_3C$	H	4	96	58–60
3i	C_6H_5	C_6H_5	6	96	198–200
3j	CH_3	$COOC_2H_5$	4	95	162–164

[a] All of the products were identified by mp, ^{1}H NMR, IR, ^{13}C NMR, and mass spectrometry and were compared with the reported data.[29,30]

[b] Isolated yields after purification.

CONCLUSION

In conclusion, we describe a practical and efficient procedure for the preparation of 2-amino-1,3-selenazoles through microwave irradiation by using ([Bmim]BF_4) ionic liquid as the catalyst. This is a fast reaction which could be completed within a duration of 4–6 min.

EXPERIMENTAL

Melting points were measured in open capillary on Buchi melting point B-540 apparatus and were uncorrected. IR spectra were recorded on ATI MATT-SON RS-1 FTIR spectrometer using KBr pellets. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in DMSO-d_6 and $CDCl_3$ on a Bruker Avance 300 instrument with the TMS at δ 0.00 ppm as an internal standard. Mass spectra (EI-MS) were taken on Perkin Elmer (SCIEX API- 2000, ESI) at 12.5 eV. Microwave KMIC-1.5KW (Korean Microwave Instrument Co.) was used to carry out the reactions. CHNS analysis was carried out on Carlo Erba EA 1108 automatic elemental analyzer. The progress of the reactions was monitored, and the purity of the compounds was checked by TLC. The chemicals, reagents, and solvents used were of commercial grade and were used without further purification unless otherwise stated.

Synthesis of 2-Amino-1,3-selenazoles: General Procedure

A mixture of α-bromocarbonyl compound (1 mmol) and selenourea (1.2 mmol) was dissolved in 1-butyl-3-methylimidazolium tetrafluoroborate ([Bmim]BF_4) (2 mL) in a stoppered RB flask, which was placed in a beaker containing water and kept in a microwave oven. The flask was irradiated at 1.5 kW for 1 min, and then the oven was opened, and the hot water contained in the beaker was changed. After 1 min of resting time, another 1 min of irradiation was applied followed by 1 min of resting and the water was changed repeatedly 3–4 times. After ensuring the completion of the reaction by TLC, the reaction mixture was poured into water (10 mL), the product was extracted using ethyl acetate (3 × 10 mL), and the extract was separated. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The resulting product was further purified by column chromatography on silica gel using ethylacetate:hexane (20:80) as eluent. The aqueous layer consisting of the ionic liquid ([Bmim]BF_4) was subjected to distillation (80 °C at 10 mmHg) for 2 h. Water was removed leaving behind the ionic liquid ([Bmim]BF_4). The ionic liquid can be reused 10 times for the remaining reactions. The characterization data are given in the Supplemental Materials (available online) and is in accord with those in Refs. 29 and 30.

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