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Synthesis, Biological Activity and Some Reactions of Triethylammonium 2-oxo-1-(2-oxoindoline-3-ylidene)-2-phenylethane-1-thiolate †

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Abstract

Treatment of triethylammonium 2-oxo-1-(2-oxoindolin-3-ylidene)-2-phenylethane-1-thiolate with γ-bromoacetoacetanilide or phenacyl bromide in DMF leads to the formation of the corresponding S-alkylation products. It has been established that the initial thiolate exhibits an antidote effect against the herbicide 2,4-D in a laboratory experiment on sunflower seedlings.

Keywords: thiocyanatoacetophenone; alkylation; isatin

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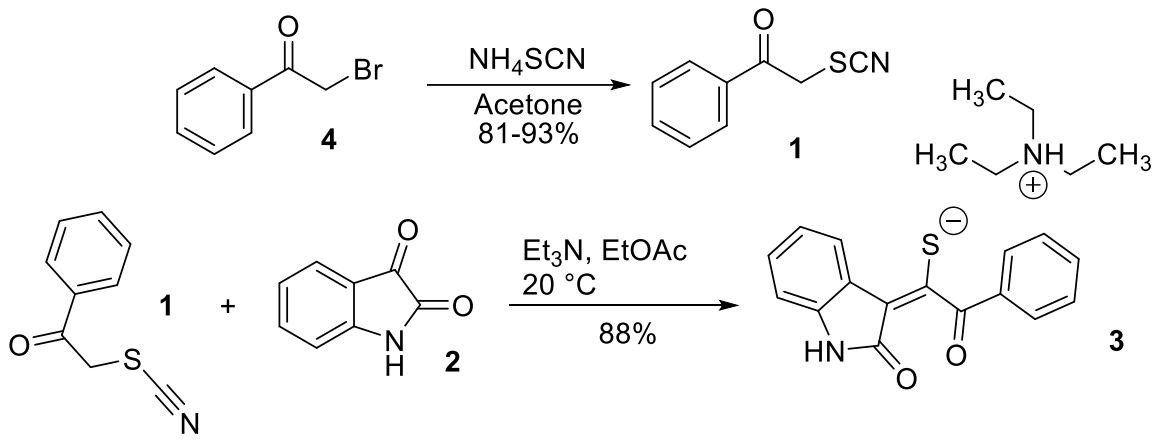
1. Introduction

The chemistry of α-thiocyanocarbonyl compounds is a promising field in modern organic synthesis, due to their significant synthetic potential and the valuable practical properties of the resulting products [1,2]. The synthesis and properties of compounds containing a thiocyanate functional group have been reviewed in several publications [1–8].

It is known from the literature that thiocyanatoacetophenone **1** reacts with isatin **2** in the presence of triethylamine to form triethylammonium 2-oxo-1-(2-oxoindolin-3-ylidene)-2-phenylethane-1-thiolate **3** [9–11] (Scheme 1). Despite its multifunctional nature and the obvious potential for numerous transformations, the reactions of thiolate **3** have not been sufficiently studied. In particular, there are no examples in the literature of even simple transformations such as S-alkylation. We decided to investigate these reactions, as well as some properties of thiolate **3**.



Scheme 1. XXXXX.

2. Results and Discussion

The starting phenacyl thiocyanate **1** was obtained from phenacyl bromide **4** and ammonium thiocyanate in acetone. Thiolate **3** was prepared according to a known procedure [9]. The structure of thiolate **3** was confirmed by NMR and IR spectroscopy. For example, Figure 1 shows the ^{1}H NMR spectrum of thiolate **3**.

The ^{1}H NMR spectrum shows signals for the protons of the CH_3CH_2 group of the triethylammonium ion: a triplet at δ 1.139 ppm and a quartet at δ 3.04 ppm, a set of signals for aromatic ring protons, and a signal for the NH proton at δ 9.54 ppm (Figure 1).

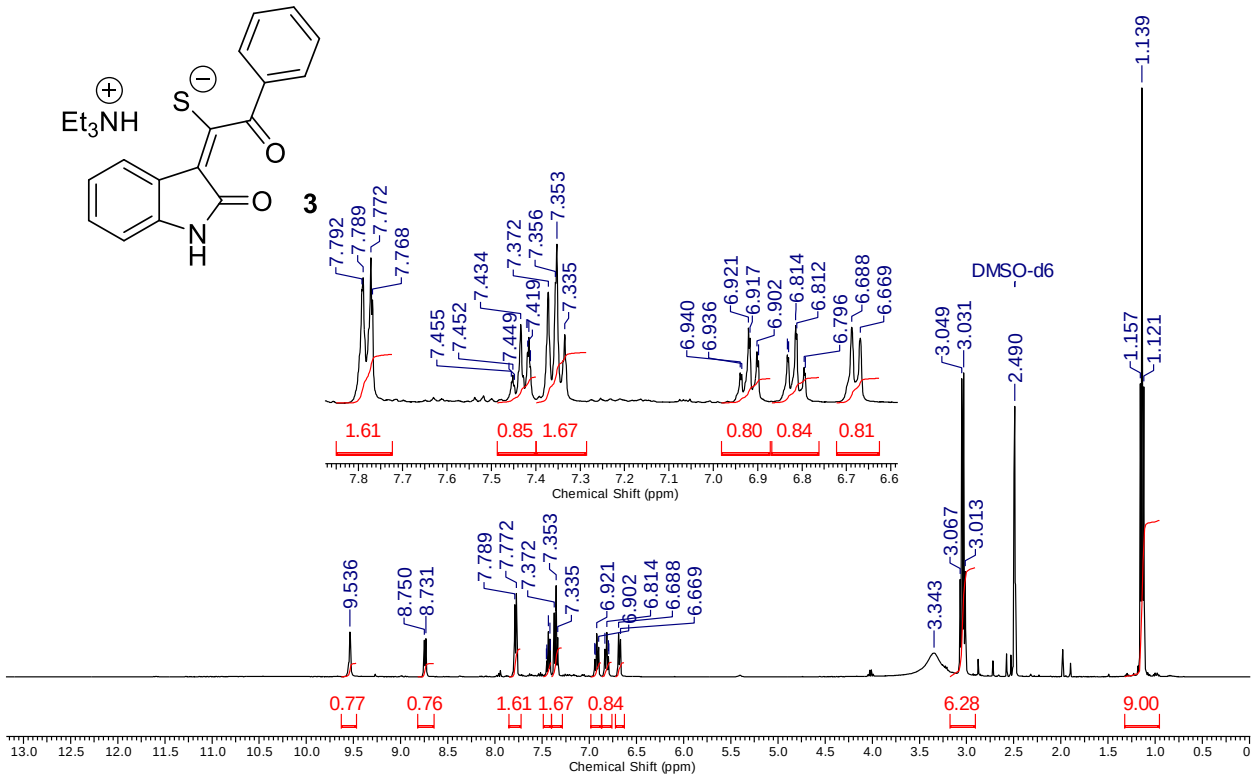
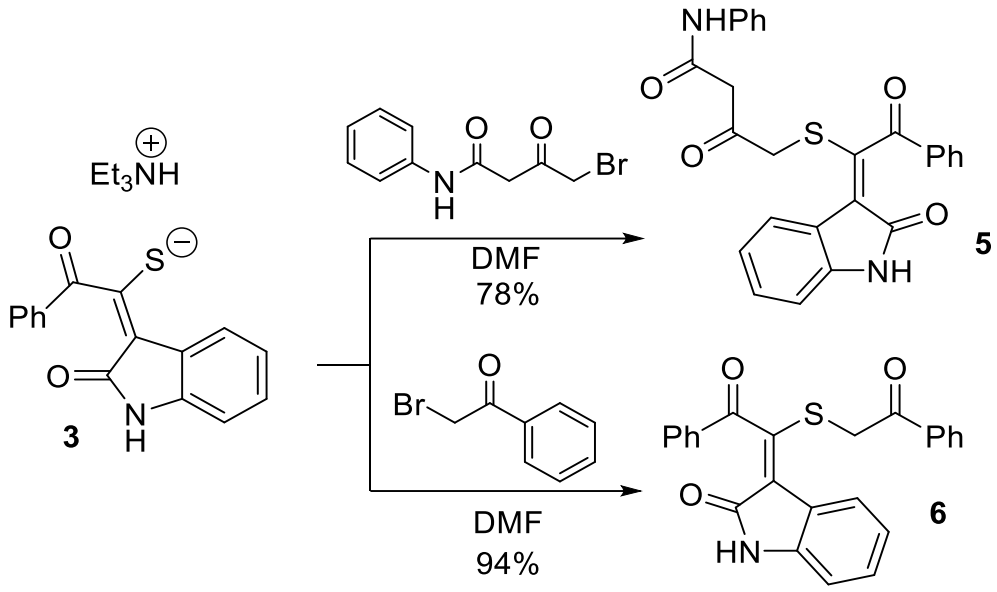


Figure 1. ^{1}H NMR spectrum of crude thiolate **3** (DMSO-d_6, 400 MHz).

We studied the alkylation of compound **3**. Thus, treatment of thiolate **3** with γ-bromoacetoacetanilide or phenacyl bromide in DMF led to the formation of the S-alkylation products **5** and **6**, respectively (Scheme 2). The structures of **5** and **6** were also confirmed by the results of spectral studies. For example, Figures 2 and 3 show the ^{1}H NMR spectra.



Scheme 2. XXXXX.

Minor signals at δ 10.057 ppm and δ 5.285 ppm are noteworthy. We believe these signals correspond to the NH and =CH- protons of the enol tautomer **5A**, which constitutes approximately 10% of the mixture in DMSO-d6 solution.

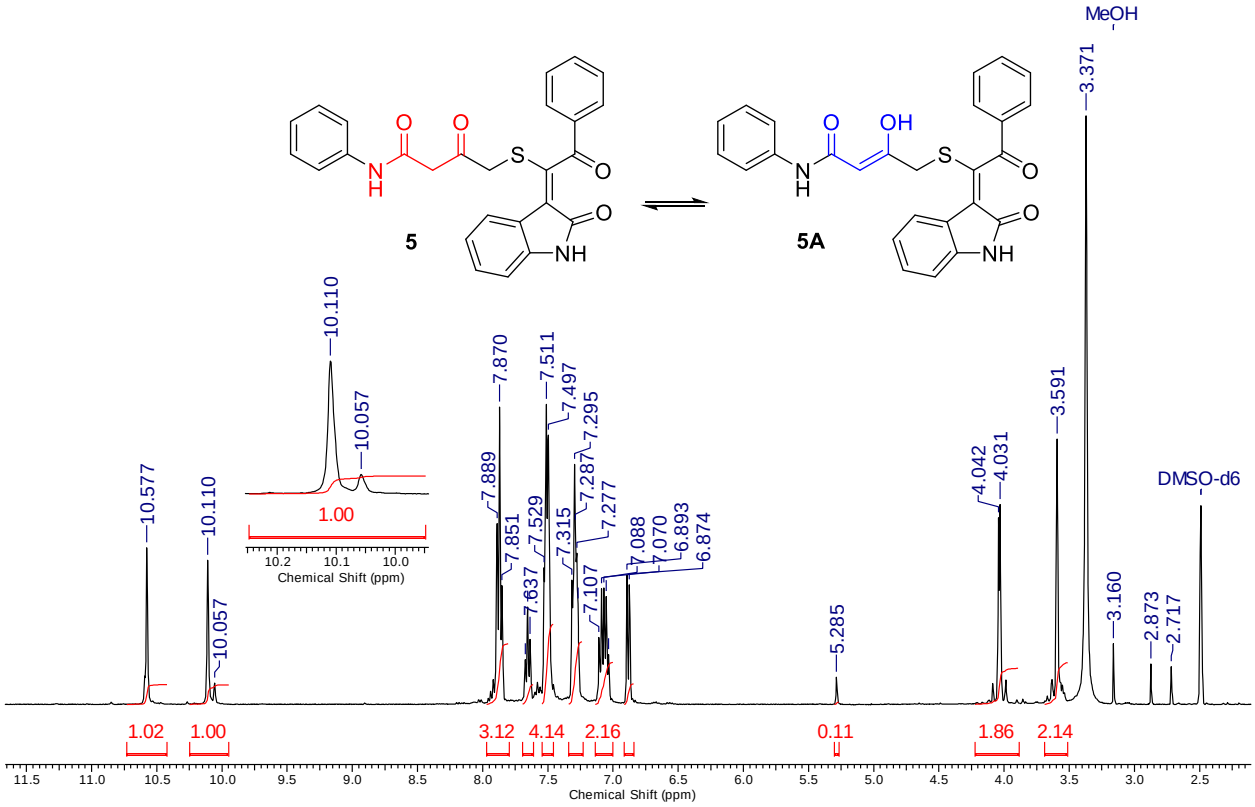


Figure 2. [1]H NMR spectrum of compound **5**.

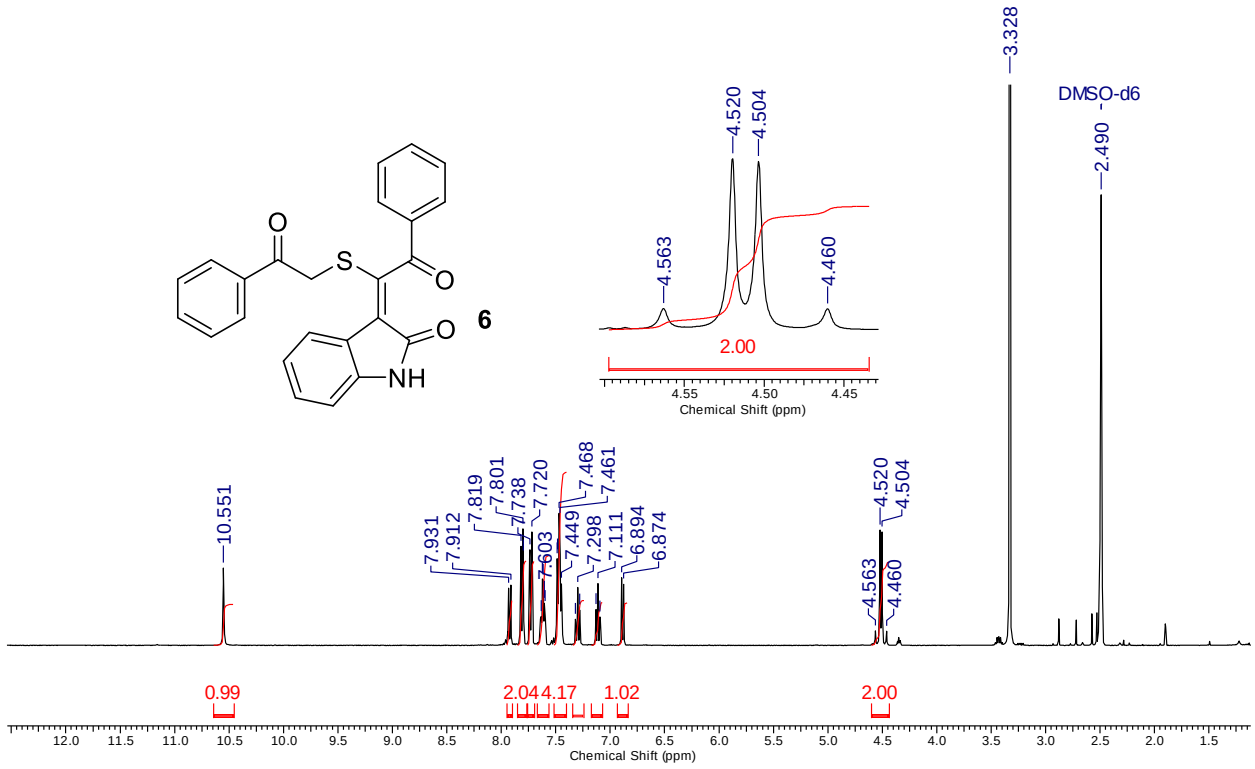


Figure 3. ^{1}H NMR spectrum of compound **6.**

The spectrum of compound **6** (Figure 3) shows a singlet for the isatin NH proton at δ 10.55 ppm, as well as an *AB*-pattern for the protons of the SCH_2 fragment (^{2}J = 17.4 Hz).

To determine the potential biological activity of compounds **3**, **5**, **6**, we performed a predictive in silico analysis using the SwissADME [12] and admetSAR [13] services. Thiolate 3 is well-absorbed in the gastrointestinal tract, can permeate the blood-brain barrier, and inhibits the cytochrome isoform CYP2C9. Compounds 5 and 6 are also likely well-absorbed in the GI tract but do not penetrate the BBB; they inhibit isoforms CYP1A2, CYP2C19, CYP2C9, and CYP3A4, but not the CYP2D6 enzyme. Since the synthesized compounds are predicted to interact with microsomal enzymes, issues of in vivo toxicity could arise, and this aspect requires further careful evaluation.

An assessment of the agrochemical potential of thiolate **3** on sunflower seedlings showed that triethylammonium 2-oxo-1-(2-oxoindolin-3-ylidene)-2-phenylethane-1-thiolate **3** reduced the inhibitory effect of 2,4-D on seedling root growth by 29–54% when used at three or more concentrations, and overall acts as an 2,4-D herbicide safener.

3. Experimental

Synthesis of thiocyanato acetophenone (1): *α*-Bromoacetophenone **4** (60.26 g, 0.3 mol) was dissolved in 120 mL of acetone with gentle heating. Ammonium thiocyanate (30.0 g, 0.4 mol) was added in portions to the resulting solution with vigorous stirring. The mixture was stirred for 5 h at 25 °C, after which the product was precipitated with an excess of cold water. A light-yellow, fine crystalline powder was obtained; yield 47.01 g (88%). The product is sufficiently pure for further transformations. For analytical purposes, the product was dissolved in acetone, boiled with activated charcoal, and the filtrate was treated with a threefold volume of water. M.p. 68–70 °C. FT-IR, ν, cm^{-1}: 2156 (S-C≡N); 1672 (C=O); 1593, 1578 (Ph).

NMR ^{1}H spectrum (400 MHz, DMSO-d_6), δ_H, ppm: 5.12 s (2H, CH_2); 7.55–7.58 m (2H, H-3 H-5 Ph); 7.69–7.73 m (1H, H-4 Ph); 8.01 dd (2H, ^{3}J = 8.3 Hz, ^{4}J = 1.2 Hz, H-2 H-6 Ph).

NMR ^{13}C DEPTQ (DMSO-d_6), δ_C, ppm: 41.8 (CH_2); 112.9 (SC≡N); 128.6* (C^3H C^5H Ph); 129.0* (C^2H C^6H Ph); 134.28 (C^1 Ph), 134.31* (C^4H Ph); 192.4 (C=O). *Signals in antiphase. Found, %: C 60.82; H 4.01; N 7.77. C_9H_7NOS. Calculated, %: C 61.00, H 3.98, N 7.90.

Triethylammonium 2-oxo-1-(2-oxoindoline-3-ylidene)-2-phenylethane-1-thiolate (3). Prepared as reported in the paper [9].

NMR ^{1}H spectrum (400 MHz, DMSO-d_6), δ_H, ppm: 1.13 t (9 H, 3 $NCH_2C\underline{H}_3$, ^3J = 7.1 Hz); 3.03 q (6 H, 3 $NC\underline{H}_2CH_3$, ^3J = 7.1 Hz); 6.68 d (1 H, H Ar, ^3J = 7.1 Hz); 6.80–6.84 (m, 1 H, H-Ar); 6.91–6.94 (m, 1 H, H-Ar); 7.34–7.44 (m, 3 H, 3 H-Ar); 7.78 (d, 2 H, H^2 H^6 Ph, ^3J = 7.2 Hz); 8.74 (d, 1 H, H Ar, ^3J = 7.1 Hz); 9.56 (br s, 1 H, NH).

NMR ^{13}C DEPTQ (DMSO-d_6), δ_C, ppm: 8.8* (3 $NCH_2\underline{C}H_3$); 45.7 (3 $N\underline{C}H_2CH_3$); 107.4* (C^7H isatin); 116.8 (=C–S); 119.4* (C^5H isatin); 120.4* (C^6H isatin); 123.2* (C^4H isatin); 127.1 (C^{3a} isatin); 127.7* (C^3H C^5H Ph); 129.1* (C^2H C^6H Ph); 131.2* (C^4H Ph); 136.8 (C^{7a} isatin); 139.0 (C^1 Ph); 166.5 (C=O isatin); 184.0 (C^3 isatin); 192.8 (C=O). * Signals in antiphase.

Synthesis of 3-oxo-4-{[2-oxo-1-(2-oxoindolin-3-ylidene)-2-phenylethyl]thio}-N-phenylbutanamide (5) and 3-(2-oxo-1-[(2-oxo-2-phenylethyl)thio]-2-phenylethylidene)indolin-2-one (6). Thiolate **3** (2 mmol) was dissolved in DMF with stirring and moderate heating, after which 2 mmol of γ-bromoacetoacetanilide or phenacyl bromide was added, respectively. The mixture was stirred with heating (40–50 °C) until complete conversion of the reagents. The reaction progress was monitored by thin-layer chromatography. Upon completion of the reaction, the product was precipitated by adding an excess of water to the reaction system. The products were filtered off and recrystallized from methanol for purification.

3-Oxo-4-{[2-oxo-1-(2-oxoindolin-3-ylidene)-2-phenylethyl]thio}-N-phenylbutanamide (5). Yellow powder, yield 78%. NMR ^{1}H spectrum (400 MHz, DMSO-d_6), δ_H, ppm (for major ketoamide tautomer): 3.59 s (2H, $C(O)CH_2$); 4.03 *AB*-pattern (2H, SCH_2, ^2J = 17.9 Hz); 6.88 d (1H, H Ar, ^3J = 7.8 Hz); 7.03–7.11 m (2H, H-Ar); 7.27–7.32 m (3H, H-Ar); 7.50–7.53 m (4H, H-Ar); 7.64–7.67 m (1H, H-Ar); 7.85–7.89 m (3H, H-Ar); 10.11 br s (1H, C(O)NH); 10.58 br s (1H, NH isatin).

3-(2-Oxo-1-[(2-oxo-2-phenylethyl)thio]-2-phenylethylidene)indolin-2-one (6). Yellow powder, yield 94 %. NMR ^{1}H spectrum (400 MHz, DMSO-d_6), δ_H, ppm: 4.51 *AB*-pattern (2H, SCH_2, ^2J = 17.4 Hz); 6.88 d (1H, H-Ar isatin, ^3J = 7.8 Hz); 7.09–7.13 m (1H, H-Ar isatin); 7.28–7.31 m (1H, H-Ar isatin); 7.44–7.49 m (4H, H-Ar); 7.60–7.64 m (2H, H-Ar); 7.77–7.78 m (2H, H-Ar); 7.80–7.82 m (2H, H-Ar); 7.92 d (1H, H-Ar isatin, ^3J = 7.6 Hz); 10.55 s (1H, NH isatin).

4. Biological Studies

The studies of efficiency of the prepared compounds as 2,4-D herbicide safeners was carried out using sunflower seedlings in All-Russian Research Institute of Biological Protection of Plants (Krasnodar) via the original technique [14] as follows: germinated sunflower seeds with 2–4 mm long embryo roots were placed in a solution of 2,4-dichlorophenoxyacetic acid (2,4-D) with concentration 10–3% (by weight) for 1 h to achieve 40–60% inhibition of hypocotyls growth. After the herbicide treatment, the seedlings were washed with pure water and placed into a solution of the tested compound (concentrations 10^{-2}, 10^{-3}, 10^{-4}, or 10^{-5}%, "herbicide + antidote" experiment). After 1 h the seedlings were washed with pure water and placed on paper stripes (10 × 75 cm, 20 seeds per stripe). The stripes were rolled and placed into beakers with water (50 mL). The reference group of seedlings ("herbicide" experiments) was kept in 2,4-D solution (10^{-3}%) for 1 h and then in water for 1 h. The "control" sample seedlings were kept in water for 2 h. The temperature of all the solutions was maintained at 28 °C. The seedlings were then thermostated for 3 days at 28 °C. Each experiment was performed in triplicate, 20 seeds were used in each experiment. The protecting (antidote) effect Ar was determined was determined as a ratio

of hypocotyls (or roots) length in the "herbicide + antidote" experiments to the length in the reference group. The statistical processing of the experimental data was performed using the Student *t*-test, $p = 0.95$.

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Informed Consent Statement:

Data Availability Statement:

Conflicts of Interest:

References

1. Castanheiro, T.; Suffert, J.; Donnard, M.; Gulea, M. Recent Advances in the Chemistry of Organic Thiocyanates. *Chem. Soc. Rev.* **2015**, *45*, 494–505. https://doi.org/10.1039/C5CS00532A.
2. Kindop, V.K.; Bespalov, A.V.; Dotsenko, V.V. A-Thiocyanato Ketones in the Synthesis of Heterocycles (Microreview). *Chem. Heterocycl. Compd.* **2024**, *60*, 345–347. https://doi.org/10.1007/s10593-024-03344-w.
3. Karmaker, P.G.; Yang, X. Recent Advancement on the Indirect or Combined Alternative Thiocyanate Sources for the Construction of S−CN Bonds. *Chem. Rec.* **2024**, *24*, e202300312. https://doi.org/10.1002/tcr.202300312.
4. Vekariya, R.H.; Patel, H.D. A-Thiocyanation of Carbonyl Compounds: A Review. *Synth. Commun.* **2017**, *47*, 87–104. https://doi.org/10.1080/00397911.2016.1255973.
5. Abonia, R.; Insuasty, D.; Castillo, J.C.; Laali, K.K. Recent Advances in the Synthesis of Organic Thiocyano (SCN) and Selenocyano (SeCN) Compounds, Their Chemical Transformations and Bioactivity. *Molecules* **2024**, *29*, 5365. https://doi.org/10.3390/molecules29225365.
6. Gouda, M.A. 1-Phenyl-2-Thiocyanatoethanone As Synthons in Heterocyclic Synthesis. *Synth. Commun.* **2013**, *43*, 2547–2574. https://doi.org/10.1080/00397911.2012.730649.
7. Chen, H.; Shi, X.; Liu, X.; Zhao, L. Recent Progress of Direct Thiocyanation Reactions. *Org. Biomol. Chem.* **2022**, *20*, 6508–6527. https://doi.org/10.1039/D2OB01018F.
8. Yan, Q.; Chen, S.; Fan, J.; Li, Z. Recent Advances in Radical Thiocyanation Cyclization Or Spirocyclization Reactions. *Org. Biomol. Chem.* **2023**, *21*, 9112–9122. https://doi.org/10.1039/D3OB01659E.
9. Jiang, B.; Tu, X.J.; Wang, X.; Tu, S.J.; Li, G. Copper(I)-Catalyzed Multicomponent Reaction Providing a New Access to Fully Substituted Thiophene Derivatives. *Org. Lett.* **2014**, *16*, 3656–3659. https://doi.org/10.1021/ol501404x.
10. Matloubi Moghaddam, F.; Moafi, A. A Facile and Convenient Synthesis of 3-Alkylidene-Oxindoles Bearing Tetrahydropyrazine Scaffold under Catalyst-Free Conditions. *Heteroat. Chem.* **2018**, *29*, e21416. https://doi.org/10.1002/hc.21416.
11. Zhu, X.T.; Zhao, Q.; Wang, S.D.; Zhang, T.S.; Cai, P.J.; Hao, W.J.; Tu, S.J.; Jiang, B. Metal-Free Base-Promoted Sulfenylation for the Synthesis of A-Arylthio-α,β-Unsaturated Ketones. *Tetrahedron* **2018**, *74*, 585–593. https://doi.org/10.1016/j.tet.2017.12.037.
12. Daina, A.; Michielin, O.; Zoete, V. SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Sci. Rep.* **2017**, *7*, 42717. https://doi.org/10.1038/srep42717.
13. Cheng, F.; Li, W.; Zhou, Y.; Shen, J.; Wu, Z.; Liu, G.; Lee, P.W.; Tang, Y. AdmetSAR: A comprehensive source and free tool for assessment of chemical ADMET properties. *J. Chem. Inf. Model.* **2012**, *52*, 3099–3105. https://doi.org/10.1021/ci300367a.
14. Strelkov, V.D.; Dyadyuchenko, L.V.; Dmitrieva, I.G. *Sintez Novykh Gerbitsidnykh Antidotov dlya Podsolnechnika (Synthesis of New Herbicide Antidotes for Sunflower)*; Prosveshchenie-Yug: Krasnodar, Russia, 2014; p. 79. (In Russian)