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ARTICLE

Synthesis of 2-Acyl-Benzo[1,3-*d*]selenazoles via Domino Oxidative Cyclization of Methyl Ketones with Bis(2-Aminophenyl) Diselenide

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A general, practical and simple one-pot synthesis of 2-acyl-benzo[1,3-*d*]selenazoles was developed by reacting a wide range of 2-arylethane-1,2-diones, generated *in situ* from commercially available aryl methyl ketones, with bis(2-aminophenyl) diselenide, promoted by $Na_2S_2O_5$ in DMSO at 100 °C. Comparatively, the reactions were conducted under conventional heating and microwave irradiation. The use of focused microwave irradiation drastically decreased the reaction time from 48 to 2 h with a gain in the reaction yield for most cases. Still, 2-phenylacyl-benzo[1,3-*d*]selenazole was elected to react with sodium borohydride and butylmagnesium bromide, giving the respective secondary and tertiary alcohols under mild reaction conditions.

Introduction

Benzochalcogenazoles, and particularly benzoxazoles and benzothiazoles, are attractive heterocyclic systems found in a diverse array of natural products,[1] probes for *in vivo* imaging[2] and new materials science.[3] They are widely present in biologically active compounds[4] and have attracted a good deal of interest from a variety of standpoints such as structure, reactivity and applications to organic syntheses.[5]

In this context, 2-substituted-1,3-benzothiazoles have attracted much attention in recent years, because they have some features that allow them to be exploited as chemiluminescent and photosensitizer agents,[6] or as precursors to therapeutic agents with, for example, antitumor, antifungal and anticonvulsant properties.[7]

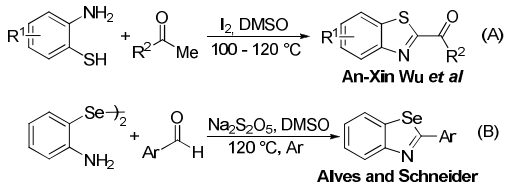
However, the chemistry of benzoselenazoles remains much less explored in comparison to benzoxazoles and benzothiazoles. Besides this, there are few reports in the literature regarding the preparation of these compounds, and these include copper-catalyzed reactions,[8] condensation of carboxylic acids promoted by tributylphosphine,[9] condensation of arylselenols with 1,3-dicarbonyl compounds,[10] cyclization of *N*-acetyl-2-haloaniline with Woollins' reagent[11] and through Br/Li exchange followed by reaction with elemental selenium.[12]

Organoselenium compounds are attractive due to their selective reactions,[13] potential as catalysts[14] and ligands for metallic complexes[15] and, more recently, association with interesting biological activities such as cancer chemopreventive[16] and the ability to act as glutathione peroxidase (GPX) mimics.[17]

In this context, the synthesis and applications of benzoselenazoles emerged as an opportunity for research. In recent years, studies regarding their biological evaluation[18] and use as cyanine dyes[19] have been reported, which support the potential applications and interest in this class.

An-Xin Wu and co-workers have explored in recent years the formation and *in situ* use of ethan-1,2-dione, generated from methyl ketones in the presence of I_2/DMSO media.[20] In this way, special attention has been given to the synthesis of 2-acyl-benzo[1,3-*d*]thiazoles, as summarized in Equation A, Scheme 1. On the other hand, Alves and Schneider in 2013 explored the use of bis(2-aminophenyl) diselenides as starting materials to direct synthesis of 2-acyl-benzo[1,3-*d*]selenazoles (Equation B, Scheme 1).[21]

Considering the chemical and biological importance of benzo[1,3-*d*]chalcogenazoles, and inspired by these recent publications, we present an efficient and direct one-pot strategy to synthesize 2-acyl-benzo[1,3-*d*]selenazoles **3** by intramolecular cyclocondensation of bis(2-aminophenyl) diselenide **2** with 2-arylethane-1,2-diones **1'**, generated *in situ*, from commercially available aryl methyl ketones in DMSO. The reaction is promoted by the non-toxic reducing agent $Na_2S_2O_5$ and, comparatively, the reactions were performed under conventional heating and focused microwave (MW) irradiation (Scheme 2).



Scheme 1. Related previous work.

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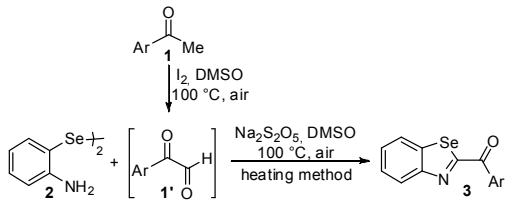


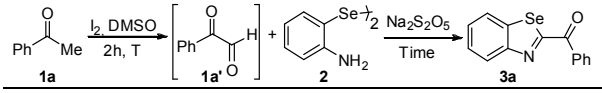
Scheme2. Strategy to the synthesis of 2-acyl-benzo[1,3-*d*]selenazole **3**.

Results and discussion

Preliminary experiments to optimize the reaction conditions were performed using acetophenone **1a** and bis(2-aminophenyl) diselenide **2** as model substrates to establish the best reaction conditions. The experiments were conducted at varying temperature, reaction time, reagent amount and heating method (conventional heating and MW) (Table 1).[22]

In a first experiment, molecular iodine (0.55 mmol) was solubilized in DMSO (1.5 mL) and the acetophenone **1a** (0.5 mmol) was added. The mixture was stirred for 2 h at 120 °C under an N_2 atmosphere, leading to the *in situ* formation of 2-phenylethane-1,2-dione **1a'**. After this time, the bis(2-aminophenyl) diselenide **2** (0.25 mmol) and $Na_2S_2O_5$ (0.5 mmol) were added. After stirring for 24 h under these conditions, the expected product **3a** was obtained in 44% yield (Table 1, entry 1). Thus, in an attempt to increase the reaction yield, we verified the influence of reaction time and observed that after 48 h the reaction yield increased moderately to 64% (Table 1, entry 2). Furthermore, a multicomponent reaction was performed under similar conditions, but after 48 h no formation of product **3a** was observed (Table 1, entry 3). With these results, we attempted to investigate parameters regarding stoichiometry and temperature (Table 1, entries 4–6). Based on this, when the reaction was performed using a slight excess of I_2 (0.7 mmol) and acetophenone **1a** (0.7 mmol) at 120 °C, a lower yield of **3a** was obtained due to the degradation of the materials under these conditions (Table 1, entry 6).

Table 1. Optimization of the reaction conditions.[a]



Entry	**1a** (mmol)	I_2 (mmol)	Time (h)	Temp. (°C)	**3a** Yield (%)
1	0.50	0.55	24	120	44
2	0.50	0.55	48	120	64
3[b]	0.50	0.55	48	120	-
4	0.70	0.70	48	120	43
5	0.70	0.70	48	100	76
6	0.70	0.70	48	80	35
7[c]	0.70	0.70	48	100	80
8[c]	0.50	0.55	48	100	58
9[c,d]	0.70	0.70	2	100	86

[a]Reaction was performed using **1a** and I_2, in DMSO (1.5 mL) for 2 h under N_2 atmosphere, followed by addition of **2** (0.25 mmol) and $Na_2S_2O_5$ (0.5 mmol). [b]Multicomponent reaction. [c]Reaction was performed in air. [d]Reaction was performed using **1a** and I_2 in DMSO (1.5 mL) for 20 min under focused MW irradiation (200 W), followed by addition of **2** (0.25 mmol) and $Na_2S_2O_5$ (0.5 mmol), maintaining this temperature for 2 h.

However, when the reaction was performed at 100 °C, a considerable increase in the yield of **3a** was obtained (Table 1, entry 5). In contrast, a lower temperature was adverse to this reaction (Table 1, entry 6). Aiming to prove the necessity of an inert atmosphere, the reaction was conducted in air (Table 1, entry 7). Interestingly, performing this reaction at 100 °C, after 48 h the best result was obtained, giving the 2-acyl-benzo[1,3-*d*]selenazole **3a** at an excellent 80% isolated yield (for the complete study see SI). On the other hand, when the stoichiometry was revised, a moderate yield was observed (Table 1, entry 7 vs 8).

In recent years, it has been shown that the use of MW irradiation in organic synthesis can considerably decrease the reaction time, often accompanied by an increase in product yield.[23] Thus, we chose to perform the reaction under focused MW irradiation, reacting the acetophenone **1a** (0.7 mmol) with molecular iodine (0.7 mmol) at 100 °C for 20 min, followed by the addition of bis(2-aminophenyl) diselenide **2** (0.25 mmol) and $Na_2S_2O_5$ (0.5 mmol), maintaining this temperature for an additional 2 h (Table 1, entry 9). This reaction resulted in the desired product **3a** being obtained in excellent yield and a short reaction time, proving this method to be a more efficient protocol in terms of time and energy economy.

To explore the scope and limitations of both methods, we envisioned extending these protocols to a variety of aryl methyl ketones **1a–l** and bis(2-aminophenyl) diselenide **2**, employing the optimal conditions under conventional heating (method A, Table 1, entry 7) and focused MW irradiation (method B, Table 1, entry 9). In a general way, all reactions proceeded smoothly, furnishing the expected products **3a–l** in moderate to excellent yields, and the results are presented in Table 2.

Several hetero or aryl methyl ketone derivatives **1a–l** reacted with **2**, furnishing the corresponding 2-acyl-benzo[1,3-*d*]selenazoles **3a–l** in moderate to excellent yields (Table 2, entries 1–12). When we used the non-substituted acetophenone **1a**, the desired product 2-acyl-benzo[1,3-*d*]selenazole **3a** was reached in 80% (method A) and 86% (method B) yields, respectively (Table 2, entry 1). As shown in Table 2, electronic effects on the aryl moiety of the aryl methyl ketone **1** seemed to have an influence on the product yield in both methods. For example, aryl methyl ketones with electron-withdrawing groups (EWG) at the aromatic ring, in a general way, gave better results than those containing electron-donating groups (EDG) (Table 2, entries 2–6 vs 8–11). These results could be explained by activation of the carbonyl group of the *in situ*generated 2-arylethane-1,2-dione by the EWG, which promotes nucleophilic attack of the nitrogen atom of the diselenide **2** to form the imine intermediate and a selenium atom through intramolecular cyclocondensation (see the plausible mechanism in Scheme 3). On the other hand, to observe steric effects, reactions were performed with aryl methyl ketones containing chloro, bromo and methoxyl substituents at the ortho positions and, to our satisfaction, good to excellent yields were obtained in both cases (Table 2, entries 3, 6 and 10). In order to complete this investigation, we performed the reaction using as starting material 1-(thiophen-2-yl)ethane-1-one **1l**, and the corresponding product **3l** could be obtained with satisfactory results (Table 2, entry 12).

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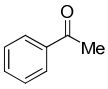
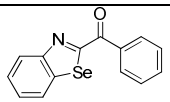
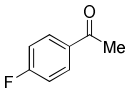
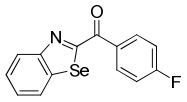
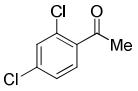
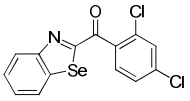
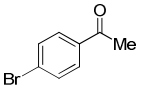
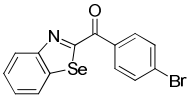
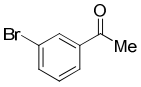
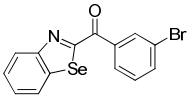
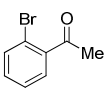
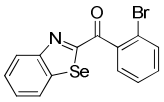
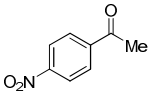
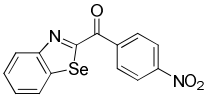
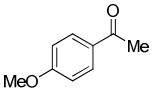
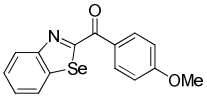
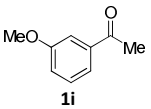
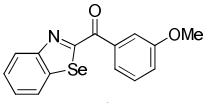
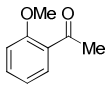
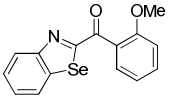
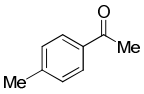
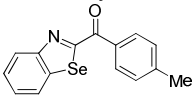
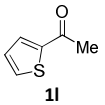
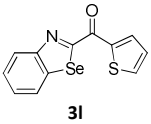
Table2. Scope of synthesis of 2-acyl-benzo[1,3-*d*]selenazole**3a–l**.[a,b]

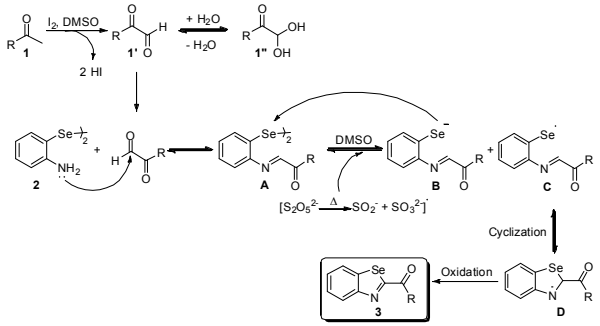
Entry	Ketone **1**	Product **3**	Yield (%) [Method]
1	 **1a**	 **3a**	80 [A] 86 [B]
2	 **1b**	 **3b**	76 [A] 80 [B]
3	 **1c**	 **3c**	83 [A] 88 [B]
4	 **1d**	 **3d**	88 [A] 89 [B]
5	 **1e**	 **3e**	72 [A] 83 [B]
6	 **1f**	 **3f**	94 [A] 94 [B]
7	 **1g**	 **3g**	55 [A] 68 [B]
8	 **1h**	 **3h**	66 [A] 75 [B]
9	 **1i**	 **3i**	33 [A] 60 [B]
10	 **1j**	 **3j**	51 [A] 70 [B]
11	 **1k**	 **3k**	70 [A] 80 [B]
12	 **1l**	 **3l**	47 [A] 73 [B]

[a]Method A: Reactions were performed using **1a–l** (0.7 mmol) and I_2 (0.7 mmol) in DMSO (1.5 mL) at 100 °C for 2 h in air, followed by addition of **2** (0.25 mmol) and $Na_2S_2O_5$ (0.5 mmol), maintaining this temperature for 48 h. [b]Method B: Reactions were performed using **1a–l** (0.7 mmol) and I_2 (0.7 mmol) in DMSO (1.5 mL) for 20 min at 100 °C under MW irradiation (200 W), followed by addition of **2** (0.25 mmol) and $Na_2S_2O_5$ (0.5 mmol), maintaining this temperature for 2 h.

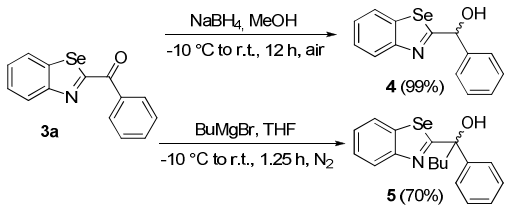
Finally, it is important to point out that comparing the described methods A and B, it is noted that for all reactions, the MW irradiation proved be more efficient, giving better yields for all synthesized products in shorter reaction times. These results are consistent with the importance of studying non-conventional methods, more economical and less aggressive to the environment.

Based on recently published reports[20,21] a possible mechanism for the synthesis of 2-acyl-benzo[1,3-*d*]selenazoles can be proposed. We believe that in the first step when methyl ketone **1** is added into the oxidizing media (I_2/DMSO) the formation of the ethane-1,2-dione derivative **1'** occurs through Kornblum oxidation.[20] After that, in the second step, the amino group of bis(2-aminophenyl) diselenide **2** reacts with ethane-1,2-dione **1'**, generated *in situ*, to form the imine diselenide intermediate **A**, followed by Se–Se bond cleavage by the radical anion $SO_2^{\bullet-}$ generated from $S_2O_5^{2-}$ by heating. This step forms the intermediates type **B** and **C**. The intermediate **B** can be reoxidized to the starting imine diselenide **A**, because of oxidizing media, and the radical **C** undergoes intramolecular cyclocondensation leading to the aminyl radical **D**. Finally, further oxidation of intermediate **D** provides the desired 2-acyl-benzo[1,3-*d*]selenazoles **3** (Scheme 3).

After synthesizing a range of new 2-acyl-benzo[1,3-*d*]selenazoles **3**, we decided to investigate synthetic applications of these compounds as starting materials to prepare differently functionalized analogues (Scheme 4).



Scheme3. Plausible Mechanism.



Scheme 4. Compound **3a** as precursor for new benzo[1,3-*d*]selenazole derivatives.

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In this way, we chose the 2-phenylacyl-benzo[1,3-*d*]selenazole **3a** to react with $NaBH_4$ to generate the corresponding secondary alcohol **4** in 99% yield after 12 h. Still, compound **3a** was allowed to react with butylmagnesium bromide in THF to produce the corresponding tertiary alcohol **5** in 70% yield (Scheme 4).

Conclusions

In summary, we have described a simple and efficient strategy for synthesizing unprecedented 2-acyl-benzo[1,3-*d*]selenazoles using aryl methyl ketones and bis(2-aminophenyl) diselenide. The use of a conventional heating method was explored to synthesize the benzo[1,3-*d*]selenazoles in moderate to excellent yields (33–94%) after 48 hours. On the other hand, microwave irradiation was shown to be more efficient in terms of time and energy economy, enabling us to prepare the benzo[1,3-*d*]selenazoles in good to excellent yields (60–94%) after 2.3 hours. Finally, the obtained 2-(phenylmethanone)benzo[1,3-*d*]selenazole was shown to be an efficient material as a precursor for synthesizing new secondary and tertiary alcohol benzo[1,3-*d*]selenazole derivatives.

Experimental

General Procedure for the Synthesis of 2-acyl-benzo[1,3-*d*]selenazole 3a-l under Conventional Heating

In a round-bottom flask 25 mL equipped with a magnetic stir bar, the aryl methyl ketone **1a-l** (0.70 mmol) was dissolved in DMSO (1.5 mL) and molecular iodine (0.7 mmol) was added. The reaction mixture was left to stir at 100 °C for about 2 hours (to *in situ* formation of 2-arylethan-1,2-dione **1'a-l**).[1] After this, bis(2-aminophenyl) disselenide **2** (0.25 mmol) and sodium metabisulfite (0.50 mmol) were added, and the reaction was maintained for 48 hours at 100 °C. After this time, the reaction mixture was cooled to room temperature, quenched with saturated solution of $Na_2S_2O_3$ (20 mL) and the reaction was extracted with ethyl acetate (3x 20 mL). The combined organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography on silica gel using hexane as eluent to provide **3a-l**.

General Procedure for the Synthesis of 2-acyl-benzo[1,3-*d*]selenazole 3a-l under Microwave Irradiation

In a 10 mL glass vial equipped with a magnetic stir bar, the aryl methyl ketone **1a-l** (0.70 mmol) was dissolved in DMSO (1.5 mL) and molecular iodine (0.7 mmol) was added. The reaction mixture was left to stir at 100 °C (measured with an IR sensor on the outer surface of the reaction vial) for about 20 minutes (to *in situ* formation of 2-arylethan-1,2-dione **1'a-l**) under microwave irradiation (irradiation power of 200 W and the ramp temperature rate was 3 min). After this, bis(2-aminophenyl) disselenide **2** (0.25 mmol) and sodium metabisulfite (0.50 mmol) were added, and the reaction was maintained for 2 hours at 100 °C. After this time, the reaction mixture was cooled to room temperature, quenched with saturated solution of $Na_2S_2O_3$ (20 mL) and the reaction was extracted with ethyl acetate (3x 20 mL). The combined organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography on silica gel using hexane as eluent to provide **3a-l**.

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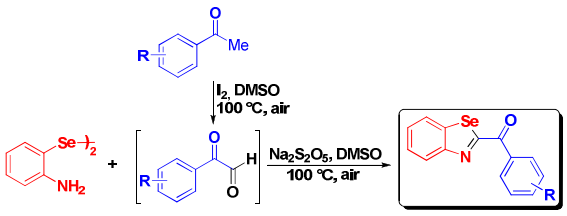

The synthesis of unprecedented 2-acyl-benzo[1,3-*d*]selenazoles is presented using bis(2-aminophenyl) diselenide and aryl methyl ketones under conventional heating and microwave irradiation.