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CHEMICAL SCIENCES

Synthesis and mechanistic study of 2-(trifluoromethyl)-10*H*-phenoselenazine from double cross coupling reaction

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Abstract: Phenoselenazines are nitrogen and selenium-based heterocyclic compounds that have important biological activities. However, their preparation methods are scarce and difficult to handle. The synthesis of a phenoselenazine from a simple and robust CuO nanoparticle catalyzed methodology, using bis-aniline-diselenide and 1,2-dihalobenzenes under microwave irradiation. Also, the double-cross-coupling reaction mechanism for C-Se and C-N bond formation, including the observation of a reaction intermediate by mass spectrometry have been studied.

Key words: Coupling reaction, CuO nanoparticles, DFT, microwave, phenoselenazine, Selenium.

INTRODUCTION

Phenoselenazines are an important class of nitrogen and selenium containing heterocyclic compounds, similar to the phenothiazines (nitrogen and sulphur). Both of these structures can be found in a variety of substances with significant biological activities (Figure 1) (Candurra et al. 1996, Philot et al. 2016, Nogueira et al. 2015). Among the phenothiazines derivates drugs, Chlorpromazine, Promazine and Trifluopromazine present pronounced antipsychotic activities, which are generally used in the treatment for schizophrenia and other psychiatric disease (Figure 1) (Adams et al. 2014, Garcia-Unzueta et al. 2003). In this context, the phenoselenazines appeared to be a potential bioisosteres of phenothiazines. Unlike to its sulphur analogous, studies about pharmacological activities of the phenoselenazines is relatively rare (El-Bayoumy 1985, Nizi et al. 2020, Tin et al. 2015). Among these, phenoselenazines present excellent pharmacological activities for the treatment of Alzheimer (Tin et al. 2015) and the activity antituberculosis (Nizi et al. 2020). Furthermore, this nucleus is well-known for their application

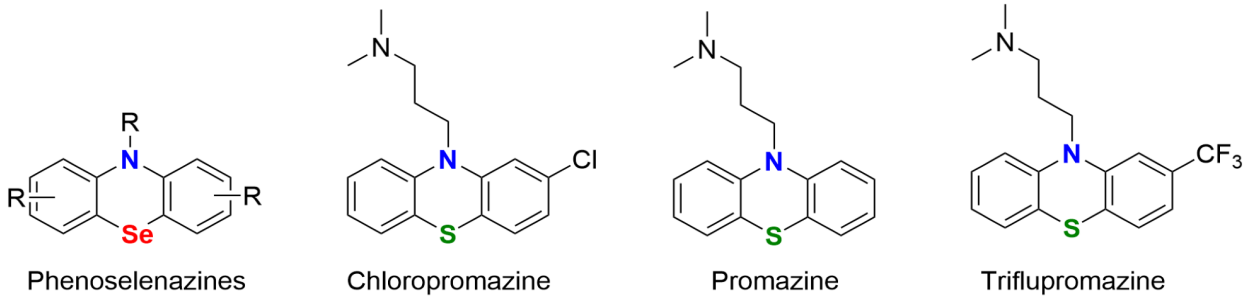

Figure 1. General structure of phenoselenazines and phenothiazine antipsychotic pharmaceuticals.

in material science, e.g., showing pronounced characteristics of organic light-emitting diode (OLED) by the mechanism of delayed thermally activated fluorescence (Kim et al. 2020, Lee et al. 2020).

Despite the interest in pharmacological and material science, the synthesis of phenoselenazines are scarce and some of previous reports suffer synthetic disadvantages, such as the harsh reaction conditions or regents of complex manipulations, multi-step reactions, long reaction time and low yield of products (El-Bayoumy 1985, Nizi et al. 2020, Kim et al. 2020, Lee et al. 2020, Müller et al. 1959, Olmsted et al. 1961, Tin et al. 2015). In this context, recently, Cremer et al. (2021) synthetized a series of phenoselenazines and phenotellurazines *via* a more efficient synthetic route, using bis(2-iodophenil)amines in the presence of elemental Se and Te, KOH, DMSO, at temperature of 110 °C for 24 hours of reaction (Cremer et al. 2021). Despite of good yields, the methodology suffers some key limitations, e.g., complex synthetic route, the synthesis of starting materials involves expensive reagents or difficult to access reagents, in addition long reaction time.

On the other hand, the use of microwave (MW) irradiation in C-Se and C-S bond formation, can provide higher yields in shorter reaction times (Baqi 2021, Godoi et al. 2012, Saba et al. 2015a, b).

Therefore, the development of a robust, efficient and quickly reaction for obtaining these heterocyclic compounds is still highly desirable. Thus, the planning of synthetic methodologies by heterogeneous catalysis, using easily accessible nanostructured catalysts and microwave-assisted reactions, can contribute significantly for this purpose. In this sense, the combination of CuO nanoparticles and microwave irradiation has been demonstrated an important tool for several catalysed organic reactions (Baqi 2021, Botteselle et al. 2012, Dias et al. 2018, Taj et al. 2019). Thus, according to our interest in studying and preparing simple reactions to obtain organoselenium compounds with biological interest (Doerner et al. 2022, 2023, Frizon et al. 2020, Godoi et al. 2012, Moraes et al. 2023, Scheide et al. 2020), herein we described the mechanistic study of double cross-coupling reaction to enable C-Se and C-N bonds formation for the synthesis of phenoselenazine.

RESULTS AND DISCUSSION

Initially, bis(2-amino-4-trifluoromethylphenyl) diselenide 3 was synthesized from a reported procedure described in literature (Botteselle et al. 2021, Menichetti et al. 2016), as shown the reaction in the Figure 2a.

The bis-aniline-diselenide 3 was used in the double cross-coupling reaction with the substrate 2-bromo-1-iodobenzene 4a for the synthesis of phenoselenazine 5, using CuO nanoparticles as catalyst, KOH as base and DMSO as solvent (Figure 2b). The reactions were conducted in a microwave aiming for the synthesis of phenoselenazine 5 with less reaction time as possible. In this context, the reactions were performed during 20, 40 and 60 minutes and it was noted that no significant alteration on the product 5 yield, establishing the reaction time as 20 min (Figure 2b). Despite the moderate yield of product 5 (52%) and considering the low reaction time, this is satisfying when comparing to the phenoseleazines yields described in the literature (El-Bayoumy 1985, Nizi et al. 2020, Kim et al. 2020, Lee et al. 2020, Müller et al. 1959, Olmsted et al. 1961, Tin et al. 2015).

The cross-coupling reaction also can be carried out with the 1,2-dibromobenzene 4b, which one is more economically accessible, even though, in general, bromides are less reactive in the cross-coupling reactions comparing to

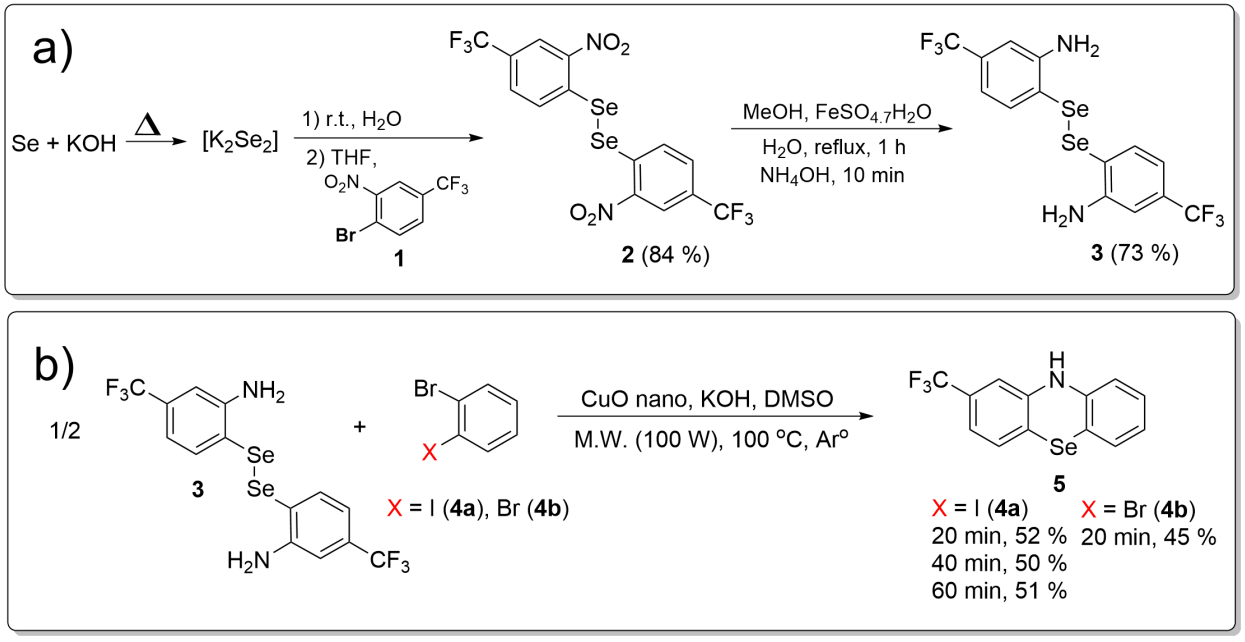

Figure 2. (a) Synthesis of bis-aniline-diselenide 3. (b) Synthesis of 2-(trifluoromethyl)-10H-phenoseleazine 5 starting from 2-bromo-1-iodobenzene 4a and 1,2-dibromo benzene 4b.

iodides. Nevertheless, the phenoselenazine 5 was obtained in 45% yield under same reactional conditions (Figure 2b).

Next, with the aim of synthesize the phenoselenazine 7 and to understand how the cross-coupling reaction occurs using the methodology developed, we accompanied the reaction between bis-aniline-diselenide 6 and substrate 4a by gas chromatography-mass spectrometry (GC/MS). Thus, it was possible to observed the formation of expected product 7 and a reaction intermediate 8, as shown in Figure S1, S6.

According to these results obtained out during the progress of the reaction, a plausible double cross-coupling reaction pathway is illustrated in Figure 3. This catalytic cycle proposed begin with an oxidative addition of the 2-bromo-1-iodobebnzene 4a (at the C-I bond) to the CuO nano catalyst, affording the formation of species A. Next, in the presence of KOH and DMSO, bis-aniline-diselenide 6 generated selenolate B (Levanova et al. 2013, Reddy et al. 2009), which could then perform a ligand exchange with species A, leading to species C. In the next step, species C could undergo a reductive elimination to the formation of C-Se bond and afford the intermediate 8. Finally, intermediate 8 could undergo an intramolecular Ullmann-type C-N cross-coupling reaction, to obtained the desired product 7.

The mechanism has been studied also by DFT (DFT-optimized coordinates are shown in supplementary material), modelling the copper nanoparticle with a single CuO moiety, with the aim to evaluate the qualitative feasibility of the mechanism depicted in Figure 3. Under this assumption, Reaction Complex (RC) is the adduct between CuO and PhBrI, with an interaction between the metal and the π electrons of the aromatic ring (RC, Figure 4). The insertion of copper in the C-I bond is easy (activation barrier for TS1 6.2 kcal/mol) and leads to the first intermediate (Int1, BrPh-Cu(O)I). Readily after this, there is a 1,2-shift of the aromatic moiety from the copper to the oxygen (activation

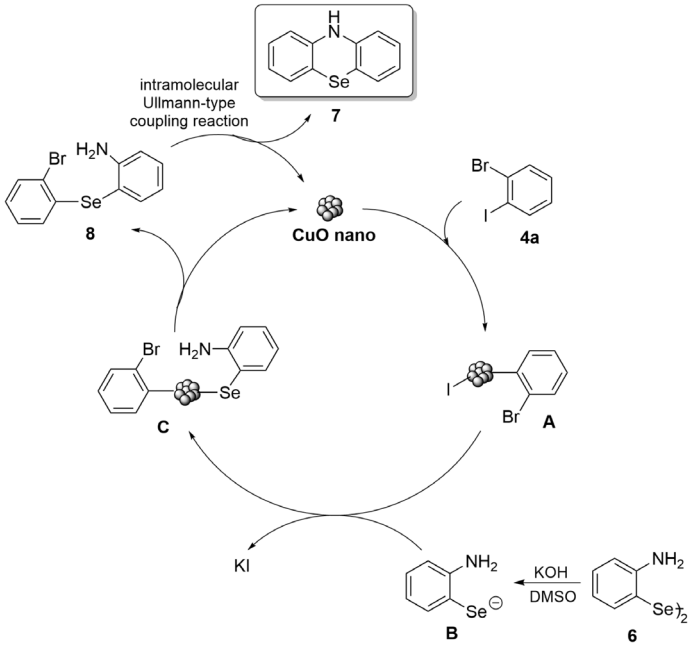

Figure 3. A plausible proposal for the mechanism of the reaction.

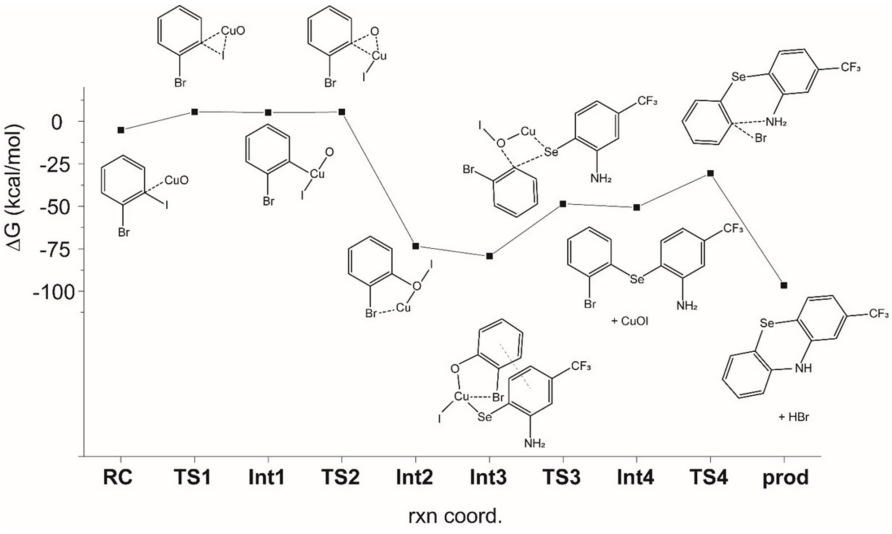

Figure 4. Energy path for the CuO-catalyzed cyclization reaction. Energies are referred to the sum of reactants.

barrier for TS2 0.1 kcal/mol) that leads to the second intermediate (Int2, BrPh-O-CuI). Now the selenide, formed by the attack of KOH to the diselenide, can coordinate the copper, leading to Int3.

In Int3, the selenium and the aromatic moiety are spatially close (4.0 Å) because of a stabilizing π/π stacking interaction between the two aromatic rings. This makes the attack of the selenium on the *ipso* carbon of phenoxide easier, forming a four terms cycle (Cu-Se-C-O) in TS3. The activation barrier for this reaction is 36.8 kcal/mol and it is the rate determining step of the entire process. After this step, the CuOI moiety leaves the adduct, leading to the selenoether Int4. The latter contains a nucleophile on one side (the amino group) and a good leaving group on the other side (bromide). For this reason, the two groups can react through TS4, with an activation barrier of 23.0 kcal/mol. This leads to HBr and the desired product (Figure 5).

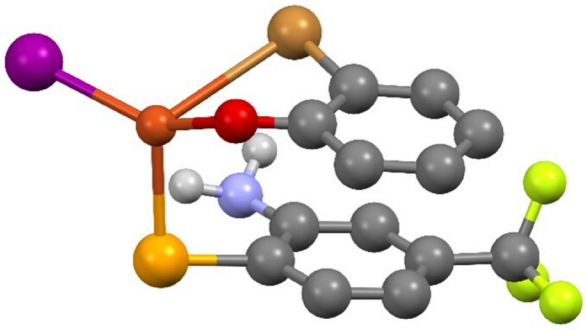

Figure 5. DFT-optimized geometry of Int3, showing the π/π interaction between the two aromatic rings.

CONCLUSIONS

A simple and robust methodology was developed for the synthesis of phenoselenazines, catalysed by nanoparticle CuO, using microwave irradiation. Despite the low yield of phenoselenazines obtained, it is still comparable to the ones described in literature, noting that the reaction conditions utilized were milder, faster and ecologically adequate. Beyond that, the double cross-coupling reaction mechanism for the formation of C-Se and C-N bonds of the heterocyclic compound was studied. It's worth mentioning that the mechanistic studies (mass analysis as well as theoretical study) demonstrate an important reaction intermediary for the understanding of the catalytic cycle of reaction.

Experimental section

General Information

All reagents and solvents were commercially available (Aldrick, Merck, Synth) without further purification, except of DMSO that was distilled in the presence of potassium hydroxide (KOH pellets) and stored under molecular 4A sieves. Thin-layered chromatography (TLC) was performed using Merck Silica60 GF254 gel (0.25 mm thickness) and visualized with UV light, iodine tube and vanillin acidic solution burned. Column chromatography (CC) was performed with silica gel 60 (230-400 mesh). The microwaved reactions were performed in a microwave reaction vial (10 mL) in a Monomode Reactor CEM Discover apparatus with infrared monitoring and non-invasive pressure transducer. The NMR ^{1}H and ^{13}C spectra were obtained on a Bruker Avance 200 spectrometer, using deuterated chloroform ($CDCl_3$) as solvent and tetramethylsilane (TMS) as the internal standard. The GC–MS analysis was performed on a Shimadzu GCMS-QP5050A, equipped with a DB-5 capillary column (30 m) and ionization voltage of 70 eV. The high-resolution mass spectra (HRSM) were obtained on a micrOTOF Q-II (Bruker Daltonics) and mass spectrometer ESI-QTOF MS (ElectroSpray Ionisation Time of Flight Mass Spectrometry) operated in positive ion.

- Synthesis of bis(4-trifluomethyl-2-nitrobenzene) diselenide (2)

The synthesis of diselenide 2 was performed from an adaptation of the methodology described in the literature (Botteselle et al. 2021, Menichetti et al. 2016). To a round-bottomed flask (25 mL), selenium powder-100 mesh (1.0 mmol, 79.0 mg) and KOH (2.0 mmol, 112.0 mg) were heating with a thermal blower until complete melting of the mixture. The resulting dark red mixture was cooled at room temperature and diluted with water (2.0 mL). Then, a solution of 1-bromo-2-nitro-4-(trifluomethyl)benzene 1 (135 mg, 0.5 mmol) and THF (0.5 mL) was added and the reaction mixture was stirred for 30 minutes. Next, the desired product 2 was extracted using ethyl acetate (10 mL) and organic phase was dried with $MgSO_4$, followed by filtering and the organic solvent was removed under vacuum. The product was purified by flash column chromatography using a mixture of hexane and ethyl acetate (98:2) as eluent. TLC (hexane): Rf = 0.3.

- Synthesis of bis(2-amino-4-trifluoromethylphenyl) diselenide (3)

The synthesis of diselenide 3 was performed from an adaptation of the methodology described in the literature (Botteselle et al. 2021, Menichetti et al. 2016). In a two-necked round-bottomed flask connected with a reflux condenser and magnetic stir bar, was added bis(4-trifluoromethyl-2-nitrobenzene) 2 (0.5 mmol, 0.270 g), methanol (10.0 mL), $FeSO_4.7H_2O$ (2.5 mmol, 0.695 g) and distilled water (10.0 mL). The reaction mixture was stirred for 1.0 h under reflux, followed by addition of NH_4OH (5.0 mL) and stirred for more 10 min. After this step, the reaction was cooled at room temperature, diluted with distilled ethyl acetate (20.0 mL), filtered, and washed with H_2O (3 x 10.0 mL) in separatory funnel. The organic phase was dried with $MgSO_4$, filtered and the organic solvent was removed under vacuum. The product was purified by flash column chromatography using a mixture of hexane/ethyl acetate (90/10) as eluent. TLC (20% ethyl acetate/hexane): Rf = 0.4.

- Synthesis of 2-(trifluoromethyl)-10H-phenoselenazine (5)

In a specific microwave tube (10.0 mL), purged with argon and equipped with a magnetic stir bar, was added bis(2-amino-4-trifluoromethylphenyl) diselenide 3 (0.25 mmol), nanoparticulate CuO (12.0 mg, 0.15 mmol), KOH (140.0 mg, 2.5 mmol) and dry DMSO (1.0 mL). Then, 2-bromo-1-iodobenzene 4a (54.0 µL, 0.5 mmol) or 1,2-dibromobenzene 4b (60.0 µL, 0.5 mmol) was added and the system was purged with argon again. The tube was sealed and placed into microwave reactor and submitted an irradiation power of 100 W until the temperature to reached 100 °C. After, the microwave instrument was automatically adjusted to maintain a constant temperature of 100 °C and stirring for 20 min. The reaction mixture was extracted with ethyl acetate (10.0 mL) and water (3 x 5.0 mL), and the organic phase was dried with $MgSO_4$ and the organic solvent was removed under vacuum. The product was purified by flash column chromatography using a mixture of hexane/ethyl acetate (98/2) as eluent. Yield of isolated product: 52% (157.0 mg). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.25-7.03 (m, 4H), 6.90 (d, *J* = 7.3 Hz, 1H), 6.83 (s, 1H), 6.63 (d, *J* = 7.8 Hz, 1H), 6.04 (br, 1H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 142.3, 141.0, 130.4 (q, $^2J_{CF}$ = 32.5 Hz), 129.7, 129.5, 128.3, 124.0 (q, $^1J_{CF}$ = 270.5 Hz); 123.88, 119.6 (q, $^3J_{CF}$ = 4.0 Hz), 118.8, 115.6, 112.8, 111.6 (q, $^3J_{CF}$ = 4.0 Hz); GC/MS (Figure S3): m/z (%) 317 (3), 316 (2), 315 (27), 314 (15), 313 (3), 312 (4), 236 (12), 235 (100), 216 (16), 215 (8), 207 (11), 185 (10), 166 (13), 157 (8), 139 (9), 117 (7), 77 (5), 75 (8), 63 (10), 44 (12); HRMS (Figure S2) m/z: calc. $C_{13}H_8F_3NSe$: 314.9769; found: 314,9766; TLC (5% ethyl acetate/hexane): Rf = 0.65. The ^{1}H and ^{13}C NMR spectra are found in the supplementary material (Figure S4, S5) and data were in agreement with reported in the literature (Cremer et al. 2021).

Computational study

All geometries were optimized with ORCA 5.0.3, using the b3lyp functional to take relativistic effects into account and in conjunction with a triple-ζ quality basis set (def2-TZVPD), which already takes relativistic effects in consideration. The dispersion corrections were introduced using the Grimme D3-parametrized correction and the Becke Johnson damping to the DFT energy. All the structures were confirmed to be local energy minima (no imaginary frequencies), or saddle points (one imaginary frequency corresponding to the reaction coordinate). The solvent was considered through the continuum-like polarizable continuum model (C-PCM, DMSO).

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SUPPLEMENTARY MATERIAL

Figures S1-S6.

How to cite

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Cássio Siqueira: data curation, methodology, writing – original draft. Gianluca Ciancaleoni: data curation, methodology, investigation, writing – review & editing. Sumbal Saba: data curation, formal analysis, funding acquisition, visualization. Antonio L. Braga: conceptualization, resources, investigation, visualization. Jamal Rafique: conceptualization, funding acquisition, formal analysis, writing – original draft and review & editing. Giancarlo V. Botteselle: funding acquisition, supervision, writing – review & editing.

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