

Chemo- and Regioselective 1,3-Dipolar Cycloaddition of Nitrile Imines to 5-Arylmethylene-2-methylthiohydantoins

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Abstract

1,3-Dipolar cycloaddition reactions of nitrile imines are a powerful tool for the construction of spirocyclic frameworks, yet controlling chemoselectivity remains challenging when dipolarophiles contain multiple reactive sites. In this study, we investigated the cycloaddition of nitrile imines with 5-arylmethylene-2-methylthiohydantoins, which possess both exocyclic C=C and endocyclic C=N bonds. Nitrile imines were generated from hydrazonoyl chlorides under basic conditions and reacted with the thiohydantoin substrates under optimized reaction conditions. The cycloaddition proceeded smoothly, affording spiro-fused thiohydantoin–pyrazoline derivatives. In all cases, the reaction occurred selectively at the exocyclic C=C bond, while the C=N bond remained unreactive even in the presence of excess dipole. This chemoselectivity is attributed to the greater steric accessibility of the exocyclic double bond. These results clarify key factors governing nitrile imine chemoselectivity and provide a reliable approach to structurally complex spirocyclic thiohydantoin derivatives.

Keywords: nitrile imines; 1,3-dipolar cycloaddition; thiohydantoin; spirocycles; imidazolones

1. Introduction

The discovery of biologically active molecules remains one of the central challenges in modern organic and medicinal chemistry. Incorporation of spirocyclic motifs into molecular frameworks is known to enhance conformational rigidity, often improving the binding affinity and selectivity of small molecules toward biological targets [1–3]. In this context, 1,3-dipolar cycloaddition reactions represent an efficient and atom-economical strategy for the construction of spiro-fused molecular architectures [4–6]. Among available 1,3-dipoles, nitrile imines are particularly attractive due to their high reactivity and their ability to introduce pyrazole or pyrazoline fragments into complex molecular frameworks [7].

The use of dipolarophiles bearing exocyclic carbon–carbon or carbon–heteroatom multiple bonds enables efficient access to structurally diverse spirocyclic heterocycles. Nitrile imines readily undergo cycloaddition with C=C bonds of varying substitution patterns as well as with carbon–heteroatom double bonds [7,8]. Notably, these dipoles exhibit especially high reactivity toward C=S bonds [9,10], followed by C=N bonds [7,11], whereas cycloaddition to C=O bonds is generally the least favorable [7,12,13]. Importantly, the electronic nature of nitrile imine substituents strongly influences both reactivity and chemoselectivity, particularly in dipolarophiles containing multiple competing reaction sites [14,15].



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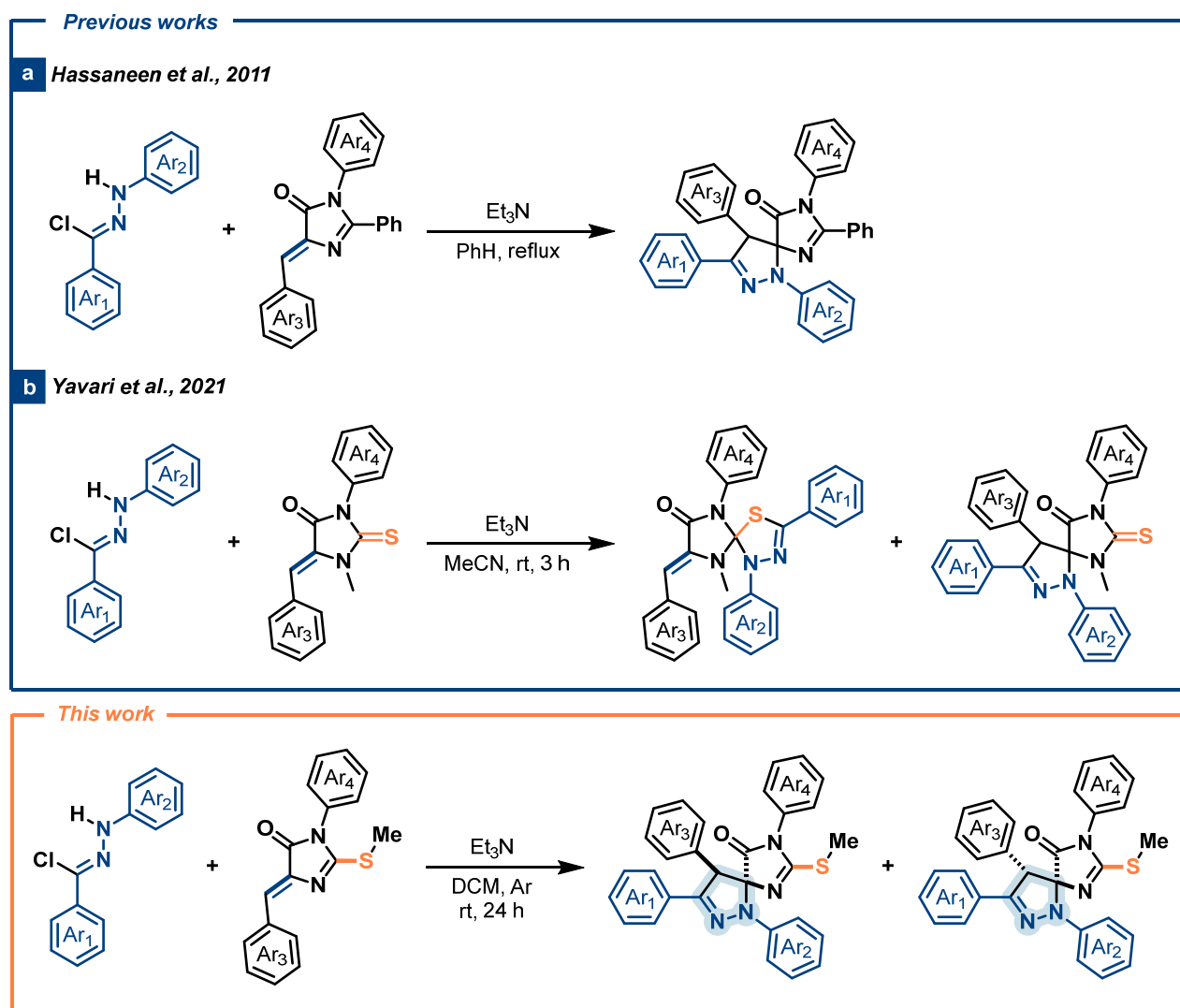
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Compounds incorporating the imidazolidine-2,4-dione (hydantoin) scaffold display a wide range of biological activities [16], and comparable levels of interest have been directed toward their thioanalogues [17–19]. Hydantoin offers five potential substitution sites, including two hydrogen-bond donors and two acceptors, and are readily accessible through established cyclization reactions, enabling facile structural diversification. Previous studies have demonstrated that thiohydantoin are highly promising substrates in 1,3-dipolar cycloaddition reactions for the synthesis of biologically active compounds, including potential anticancer agents. In particular, thiohydantoin-based dispiroindolinone derivatives have shown potent anticancer activity in both *in vitro* and *in vivo* models [20–22].

Hassaneen and co-workers conducted a detailed investigation of the regioselectivity of the cycloaddition of nitrile imine to imidazolinone derivatives [23] (Scheme 1a). The examined dipolarophile contains both an exocyclic C=C bond and an endocyclic C=N bond. Using equimolar amounts of the reactants, the authors observed complete regioselectivity, involving an attack of the nitrile imine nitrogen terminus at the more sterically hindered carbon of the exocyclic C=C bond. However, the possibility of cycloaddition at the endocyclic C=N bond upon increasing the concentration of the nitrile imine remains unexplored.



Scheme 1. 1,3-Dipolar Cycloaddition of Nitrile Imines to Imidazolinone Derivatives (a) [23] and Arylidenehydantoin (b) [24].

Yavari and co-workers reported that cycloaddition of nitrile imines to 5-arylidene-1-methyl-2-thiohydantoin proceeds competitively across both C=S and C=C bonds (Scheme 1b). While the C=S adduct typically predominates, the use of nitrile imines bearing electron-withdrawing nitro substituents results exclusively in cycloaddition at the C=S bond [24].

Building on our ongoing interest in nitrile imine cycloadditions with dipolarophiles containing multiple unsaturated functionalities [15,25,26], we report herein the use of 5-arylmethylene-2-methylthiohydantoin **5** as dipolarophiles for the construction of spiro-fused frameworks incorporating both thiohydantoin and pyrazoline fragments. These substrates contain two potentially reactive sites—C=C and C=N bonds—rendering them well suited for probing chemoselectivity in nitrile imine cycloaddition reactions (Scheme 1). In addition, the presence of a methylthio substituent provides a handle for further postsynthetic modification, as the S-Me group can be transformed into carbonyl [21], selenocarbonyl [27] functionalities or glycocynamidines [28,29].

2. Materials and Methods

2.1. General Methods

All solvents were purified and dried according to established procedures described previously in [30]. Commercially available reagents were used as received and were obtained from Sigma-Aldrich (St. Louis, MO, USA), ABCR (Karlsruhe, Germany), and AKSci (Burlington, VT, USA). Reaction progress was routinely monitored by thin-layer chromatography on silica gel plates containing a fluorescent indicator (254 nm), with visualization under UV light, unless stated otherwise.

^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectra were recorded on a BrukerAvance (Bruker BioSpin, Billerica, MA, USA) and Agilent 400-MR (Agilent Technologies, Santa Clara, CA, USA) spectrometers operating at 400 MHz for ^1H and 101 MHz for $^{13}\text{C}\{^1\text{H}\}$. Chemical shifts (δ) are reported in ppm relative to residual solvent signals [^1H NMR: CDCl_3 (7.27), $\text{DMSO}-d_6$ (2.50); $^{13}\text{C}\{^1\text{H}\}$ NMR: CDCl_3 (77.16), $\text{DMSO}-d_6$ (39.52)]. Coupling constants (J) are given in Hertz (Hz). Signal multiplicities are denoted as s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, hept = heptet, m = multiplet, br = broad signal.

High-resolution mass spectra were acquired on a TripleTOF 5600+ quadrupole time-of-flight mass spectrometer (AB Sciex, Concord, Vaughan, ON, Canada) equipped with a DuoSpray ion source, using electrospray ionization in positive-ion mode. Typical acquisition parameters included a capillary voltage of 5.5 kV, nebulizer and curtain gas pressures of 15 and 25 psi, respectively, an ambient source temperature, a declustering potential of 20 V, and an m/z range of 100–1200. Elemental compositions were assigned based on accurate mass measurements and isotopic pattern analysis using PeakView software version 2.2 with Formula Finder module (SCIEX, Framingham, MA, USA), with a mass accuracy tolerance of ± 5 ppm.

Infrared (IR) spectra were recorded on a Thermo Scientific Nicolet iS5 FT-IR spectrometer (Thermo Fisher Scientific, Waltham, MA, USA) equipped with iD1 transmission and/or iD7 ATR accessories. Samples were prepared as solids directly on the ATR diamond crystal or as thin films between NaCl plates for transmission mode, with spectra acquired in the range of $4000\text{--}400\text{ cm}^{-1}$ at a resolution of 4 cm^{-1} .

Experimental procedures and characteristic data for all synthesized compounds are given in the Supplementary Information [25,30–37].

2.2. The 1,3-Dipolar Cycloaddition Reaction of Nitrile Imines with 5-Arylmethylene-2-methylthiohydantoins **5**

General procedure: To a solution of hydrazoneyl chloride **2** (2.20 equiv.) and 5-arylmethylene-2-methylthiohydantoin **5** (1.00 equiv.) in 28 mL/1 mmol of DCM under an inert atmosphere, triethylamine (4.40 equiv.) in 21 mL/1 mmol of DCM was added dropwise while stirring for 15–20 min. After the addition, the reaction mixture was stirred for 24 h. Upon completion of the reaction, as monitored by TLC, the solvent was removed under reduced pressure. The crude mixture was then purified by column chromatography on silica gel using CH₂Cl₂/petroleum ether (1:1)—CH₂Cl₂ or CHCl₃/petroleum ether (1:1)—CHCl₃/MeOH (100:1) as the eluent to obtain the pure product.

(4*R*,5*R*)-4-(4-chlorophenyl)-8-(4-ethoxyphenyl)-7-(methylthio)-1,3-diphenyl-1,2,6,8-tetraaza spiro[4.4]nona-2,6-dien-9-one (**6a**)

Compound **6a** was prepared from hydrazoneyl chloride **2a** (0.081 g, 0.35 mmol), 5-arylmethylene-2-methylthiohydantoin **5a** (0.060 g, 0.16 mmol) and TEA (0.098 mL, 0.7 mmol). Yield 0.053 g (59%). White solid.

Diastereomer **7a** could be obtained only as a mixture with diastereomer **6a**, and its yield was determined by ¹H NMR analysis of the resulting mixture. Yield **7a** 3%.

Chromatography: CHCl₃/petroleum ether (3:1), R_f 0.55.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.61–7.54 (m, 2H), 7.43–7.31 (m, 7H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 9.0 Hz, 2H), 7.09 (d, *J* = 8.9 Hz, 2H), 7.04 (d, *J* = 7.9 Hz, 2H), 6.96 (t, *J* = 7.4 Hz, 1H), 5.54 (s, 1H), 4.08 (q, *J* = 7.0 Hz, 2H), 2.00 (s, 3H), 1.35 (t, *J* = 7.0 Hz, 3H).

¹³C{¹H} NMR (101 MHz, DMSO-*d*₆) δ 177.74, 159.42, 149.18, 143.19, 132.53, 132.15, 131.84, 130.74, 129.40, 129.14, 128.99, 128.60, 128.05, 126.79, 123.59, 121.36, 115.38, 114.66, 91.02, 63.58, 61.94, 14.55, 12.46.

HRMS (ESI): calcd for C₃₂H₂₇ClN₄O₂S (M+Na) 589.1436, found 589.1439.

IR (cm^{−1}): 1742 (C=O), 1597, 1564, 1509 (C=N, C=C arom.).

Mp 211–214 °C.

(4*R*,5*R*)-4-(4-chlorophenyl)-8-(4-ethoxyphenyl)-3-(4-methoxyphenyl)-7-(methylthio)-1-phenyl-1,2,6,8-tetraazaspiro[4.4]nona-2,6-dien-9-one (**6b**)

Compound **6b** was prepared from hydrazoneyl chloride **2c** (0.133 g, 0.51 mmol), 5-arylmethylene-2-methylthiohydantoin **5a** (0.086 g, 0.23 mmol) and TEA (0.142 mL, 1.02 mmol). Yield 0.080 g (56%). White solid.

Chromatography: CHCl₃/petroleum ether (3:1), R_f 0.35.

¹H NMR (400 MHz, CDCl₃) δ 7.47 (d, *J* = 8.9 Hz, 2H), 7.31–7.26 (m, 4H), 7.18–7.12 (m, 4H), 7.04–6.93 (m, 5H), 6.80 (d, *J* = 9.0 Hz, 2H), 5.19 (s, 1H), 4.06 (q, *J* = 7.0 Hz, 2H), 3.79 (s, 3H), 2.06 (s, 3H), 1.44 (t, *J* = 7.0 Hz, 3H).

¹³C{¹H} NMR (600 MHz, CDCl₃) δ 178.92, 164.34, 160.21, 159.96, 148.44, 143.83, 134.08, 131.74, 131.04, 129.11, 128.68, 128.63, 128.35, 124.13, 123.96, 121.96, 116.38, 115.48, 113.93, 92.20, 64.00, 63.86, 55.39, 14.87, 13.00.

HRMS (ESI): calcd for C₃₃H₂₉ClN₄O₃S (M+Na) 619.1541, found 619.1546.

IR (cm^{−1}): 1752 (C=O), 1599, 1564 (C=N, C=C arom.).

Mp 170–171 °C.

(4*R*,5*R*)-3-(4-bromophenyl)-8-(3-chloro-4-fluorophenyl)-4-(4-methoxyphenyl)-7-(methylthio)-1-phenyl-1,2,6,8-tetraazaspiro[4.4]nona-2,6-dien-9-one (**6c**)

Compound **6c** was prepared from hydrazoneyl chloride **2d** (0.090 g, 0.29 mmol), 5-arylmethylene-2-methylthiohydantoin **5b** (0.050 g, 0.13 mmol) and TEA (0.081 mL, 0.58 mmol). Yield 0.054 g (63%). White solid.

Diastereomer **7c** could be obtained only as a mixture with diastereomer **6c**, and its yield was determined by ^1H NMR analysis of the resulting mixture. Yield **7c** 2%.

Chromatography: CHCl_3 /petroleum ether (3:1), R_f 0.59.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.70–7.62 (m, 2H), 7.59–7.47 (m, 4H), 7.39–7.29 (m, 3H), 7.11 (d, J = 8.2 Hz, 2H), 7.07–7.01 (m, 2H), 6.96 (tt, J = 7.3, 1.1 Hz, 1H), 6.92–6.86 (m, 2H), 5.45 (s, 1H), 3.72 (s, 3H), 2.04 (s, 3H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, $\text{DMSO}-d_6$) δ 177.35, 162.51, 158.97, 156.55, 148.68, 143.02, 131.57, 131.23, 130.19, 129.90, 129.52, 128.73, 128.65, 128.43 (d, J = 3.6 Hz), 124.34, 122.41, 121.39, 120.71 (d, J = 19.0 Hz), 118.22 (d, J = 22.6 Hz), 114.69, 113.53, 91.39, 62.43, 55.10, 12.65.

HRMS (ESI): calcd for $\text{C}_{31}\text{H}_{23}\text{BrClFN}_4\text{O}_2\text{S}$ ($\text{M}+\text{Na}$) 671.0290, found 671.0285.

IR (cm^{-1}): 1753 (C=O), 1596, 1564 (C=N, C=C arom.).

Mp 179–180 °C.

(4*R*,5*R*)-8-(3-chloro-4-fluorophenyl)-3,4-bis(4-chlorophenyl)-7-(methylthio)-1-phenyl-1,2,6,8-tetraazaspiro[4.4]nona-2,6-dien-9-one (**6d**)

Compound **6d** was prepared from hydrazonoyl chloride **2b** (0.118 g, 0.44 mmol), 5-arylmethylene-2-methylthiohydantoin **5c** (0.077 g, 0.20 mmol) and TEA (0.123 mL, 0.88 mmol). Yield 0.096 g (78%). White solid.

Chromatography: CHCl_3 /petroleum ether (3:1), R_f 0.47.

^1H NMR (400 MHz, CDCl_3) δ 7.49–7.43 (m, 2H), 7.34–7.26 (m, 4H), 7.26–7.21 (m, 3H), 7.18 (dd, J = 6.3, 2.6 Hz, 1H), 7.15–7.10 (m, 4H), 7.06–6.97 (m, 2H), 5.17 (s, 1H), 2.10 (s, 3H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 178.13, 163.11, 159.96, 157.44, 147.69, 143.32, 134.93, 134.53, 131.57, 131.04, 129.66 (d, J = 4.5 Hz), 129.26, 128.79, 128.62, 128.30, 127.24 (d, J = 7.9 Hz), 122.89, 122.60, 117.83, 117.60, 116.94, 92.50, 63.45, 13.12.

HRMS (ESI): calcd for $\text{C}_{30}\text{H}_{20}\text{Cl}_3\text{FN}_4\text{OS}$ ($\text{M}+\text{Na}$) 631.0300, found 631.0298.

IR (cm^{-1}): 1752 (C=O), 1597, 1564 (C=N, C=C arom.).

Mp 160–161 °C.

(4*R*,5*R*)-4-(4-chlorophenyl)-8-(4-ethoxyphenyl)-7-(methylthio)-3-(4-nitrophenyl)-1-phenyl-1,2,6,8-tetraazaspiro[4.4]nona-2,6-dien-9-one (**6e**)

Synthesis of the compound **6e** was carried out according to general procedure from hydrazonoyl chloride **2e** (0.161 g, 0.58 mmol), 5-arylmethylene-2-methylthiohydantoin **5a** (0.099 g, 0.27 mmol) and TEA (0.162 mL, 1.16 mmol). Among the reaction mixture the target compound was not found.

(4*R*,5*R*)-4-(4-chlorophenyl)-8-(4-ethoxyphenyl)-7-(methylthio)-1-(4-nitrophenyl)-3-phenyl-1,2,6,8-tetraazaspiro[4.4]nona-2,6-dien-9-one (**6f**)

Compound **6f** was prepared from hydrazonoyl chloride **2f** (0.166 g, 0.60 mmol), 5-arylmethylene-2-methylthiohydantoin **5a** (0.102 g, 0.27 mmol) and TEA (0.167 mL, 1.20 mmol). Owing to the very similar R_f values of the starting material **5a** and the spiro adduct **6e**, the latter could be isolated only as a mixture with **5a**. As a result, we were able to isolate only traces (<5%) of the target compound **6f**.

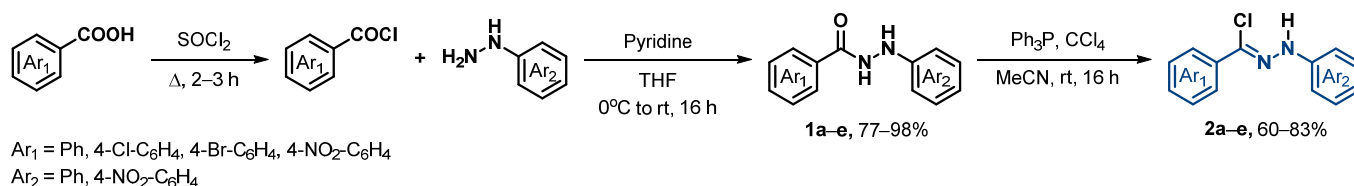
Chromatography: CHCl_3 /petroleum ether (3:1), R_f 0.43.

HRMS (ESI): calcd for $\text{C}_{32}\text{H}_{26}\text{ClN}_5\text{O}_4\text{S}$ ($\text{M}+\text{Na}$) 634.1286, found 634.1281.

3. Results and Discussion

Hydrazonoyl chlorides served as nitrile imine precursors in this work and were prepared according to literature procedures [32] (Scheme 2).

Synthesis of Hydrazonoyl Chlorides

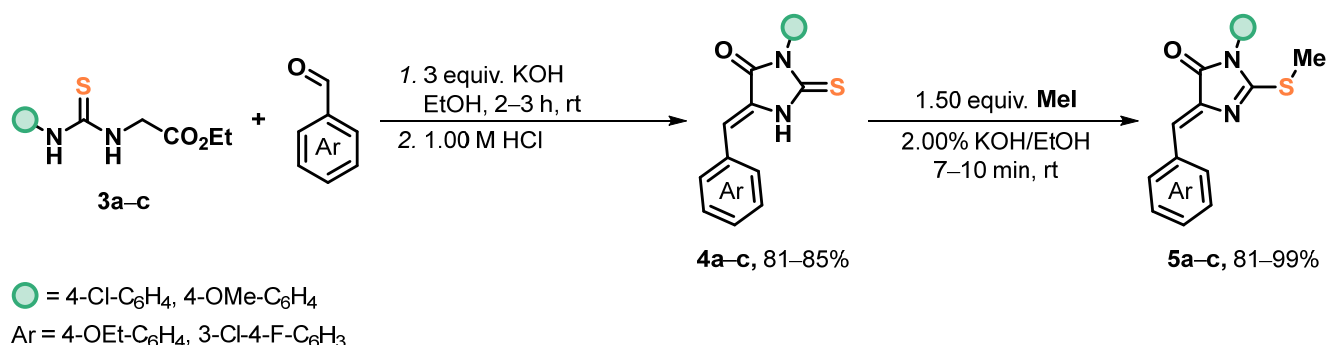


Scheme 2. Synthesis of hydrazonoyl chlorides **2a–e**.

Hydrazonoyl chlorides are convenient preparative precursors for the in situ generation of nitrile imines via base-promoted dehydrohalogenation. A series of hydrazonoyl chlorides **2a–e** was synthesized from commercially available benzoic acids and phenylhydrazines (Scheme 2). Following a reported protocol [32], phenylhydrazines were acylated with benzoyl chlorides to afford acylhydrazides **1a–e**, which were subsequently chlorinated using PPh₃/CCl₄ in anhydrous MeCN, providing nitrile imine precursors **2a–e** in good to excellent overall yields (see Supplementary Information, pp. S3–S5).

5-Arylmethylene-2-methylthiohydantoins were used as dipolarophiles in the 1,3-dipolar cycloaddition reactions and were prepared according to a reported method [34]. Condensation of thioureas **3a–c** [21] with aromatic aldehydes in 2% KOH/EtOH, followed by acidification, afforded 5-arylmethylene-2-thiohydantoins **4a–c**. Subsequent S-methylation under basic conditions yielded dipolarophiles **5a–c** in good to excellent yields (Scheme 3; see Supplementary Information, pp. S5–S10).

Synthesis of S-methylated thiohydantoins

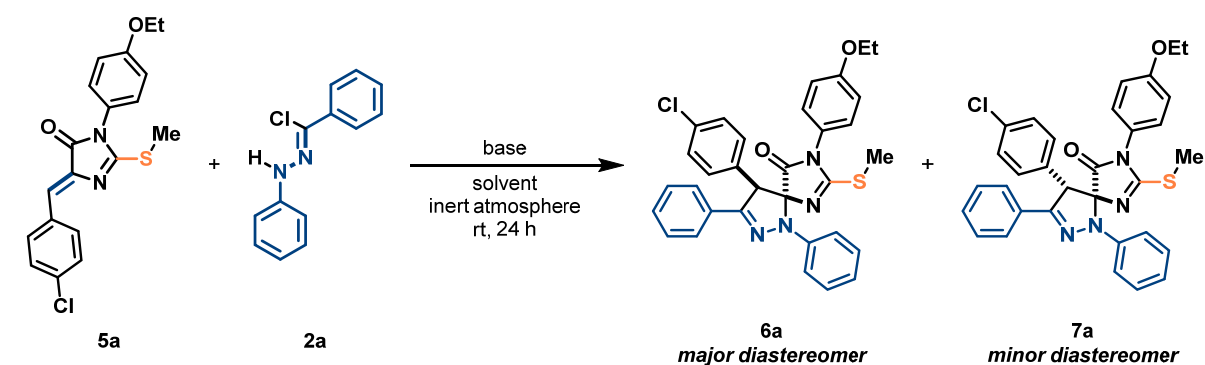


Scheme 3. Synthesis of 5-arylmethylene-2-methylthiohydantoins **5a–c**.

Next, the reaction conditions for the 1,3-dipolar cycloaddition of nitrile imines with 5-arylmethylene-2-methylthiohydantoins were optimized. Hydrazonoyl chloride **2a** and 5-arylmethylene-2-methylthiohydantoin **5a** were selected as model substrates. According to a previously reported protocol [25], hydrazonoyl chloride **2a** and dipolarophile **5a** were dissolved in dichloromethane (DCM), followed by dropwise addition of a triethylamine solution in DCM over 10–15 min under an inert atmosphere. The reaction mixture was then stirred at room temperature for 24 h (Figure 1).

A series of experiments demonstrated that altering the hydrazonoyl chloride **2a**/Et₃N ratio (entries 1–6) significantly influenced the reaction outcome. Increasing the nitrile imine concentration led to higher yields of **6a**, with optimal results achieved using 2.2 equiv. of **2a** and 4.4 equiv. of Et₃N (entry 4). Under these conditions, however, a diastereomeric mixture of **6a** (94%) and **7a** (4%) was formed. Sequential addition of two equivalents of nitrile imine (entry 5), as well as further increases in its amount (entry 6), resulted in a higher proportion of diastereomer **7a**.

Reaction optimization



Entry	Solvent	Base	2a, equiv.	Base, equiv.	Yield ^a	
					6a	7a
1	DCM	Et ₃ N	1	1	28%	-
2	DCM	Et ₃ N	1	2	36%	-
3	DCM	Et ₃ N	1.1	2.2	42%	-
4	DCM	Et₃N	2.2	4.4	94%	4%
5 ^b	DCM	Et ₃ N	2.2	4.4	91%	7%
6	DCM	Et ₃ N	3	6	85%	14%
7	CHCl ₃	Et ₃ N	2.2	4.4	97%	-
8	MeCN	Et ₃ N	2.2	4.4	58%	-
9	MeOH	Et ₃ N	2.2	4.4	36%	8%
10	Acetone	Et ₃ N	2.2	4.4	18%	-
11	Toluene	Et ₃ N	2.2	4.4	16%	-
12	DCM	DIPEA	2.2	4.4	97%	-

Figure 1. Optimization of cycloaddition reaction conditions of hydrazonoyl chloride **2a** with 5-arylmethylene-2-methylthiohydantoin **5a**. Unless otherwise noted, reactions were carried out at room temperature under an argon atmosphere using 5-arylmethylene-2-methylthiohydantoin **5a** (0.071 mmol, 0.026 g) and the corresponding hydrazonoyl chloride **2a** in 3.5 mL of solvent for 24 h. ^a Product yields were determined by ¹H NMR analysis of the crude reaction mixtures using CH₂Br₂ as an internal standard. ^b Initially, 1.1 equiv. of hydrazonoyl chloride **2a** and 2.2 equiv of Et₃N were added and the mixture was stirred for 6 h; a second portion of **2a** (1.1 equiv) and Et₃N (2.2 equiv) was then introduced, followed by stirring for an additional 6 h.

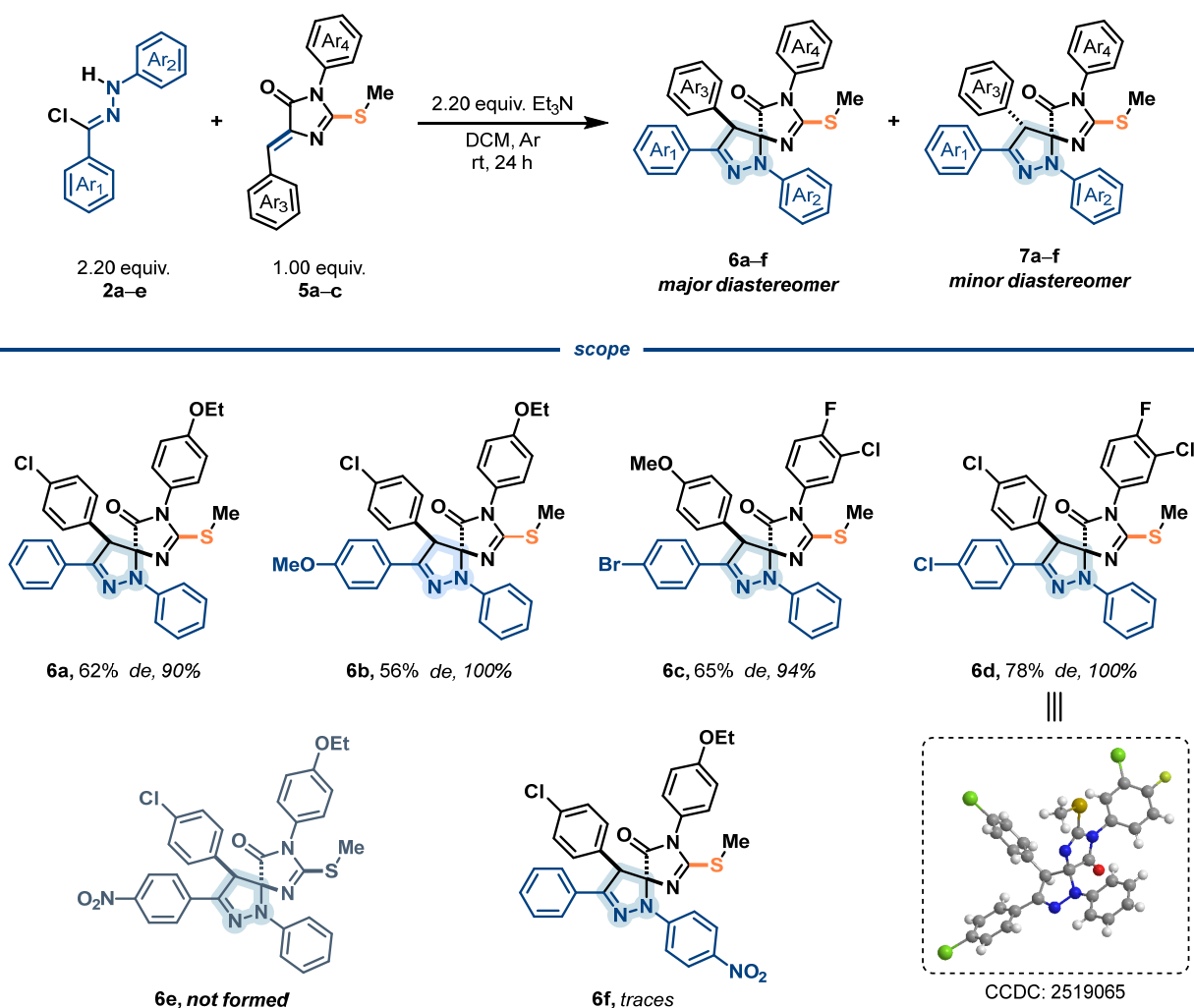
Solvent screening (entries 7–11) showed that the highest yields were obtained in DCM and CHCl₃ (entries 4 and 7). In contrast, the use of more polar solvents—MeCN (entry 8), MeOH (entry 9), acetone (entry 10), as well as toluene (entry 11)—led to decreased yields of cycloaddition product **6a**, likely due to the limited solubility of **5a** in these media. Substitution of Et₃N with DIPEA had no significant effect on the reaction outcome (entry 12).

Thus, the cycloaddition of nitrile imines to 5-arylmethylene-2-methylthiohydantoin **5a** proceeds chemoselectively at the exocyclic C=C bond, while the endocyclic C=N bond remains unreactive, even in the presence of excess nitrile imine (entry 6). The observed chemoselectivity can be attributed to the higher steric accessibility of the exocyclic double bond. Both outcomes—selective cycloaddition at an exocyclic C=C bond in the presence of an endocyclic C=N bond [23,38,39], as well as the reverse selectivity [40,41]—have been reported previously, indicating that chemoselectivity in nitrile imine cycloadditions is highly substrate- and substituent-dependent. In particular, nitrile imines bearing electron-

withdrawing ethoxycarbonyl substituents favor cycloaddition at C=N bonds, whereas diaryl-substituted nitrile imines exhibit strict chemoselectivity toward C=C bonds [42].

Formation of a diastereomeric mixture is likely associated with partial E/Z isomerization of the exocyclic C=C bond of the starting dipolarophile under reaction conditions. Indeed, the ^1H NMR spectrum of **5a** recorded in CDCl_3 shows partial signal doubling, indicating an isomeric mixture, whereas a single set of signals is observed in $\text{DMSO}-d_6$. Accordingly, under reaction conditions in DCM or CHCl_3 , partial isomerization of the initial (Z)-**5a** to the E-isomer occurs, leading to formation of diastereomers **6a** and **7a**.

Using the optimized conditions, a series of compounds **6a–f** was synthesized (Scheme 4). In some cases, diastereomers **7a** and **7c** were detected but they could be isolated only as mixtures with the major diastereomers **6**. In contrast, cycloaddition products **6b** and **6d** were formed as single diastereomers. For compounds **6a** and **7a**, the reaction was also carried out using an alternative procedure described earlier (Figure 1, entry 5), in which 1.1 equiv of hydrazonoyl chloride **2a** and 2.2 equiv of Et_3N were initially added and the mixture was stirred for 2 days. A second portion of **2a** (1.1 equiv) and Et_3N (2.2 equiv) was then introduced, followed by stirring for an additional 3 days. Under these conditions, an increased proportion of the minor diastereomer **7a** (16%) was observed, accompanied by a decrease in the yield of the major diastereomer **6a** (36%).



Scheme 4. Cycloaddition of hydrazonoyl chlorides **2** to 5-arylmethylene-2-methylthiohydantoins **5** in the presence of Et_3N and the reaction scope.

The use of halogen-substituted hydrazonoyl chlorides **2b** and **2d**, unsubstituted **2a**, and the electron-donating methoxy-substituted analog **2c** afforded the corresponding cycloaddition products in good yields (56–78%). In contrast, reactions involving nitrile imines bearing electron-withdrawing substituents resulted in significantly lower yields of spiroimidazolones. Thus, when hydrazonoyl chloride **2e** was employed, cycloaddition product **6e** could not be isolated, and incomplete reagents conversion was observed, with starting materials recovered from the reaction mixture. In the case of hydrazonoyl chloride **2f**, incomplete conversion of the starting 5-arylmethylene-2-methylthiohydantoin **5a** also took place. Owing to the very similar R_f values of the starting material **5a** and the spiro adduct **6f**, the latter could be isolated only as a mixture with **5a** in trace amounts (<5%).

The observed decrease in reactivity upon introduction of more electron-withdrawing substituents into the nitrile imine structure is consistent with literature reports indicating that such substituents reduce the reactivity of 1,3-dipoles toward the exocyclic C=C bond at the 5-position of thiohydantoin derivatives [15,24]. Although the introduction of electron-withdrawing substituents into the nitrile imine structure, as in the cases of compounds **6e** and **6f**, might be expected to alter the chemoselectivity of the cycloaddition toward addition at the C=N bond, as reported in related systems [42], no such cycloaddition products were observed in the present study.

Product structures were confirmed by ^1H and ^{13}C NMR spectroscopy and HRMS, while the structure of compound **6d** was unambiguously established by single-crystal X-ray diffraction (see Supplementary Information, pp. S15–S16).

Overall, the results demonstrate that, regardless of the electronic nature of the nitrile imine, the 1,3-dipolar cycloaddition with 5-arylmethylene-2-methylthiohydantoins **5** proceeds regioselectively, with the *N*-terminus of the C–N–N fragment adding to the more sterically hindered carbon atom of the exocyclic C=C bond, in agreement with literature precedents [7,23]. In all cases, the reaction also remains chemoselective for the C=C bond.

4. Conclusions

In summary, we have demonstrated that 5-arylmethylene-2-methylthiohydantoins are effective dipolarophiles in the 1,3-dipolar cycloaddition of nitrile imines, despite the presence of multiple potentially reactive sites. Nitrile imines, generated in situ from hydrazonoyl chlorides, undergo cycloaddition in a highly chemo- and regioselective manner, reacting exclusively at the exocyclic C=C bond, while the endocyclic C=N bond remains inert even under conditions of excess dipole. Systematic optimization of the reaction conditions enabled the synthesis of a series of spiro-fused thiohydantoin–pyrazoline derivatives, with the observed diastereoselectivity explained by partial *E/Z* isomerization of the dipolarophile in the reaction conditions.

The dependence of reaction efficiency on the electronic nature of the nitrile imine substituents is consistent with known trends in nitrile imine reactivity and further supports the proposed selectivity rationale. Structural assignments were confirmed by spectroscopic methods and single-crystal X-ray diffraction.

Overall, this study expands the understanding of nitrile imine chemoselectivity toward multifunctional dipolarophiles and highlights 5-arylmethylene-2-methylthiohydantoins as versatile building blocks for the construction of structurally complex spirocyclic frameworks. The presence of a methylthio substituent additionally provides opportunities for postsynthetic modification, further enhancing the synthetic utility of the developed methodology.

Supplementary Materials: The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/org7010007/s1>. Figure S1: X-ray structure of compound **6d**; Table S1: Crystal data and structure refinement for **6d**. Experimental procedures and characteristic data for all synthesized compounds are given in the Supplementary Information [25,30–37].

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References

1. Gupta, A.K.; Bharadwaj, M.; Kumar, A.; Mehrotra, R. Spiro-Oxindoles as a Promising Class of Small Molecule Inhibitors of P53–MDM2 Interaction Useful in Targeted Cancer Therapy. *Top. Curr. Chem.* **2017**, *375*, 3. [CrossRef]
2. Hiesinger, K.; Dar'in, D.; Proschak, E.; Krasavin, M. Spirocyclic Scaffolds in Medicinal Chemistry. *J. Med. Chem.* **2021**, *64*, 150–183. [CrossRef]
3. Bora, D.; Kaushal, A.; Shankaraiah, N. Anticancer Potential of Spirocompounds in Medicinal Chemistry: A Pentennial Expedition. *Eur. J. Med. Chem.* **2021**, *215*, 113263. [CrossRef]
4. Kotha, S.; Deb, A.C.; Lahiri, K.; Manivannan, E. Selected Synthetic Strategies to Spirocyclics. *Synthesis* **2009**, *2009*, 165–193. [CrossRef]
5. Dadiboyena, S. Cycloadditions and Condensations as Essential Tools in Spiropyrazoline Synthesis. *Eur. J. Med. Chem.* **2013**, *63*, 347–377. [CrossRef]
6. Sami Shawali, A.; Osman Abdelhamid, A. Synthesis of Spiro-Heterocycles via 1,3-Dipolar Cycloadditions of Nitrilimines to Exoheterocyclic Enones. Site-, Regio- and Stereo-Selectivities Overview. *Curr. Org. Chem.* **2012**, *16*, 2673–2689. [CrossRef]
7. Jamieson, C.; Livingstone, K. *The Nitrile Imine 1,3-Dipole*; Springer International Publishing: Cham, Switzerland, 2020.
8. Deepthi, A.; Acharjee, N.; Sruthi, S.L.; Meenakshy, C.B. An Overview of Nitrile Imine Based [3+2] Cycloadditions over Half a Decade. *Tetrahedron* **2022**, *116*, 132812. [CrossRef]
9. Huisgen, R.; Langhals, E. Thiones as Superdipolarophiles. *Tetrahedron Lett.* **1989**, *30*, 5369–5372. [CrossRef]
10. Shawali, A.S.; Farghaly, T.A. Reactions of Hydrazonoyl Halides with Heterocyclic Thiones. Convenient Methodology for Heteroannulation, Synthesis of Spiroheterocycles and Heterocyclic Ring Transformation. *Arkivoc* **2008**, *2008*, 18–64. [CrossRef]
11. Petrova, J.V.; Kukushkin, M.E.; Beloglazkina, E.K. 1,3-Dipolar Cycloaddition of Nitrile Imines and Nitrile Oxides to Exocyclic C=N Bonds—An Approach to Spiro-N-Heterocycles. *Int. J. Mol. Sci.* **2025**, *26*, 8673. [CrossRef] [PubMed]
12. Guo, C.X.; Zhang, W.Z.; Zhang, N.; Lu, X.B. 1,3-Dipolar Cycloaddition of Nitrile Imine with Carbon Dioxide: Access to 1,3,4-Oxadiazole-2(3H)-Ones. *J. Org. Chem.* **2017**, *82*, 7637–7642. [CrossRef]
13. Huisgen, R.; Grashey, R.; Seidel, M.; Knapfer, H.; Schmidt, R. 1,3-Dipolare Additionen, III. Umsetzungen Des Diphenylnitrilimins Mit Carbonyl Und Thiocarbonyl-Verbindungen. *Justus Liebigs Ann. Chem.* **1962**, *658*, 169–180. [CrossRef]
14. Wang, Y.; Song, W.; Hu, W.J.; Lin, Q. Fast Alkene Functionalization In Vivo by Photoclick Chemistry: HOMO Lifting of Nitrile Imine Dipoles. *Angew. Chem. Int. Ed.* **2009**, *48*, 5330–5333. [CrossRef] [PubMed]
15. Filkina, M.E.; Zhukov, E.A.; Tafeenko, V.A.; Semykin, A.V.; Kukushkin, M.E.; Nechaev, M.S.; Beloglazkina, E.K. Reactions of Nitrile Imines with Thiohydantoin Derivatives: Unexpected Chemoselectivity of the 1,3-Dipolar Cycloaddition: Preferential Addition of C=C Rather than C=S Bonds. *ACS Omega* **2025**, *10*, 40658–40667. [CrossRef] [PubMed]
16. Konnert, L.; Lamaty, F.; Martinez, J.; Colacino, E. Recent Advances in the Synthesis of Hydantoins: The State of the Art of a Valuable Scaffold. *Chem. Rev.* **2017**, *117*, 13757–13809. [CrossRef]

17. Cho, S.H.; Kim, S.H.; Shin, D. Recent Applications of Hydantoin and Thiohydantoin in Medicinal Chemistry. *Eur. J. Med. Chem.* **2019**, *164*, 517–545. [[CrossRef](#)] [[PubMed](#)]
18. Dlin, E.A.; Averochkin, G.M.; Finko, A.V.; Vorobyeva, N.S.; Beloglazkina, E.K.; Zyk, N.V.; Ivanenkov, Y.A.; Skvortsov, D.A.; Koteliarsky, V.E.; Majouga, A.G. Reaction of Arylboronic Acids with 5-Aryl-3-Substituted-2-Thioxoimidazolin-4-Ones. *Tetrahedron Lett.* **2016**, *57*, 5501–5504. [[CrossRef](#)]
19. Khodair, A.I.; Bakare, S.B.; Awad, M.K.; Al-Issa, S.A.; Nafie, M.S. Design, Synthesis, and Computational Explorations of Novel 2-Thiohydantoin Nucleosides with Cytotoxic Activities. *J. Heterocycl. Chem.* **2022**, *59*, 664–685. [[CrossRef](#)]
20. Ivanenkov, Y.A.; Kukushkin, M.E.; Beloglazkina, A.A.; Shafikov, R.R.; Barashkin, A.A.; Ayginin, A.A.; Serebryakova, M.S.; Majouga, A.G.; Skvortsov, D.A.; Tafeenko, V.A.; et al. Synthesis and Biological Evaluation of Novel Dispiro-Indolinones with Anticancer Activity. *Molecules* **2023**, *28*, 1325. [[CrossRef](#)]
21. Kukushkin, M.; Novotortsev, V.; Filatov, V.; Ivanenkov, Y.; Skvortsov, D.; Veselov, M.; Shafikov, R.; Moiseeva, A.; Zyk, N.; Majouga, A.; et al. Synthesis and Biological Evaluation of S-, O- and Se-containing Dispirooxindoles. *Molecules* **2021**, *26*, 7645. [[CrossRef](#)]
22. Beloglazkina, A.; Barashkin, A.; Polyakov, V.; Kotovsky, G.; Karpov, N.; Mefedova, S.; Zagribelny, B.; Ivanenkov, Y.; Kalinina, M.; Skvortsov, D.; et al. Synthesis and Biological Evaluation of Novel Dispiro Compounds Based on 5-Arylidenehydantoins and Isatins as Inhibitors of P53–MDM2 Protein–Protein Interaction. *Chem. Heterocycl. Compd.* **2020**, *56*, 747–755. [[CrossRef](#)]
23. Miqdad, O.A.; Abunada, N.M.; Hassaneen, H.M. Regioselectivity of Nitrilimines 1,3-dipolar Cycloaddition: Novel Synthesis of Spiro[4,4]Nona-2,8-dien-6-one Derivatives. *Heteroat. Chem.* **2011**, *22*, 131–136. [[CrossRef](#)]
24. Yavari, I.; Taheri, Z.; Sheikhi, S.; Bahemmat, S.; Halvagar, M.R. Synthesis of Thia- and Thioxo-Tetraazaspiro[4.4]Nonenones from Nitrile Imines and Arylidenethiohydantoins. *Mol. Divers.* **2021**, *25*, 777–785. [[CrossRef](#)]
25. Filkina, M.E.; Baray, D.N.; Beloglazkina, E.K.; Grishin, Y.K.; Roznyatovsky, V.A.; Kukushkin, M.E. Regioselective Cycloaddition of Nitrile Imines to 5-Methylidene-3-Phenyl-Hydantoin: Synthesis and DFT Calculations. *Int. J. Mol. Sci.* **2023**, *24*, 1289. [[CrossRef](#)]
26. Petrova, J.V.; Filkina, M.E.; Grishin, Y.K.; Roznyatovsky, V.A.; Tafeenko, V.A.; Nechaev, M.S.; Ugrak, B.I.; Dutova, T.Y.; Savin, A.M.; Boldyrikhin, A.Y.; et al. 1,3-Dipolar Cycloaddition of Nitrile Imines to 2-Imino-Thiazolo[3,2-*a*]Pyrimidin-3-Ones: Dipole-Initiated Thiazolone-Imidazolone Rearrangement. *J. Org. Chem.* **2025**, *90*, 14861–14870. [[CrossRef](#)] [[PubMed](#)]
27. Alhasan, R.; Martins, G.M.; de Castro, P.P.; Saleem, R.S.Z.; Zaiter, A.; Fries-Raeth, I.; Kleinclauss, A.; Perrin-Sarrado, C.; Chaimbault, P.; da Silva Júnior, E.N.; et al. Selenoneine-Inspired Selenohydantoins with Glutathione Peroxidase-like Activity. *Bioorg Med. Chem.* **2023**, *94*, 117479. [[CrossRef](#)] [[PubMed](#)]
28. Daboun, H.A.; Abd-Elfattah, A.M.; Hussein, M.M.; Shalaby, A.F.A. Reactions of Amino Acids on 2-Methylmercaptohydantoin Derivatives. Synthesis of Imidazoimidazoline and Imidazoquinazoline Derivatives. *Z. Naturforschung B* **1981**, *36*, 366–369. [[CrossRef](#)]
29. Daboun, H.A.; Ibrahim, Y.A. Rearrangement of 3-arylhydantoins into 3-aminoglycocyamidines. *J. Heterocycl. Chem.* **1982**, *19*, 41–43. [[CrossRef](#)]
30. Tietze, L.F.; Eicher, T. *Reaktionen Und Synthesen Im Organisch-Chemischen Praktikum Und Forschungslaboratorium* (2. Auflage), 117th ed.; Thieme Verlag: Stuttgart, Germany; New York, NY, USA, 1991.
31. Jayaraman, A.; Cho, E.; Irudayanathan, F.M.; Kim, J.; Lee, S. Metal-Free Decarboxylative Trichlorination of Alkynyl Carboxylic Acids: Synthesis of Trichloromethyl Ketones. *Adv. Synth. Catal.* **2018**, *360*, 130–141. [[CrossRef](#)]
32. Giustiniano, M.; Meneghetti, F.; Mercalli, V.; Varese, M.; Giustiniano, F.; Novellino, E.; Tron, G.C. Synthesis of Aminocarbonyl *N*-Acyldhydrazones by a Three-Component Reaction of Isocyanides, Hydrazonoyl Chlorides, and Carboxylic Acids. *Org. Lett.* **2014**, *16*, 5332–5335. [[CrossRef](#)]
33. Remy, R.; Bochet, C.G. Application of Photoclick Chemistry for the Synthesis of Pyrazoles via 1,3-Dipolar Cycloaddition between Alkynes and Nitrilimines Generated In Situ. *Eur. J. Org. Chem.* **2018**, *2018*, 316–328. [[CrossRef](#)]
34. Kuznetsova, O.Y.; Antipin, R.L.; Udina, A.V.; Krasnovskaya, O.O.; Beloglazkina, E.K.; Terenin, V.I.; Koteliarsky, V.E.; Zyk, N.V.; Majouga, A.G. An Improved Protocol for Synthesis of 3-Substituted 5-Arylidene-2-Thiohydantoins: Two-Step Procedure Alternative to Classical Methods. *J. Heterocycl. Chem.* **2016**, *53*, 1570–1577. [[CrossRef](#)]
35. Sun, Y.; Ding, M.W. Synthesis and Fungicidal Activities of 2-Alkylthio-5-Phenylmethylene-4H-Imidazol-4-Ones. *Phosphorus Sulfur. Silicon Relat. Elem.* **2003**, *178*, 2137–2145. [[CrossRef](#)]
36. Ding, M.W.; Sun, Y.; Liu, Z.J. An Efficient Synthesis of 2-Alkylthio-5-Phenylmethylidene-4H-Imidazolin-4-Ones. *Synth. Commun.* **2003**, *33*, 1267–1274. [[CrossRef](#)]
37. Renault, S.; Bertrand, S.; Carreaux, F.; Bazureau, J.P. Parallel Solution-Phase Synthesis of 2-Alkylthio-5-Arylidene-3,5-Dihydro-4H-Imidazol-4-One by One-Pot Three-Component Domino Reaction. *J. Comb. Chem.* **2007**, *9*, 935–942. [[CrossRef](#)] [[PubMed](#)]
38. Papadopoulos, S.; Stephanidou-Stephanatou, J. 1,3-Dipolar Cycloaddition Reactions of Nitrilimines with 1-aryl-4,5-dihydro-3,4,4-trimethyl-5-methylene-1*H*-pyrazoles. Synthesis of 6-aryl-8,9,9-trimethyl-1,2,6,7-tetraazaspiro[4.4]Nona-2,7-dienes. *J. Heterocycl. Chem.* **1987**, *24*, 309–312. [[CrossRef](#)]

39. Baba, N.; Soufiaoui, M. Cycloaddition Dipolaire 1,3 Des 4-Arylidene Oxazol-5- Ones Avec La Diphenylnitrilimine. *Tetrahedron Lett.* **1990**, *31*, 1709–1712. [[CrossRef](#)]
40. Abdel Hafez, N.A.; Hassaneen, H.M.E.; Farghaly, T.A.; Riyadh, S.M.; Elzahabi, H.S.A. Synthesis of New Bis-Spiropyrazoles as Antitumor Agents under Ultrasound Irradiation. *Mini-Rev. Med. Chem.* **2018**, *18*, 631–637. [[CrossRef](#)]
41. Liu, B.; Li, X.F.; Liu, H.C.; Yu, X.Y. Unexpected Nitrilimine Cycloaddition of Thiazolo[3,2-a]Pyrimidine Derivatives. *Tetrahedron Lett.* **2013**, *54*, 6952–6954. [[CrossRef](#)]
42. Farghaly, T.A.; Abbas, I.M.; Hassan, W.M.I.; Lotfy, M.S.; Al-Qurashi, N.T.; Hadda, T. Ben Structure Determination and Quantum Chemical Analysis of 1,3-Dipolar Cycloaddition of Nitrile Imines and New Dipolarophiles and POM Analyses of the Products as Potential Breast Cancer Inhibitors. *Russ. J. Org. Chem.* **2020**, *56*, 1258–1271. [[CrossRef](#)]

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