Journal Pre-proof

Facile synthesis of phthalidyl fused spiro thiohydantoins through silica sulfuric acid induced oxidative rearrangement of ninhydrin adducts of thioureas

Subhro Mandal, Animesh Pramanik

PII: S0040-4020(19)31225-6

DOI: https://doi.org/10.1016/j.tet.2019.130817

Reference: TET 130817

To appear in: *Tetrahedron*

Received Date: 12 September 2019

Revised Date: 20 November 2019

Accepted Date: 21 November 2019

Please cite this article as: Mandal S, Pramanik A, Facile synthesis of phthalidyl fused spiro thiohydantoins through silica sulfuric acid induced oxidative rearrangement of ninhydrin adducts of thioureas, *Tetrahedron* (2019), doi: https://doi.org/10.1016/j.tet.2019.130817.

Graphical Abstract

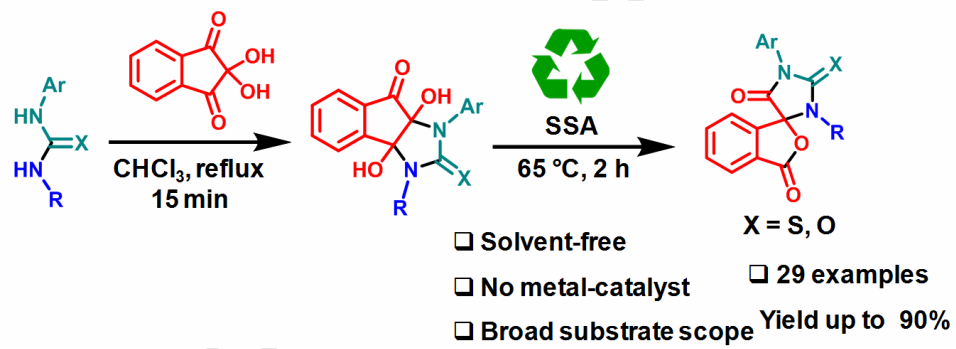
Facile synthesis of phthalidyl fused spiro thiohydantoins through silica sulfuric acid induced oxidative rearrangement of ninhydrin adducts of thioureas

Subhro Mandal[a], Animesh Pramanik[a,*]

[a]*Department of Chemistry, University of Calcutta, 92, A. P. C. Road, Kolkata-700 009, India*

Fax: +91-33-2351-9755; Tel: +91 9830107470

E-mail: pramanikanimesh61@gmail.com



Facile synthesis of phthalidyl fused spiro thiohydantoins through silica sulfuric acid induced oxidative rearrangement of ninhydrin adducts of thioureas

Subhro Mandal[a], Animesh Pramanik[a,*]

[a]*Department of Chemistry, University of Calcutta, 92, A. P. C. Road, Kolkata-700 009, India*

Fax: +91-33-2351-9755; Tel: +91 9830107470

E-mail: pramanikanimesh61@gmail.com

ABSTRACT

A one-pot three-component sequential synthetic protocol produces structurally and biologically important phthalidyl fused spiro *N,N'*-disubstituted thiohydantoins from readily available aromatic isothiocyanates, primary amines and ninhydrin. In this three-step synthesis while the initial two steps are catalyst-free, in the final step silica sulfuric acid (SSA) induces an oxidative rearrangement in [3.3.0]-bicyclic 1,2-diol adducts of ninhydrin and thioureas under solvent-free condition to generate the final products spiro-fused thiohydantoins. The adequate acidity of SSA in cooperation with moderate oxidizing property promotes a facile oxidative rearrangement in 1,2-diol intermediates to produce the spiro-fused thiohydantoins with diverse functionalities. Easy recyclability of SSA, good to excellent yield of the products, wider substrate scope, shorter reaction time, solvent-free two steps out of three and high atom economy make this method attractive and practicable.

Keywords: Thiohydantoins, Phthalide, Spiro-fused bi-heterocycles, Heterogeneous solid-support, Recyclable SSA, Solvent-free oxidative rearrangement

1. Introduction

2-thioxoimidazolidin-4-ones (thiohydantoins), a class of nitrogen and sulfur containing heterocyclic analogues of imidazolidine family are found to possess a diverse

range of biological and pharmacological activities. For example, *N*-substituted thiohydantoins are promising pharmacophores due to their antifungal [1], anti-prostate cancer [2] (compound I, Fig. 1), and antiandrogenic activities [3] (compound II, Fig. 1). 5-arylidene thiohydantoins are another group of structural units that act as antimycobacterial agents [4] as well as NADPH oxidase (NOX) inhibitiors [5]. Moreover, a number of 5-arylidene thiohydantoin analogues are used for the treatment of schistosomiasis infections [6] (compound III, Fig. 1). Therefore, the synthesis of thiohydantoin scaffolds and assessment of their biological activities generate considerable interest among the synthetic and pharmaceutical chemists. However, a literature survey revealed that only a few synthetic procedures have been reported for spiro-fused thiohydantoin derivatives [7-10]. These conformationally constrained sulfur containing bi-heterocyclic spiro frameworks might be significant for exhibiting drug-like activities inside the living body [7]. Recently, Takahashi and co-workers developed a one-step synthetic route to produce 3-allyl-2-thiohydantoin-5-spiro-2'-piperidine and evaluated it as a potential anti-mutagenic agent [8] (compound IV, Fig. 1). In 2009, Rutjes *et al.* reported a base catalysed formation of pyrrolidine fused spiro thiohydantoins which were testified as potential CNS ligands [9] (compound V, Fig. 1). Docsa *et al.* assembled a novel semirigid heterocyclic motif by spiro-fusion of glucopyranosyl unit to thiohyantoin ring system and the preliminary studies revealed this composite as antidiabetic agent [10] (compound VI, Fig. 1). Because of their biological importance, the synthesis of new spiro-fused thiohydantoin cores remains an immensely valid exercise. Keeping this in view, we would like to explore the synthetic aspect of bioactive phthalidyl[11] fused spiro thiohydantoins. The structural complexity of this spiro-fused skeleton along with its medicinal potential due to the presence of both bioactive heterocyclic core thiohydantoin and phthalide, stimulated us to design a general and efficient synthetic strategy, feasible under benign reaction conditions.

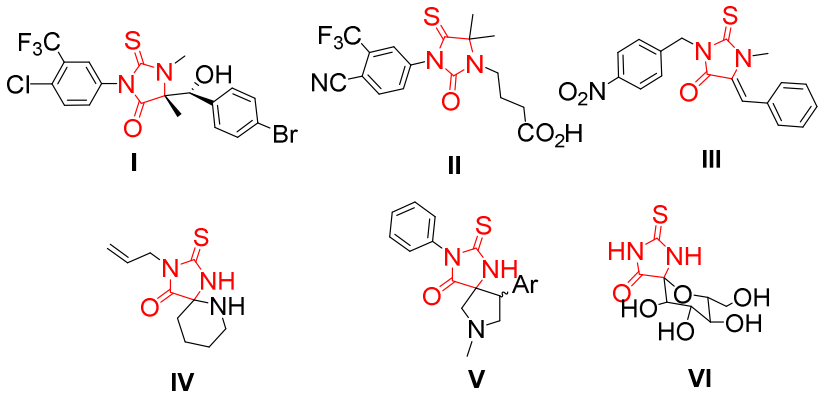


Fig. 1. Selected bio-active thiohydantoin molecules.

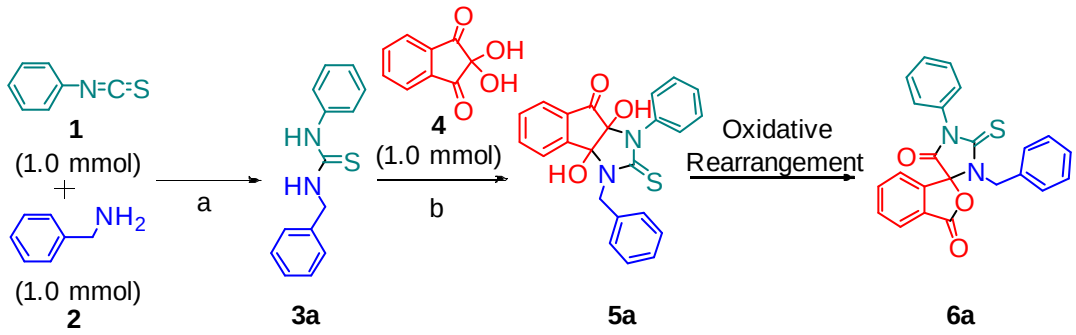
The multicomponent domino reactions have drawn considerable attention of the synthetic organic chemists due to their inherent ability to introduce structural complexity in organic molecules through convergent addition of the starting materials. In addition, high atom economy and short reaction time make this protocol strategically efficient [12,13]. On the other hand, the implementation of heterogeneous solid-support/catalyst in organic reactions under solvent-free condition offers several advantages such as elimination of hazardous solvent and easy recovery and recyclability of the solid-support/catalyst which make the process economically viable. Moreover, the wide surface area of the solid-support absorbs more number of reacting substances which can interact rapidly with large number of catalytic active sites. By virtue of these, the heterogeneous solid-support promotes efficient organic transformations, and amazingly in some cases in a chemo- or regio-selective manner [14,15]. Silica sulfuric acid (SiO_2-OSO_3H or SSA), a familiar heterogeneous acidic solid-support, easily prepared from silica gel and chlorosulfonic acid, has been exploited in various organic reactions successfully [16-20]. Now we would like to introduce a facile SSA mediated solvent-free intramolecular rearrangement of 3a,8a-dihydroxy-2-thioxo-indenoimidazolones, the [3.3.0]-bicyclic 1,2-diol intermediates derived from the condensation of thioureas and ninhydrin. The acidic and oxidizing property of SSA competently assisted the oxidative rearrangement in 1,2-diol intermediates to produce spiro-

fused *N,N'*-disubstituted thiohydantoins through a number of bond-breaking and bond-formation on the surface of the solid-support.

2. Results and Discussion

In search of an optimal reaction condition, an exploratory study was initiated by taking 1,2-diol intermediate **5a** as the model substrate (Scheme 1, Table 1). A typical one-pot sequential addition of phenyl isothiocyanate **1**, benzylamine **2** and ninhydrin **4** at open-air delivered *N*-benzyl-*N'*-phenyl-3a,8a-dihydroxy-2-thioxo-indenoimidazolone intermediate **5a** in almost quantitative yield (Scheme 1). First, the rapid formation of *N*-benzyl-*N'*-phenylthiourea **3a** was achieved within 2-3 minutes by successive addition of phenyl isothiocyanate **1** (1.0 mmol) and benzylamine **2** (1.0 mmol) under neat condition at 0 °C. Then the crude product **3a** (1.0 mmol) and ninhydrin **4** (1.0 mmol) were dissolved in 10 mL chloroform and the resulting mixture was refluxed for 15 minutes to produce the condensation product **5a**. Subsequently, the intermediate **5a** which preferentially persists in bicyclo[3.3.0]-hemiketal form was screened in presence of various solvents, solid-supports and catalysts at different temperatures to find out the optimal reaction condition for rearrangement in the final step of the synthesis (Table 1). Initially, **5a** (1.0 mmol) was dissolved in different polar protic solvents such as water and ethanol, and the reaction mixtures were refluxed without adding any catalyst. But in both the cases no product was formed even after 10 h of refluxing (Table 1, entries 1 and 2). A Similar outcome was also observed in refluxing acetic acid medium containing **5a** (Table 1, entry 3). Surprisingly, when 1 mol% of sulfuric acid was added as catalyst to acetic acid a new compound was generated from **5a** upon 6 h of reflux. Chromatographic purification and spectroscopic analysis revealed the formation of the desired product **6a**, although the yield was only 20% (Table 1, entry 4). The sulfuric acid which acts as a proton source, as well as an oxidizing agent, was suitable to promote the product formation by virtue of these properties.

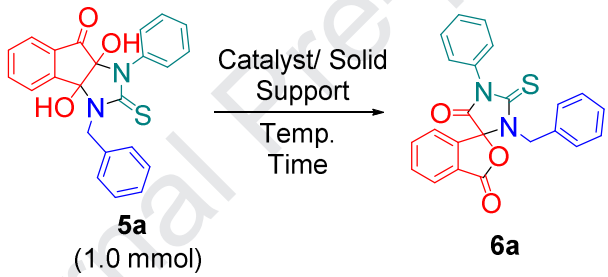
Unfortunately, further addition of sulfuric acid resulted adversely as the reaction mixture was charred due to high acidity (Table 1, entries 5 and 6). Then we looked for an effective acid-catalyst which will display oxidizing property without damaging the reaction mass at elevated temperature. Therefore, we implemented melamine sulfonic acid (MSA), PEG sulfonic acid (PEG-OSO_3H) and silica sulfuric acid (SSA) as different heterogeneous solid-supports. A uniform composition of **5a** (1.0 mmol) and heterogeneous solid-support (300 mg) was heated at 80 °C in absence of solvent. In case of MSA and PEG-OSO_3H very low yield of **6a** was observed even after 10 h of continuous heating (Table 1, entries 7 and 8). However, an effective result was evolved in case of SSA after 2 h of heating which produced **6a** in ~ 50% yield (Table 1, entry 9). Interestingly, when the amount of SSA was enhanced to 400 mg, the yield of **6a** was also increased to ~65% (Table 1, entry 10). Likewise, 600 mg of SSA load boosted the yield up to ~75 %, which remained unchanged till the addition of 700 mg of SSA (Table 1, entries 11-13). Surprisingly, further addition of SSA caused a sharp fall in the product yield (Table 1, entries 14 and 15). This observation suggested that the presence of moderately strong sulfonic acid group on the surface of SSA causes decomposition of the product **6a** at high temperature. Upon lowering the reaction temperature from 80 °C to 65 °C the yield of the product **6a** was improved up to ~ 83% using 600 mg of SSA (Table 1, entries 16 and 17). But further lowering of the reaction temperature caused worsening of the product yield (Table 1, entry 18). Therefore, a series of studies established that the maximum yield of **6a** (~ 83%) can be obtained through heating of **5a** (1.0 mmol) at 65 °C for 2 h in presence of 600 mg of SSA under solvent-free condition.



Scheme 1. (a) Neat condition, 0 °C, 2-3 min; (b) $CHCl_3$, reflux, 15 min. Yields in the initial two steps are quantitative.

Table 1

Optimization of reaction conditions for the synthesis of 3-benzyl-1-phenyl-2-thioxo-3'*H*-spiro[imidazolidine-4,1'-isobenzofuran]-3',5-dione **6a** from **5a**.[a]



Entry	Solvent (10 mL)	Catalyst/ solid-support	Amount	Temp.(°C)	Time (h)	Yield[b] (%)
1	H_2O	-	-	100	10	-
2	EtOH	-	-	80	10	-
3	AcOH	-	-	110	10	-
4	AcOH	H_2SO_4	1 mol %	110	6	20
5	AcOH	H_2SO_4	2 mol %	110	6	18
6	AcOH	H_2SO_4	3 mol %	110	6	12
7	-	MSA	300 mg	80	10	15
8	-	PEG-OSO_3H	300 mg	80	10	17
9	-	SSA	300 mg	80	2	50

10	-	SSA	400 mg	80	2	65
11	-	SSA	500 mg	80	2	70
12	-	SSA	600 mg	80	2	75
13	-	SSA	700 mg	80	2	75
14	-	SSA	800 mg	80	2	68
15	-	SSA	1000 mg	80	2	45
16	-	SSA	600 mg	70	2	80
17	**-**	**SSA**	**600 mg**	**65**	**2**	**83**
18	-	SSA	600 mg	60	2	75

[a]Substrate **5a** (1.0 mmol) was treated with different catalysts or solid-support or in different solvents and heated at different temperatures (**bold row 17 indicates the optimized reaction conditions**). [b]Isolated yield of **6a** in the final step

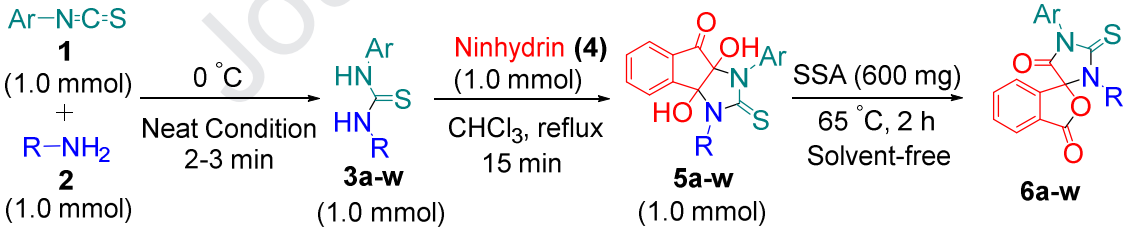
The substrate scope of the present synthetic strategy was thoroughly investigated under the optimized reaction condition (Table 1, entry 17). Initially, a series of *N*,*N*'-disubstituted thioureas (**3a-w)** were synthesized by addition of differently substituted aromatic isothiocyanates **1** with primary amines **2**. Then the mixtures of thioureas **3** and ninhydrin **4** in chloroform were refluxed for 15 minutes to produce a broad spectrum of 1,2-diol intermediates **5a-w** (Table 2). It was observed that the nucleophilicity of the two nitrogen atoms of the disubstituted thioureas (**3a-w**) are different. The nitrogen atom attached to the aryl group is less nucleophilic due to the lone pair delocalization with the aromatic ring which makes the nitrogen a hard centre. On the other hand, the nitrogen atom attached to the aliphatic group is more nucleophilic and acts as a soft centre. In case of ninhydrin, the presence of two strong electron-withdrawing carbonyl groups makes the C-2 centre as a hard site. Thereafter a preferential hard-hard interaction occurred during the condensation of ninhydrin and thioureas to produce particularly one isomeric 1,2-diol intermediate through a regioselective reaction (Table 2, **5a-w**). All the intermediates **5a-w** with electron-withdrawing

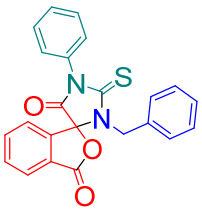
as well as electron-donating substituents were successfully rearranged by SSA to the desired spiro-fused thiohydantoins **6a-w** under the optimized reaction conditions in good to excellent yield (Table 2). In general, the presence of sterically hindered substituents at R caused lowering of the overall yield of the products (Compounds **6f**, **6g** and **6u**, Table 2). The ^{13}C NMR spectra of the purified solid products **6a-w** displayed three characteristic carbon peaks at ~ δ 166.6, 166.0 and 91.0 indicating the lactone carbonyl carbon, amide carbonyl carbon and spiro carbon respectively. This novel synthetic strategy was further extended to synthesize a series of new spiro-fused hydantoin derivatives (**7a-f**) using SSA (Table 3) instead of the strongly oxidizing $NaIO_4$ as reported earlier [21].

The structures of the synthesized compounds **6** and **7** were confirmed by FTIR, ^{1}H and ^{13}C NMR spectroscopy, HRMS and elemental analysis. Moreover, single-crystal X-ray diffraction analysis confirmed the formation of compounds **6a** and **6c** (Fig. 2).

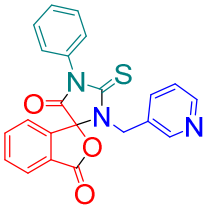
Table 2

Library synthesis of *N*,*N'*-disubstituted-2-thioxo-3'*H*-spiro[imidazolidine-4,1'-isobenzofuran]-3',5-diones **6** from **5**.[a]

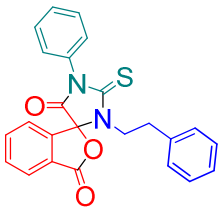




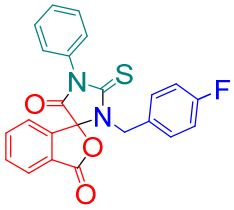
6a (83%)



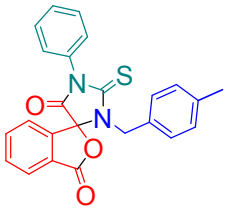
6b (80%)



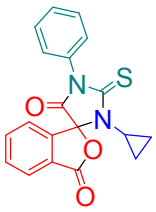
6c (88%)



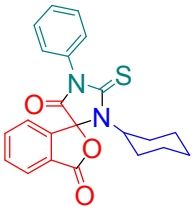
6d (80%)



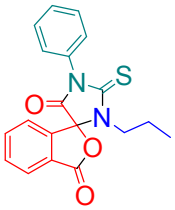
6e (85%)



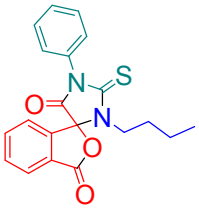
6f (68%)



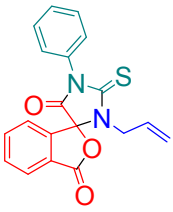
6g (70%)



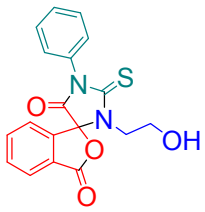
6h (84%)



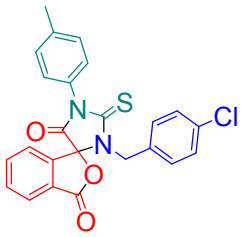
6i (84%)



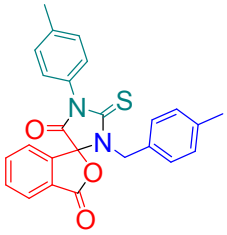
6j (78%)



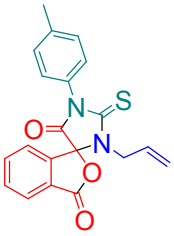
6k (75%)



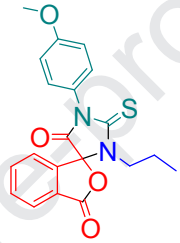
6l (82%)



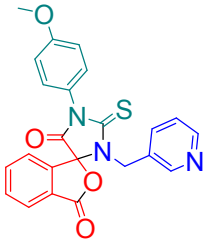
6m (85%)



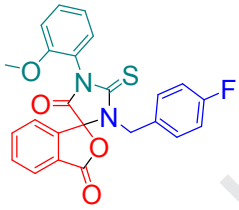
6n (79%)



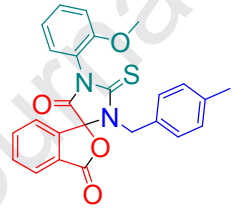
6o (86%)



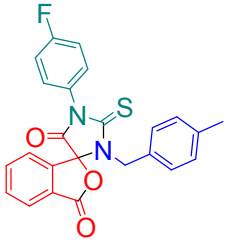
6p (84%)



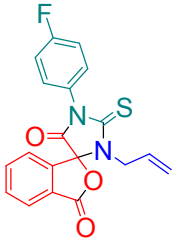
6q (82%)



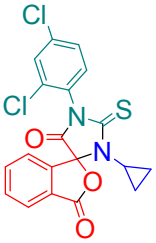
6r (87%)



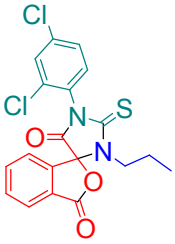
6s (90%)



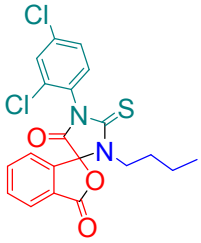
6t (88%)



6u (70%)



6v (85%)

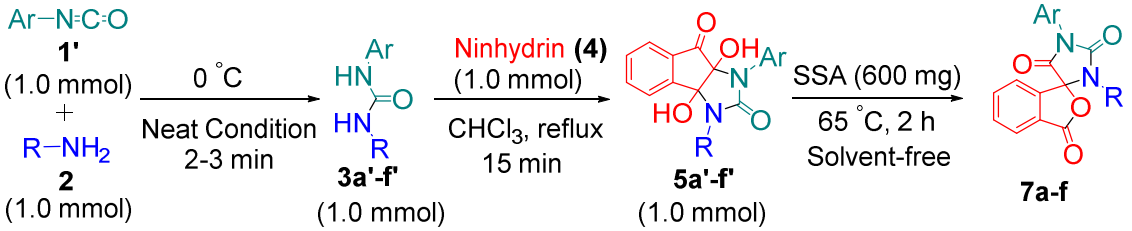


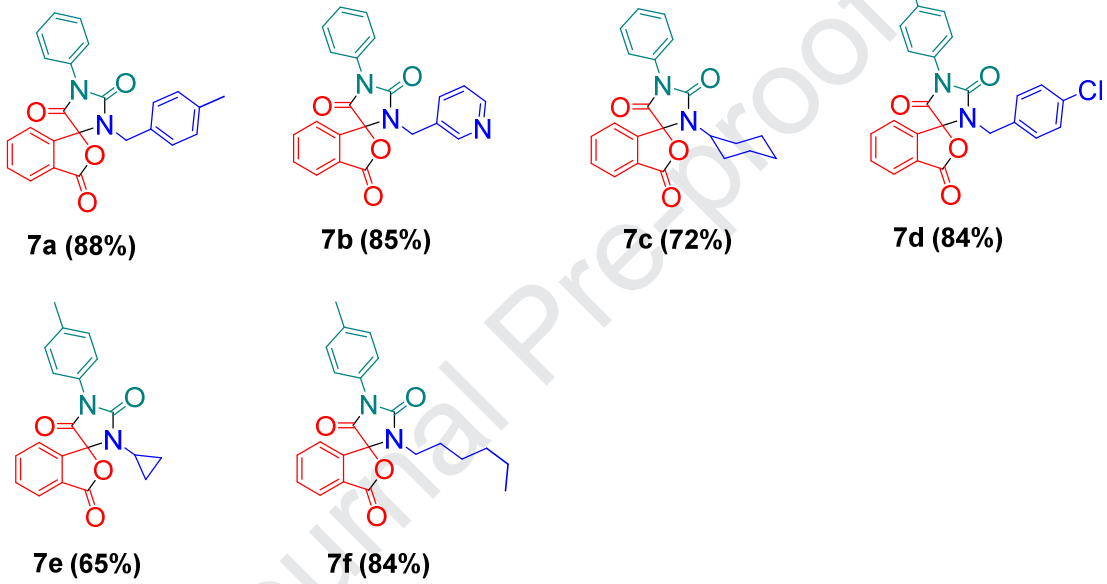
6w (86%)

[a] Isolated yields (%) of **6** in the final step; yields in the initial two steps are quantitative.

Table 3

Library synthesis of *N*,*N'*-disubstituted-2-oxo-3'*H*-spiro[imidazolidine-4,1'-isobenzofuran]-3',5-diones **7** from **5'**.[a]





[a] Isolated yields (%) of 7 in the final step; yields in the initial two steps are quantitative.

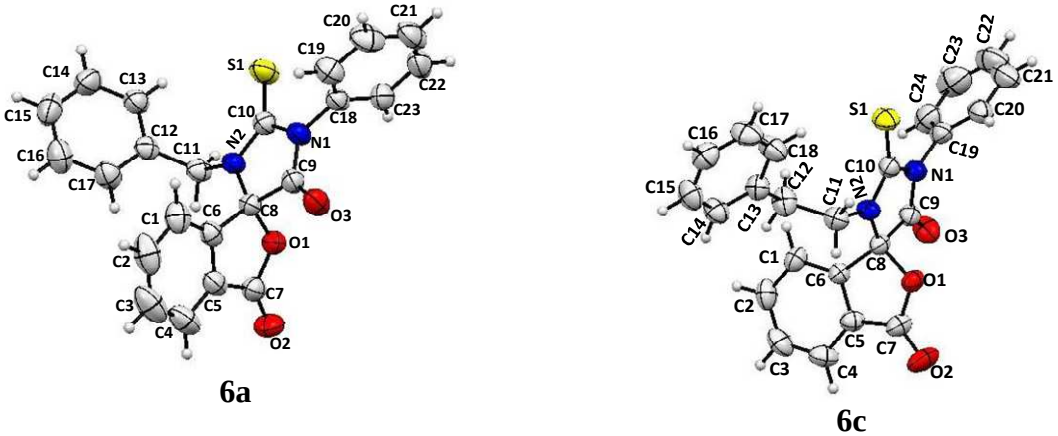
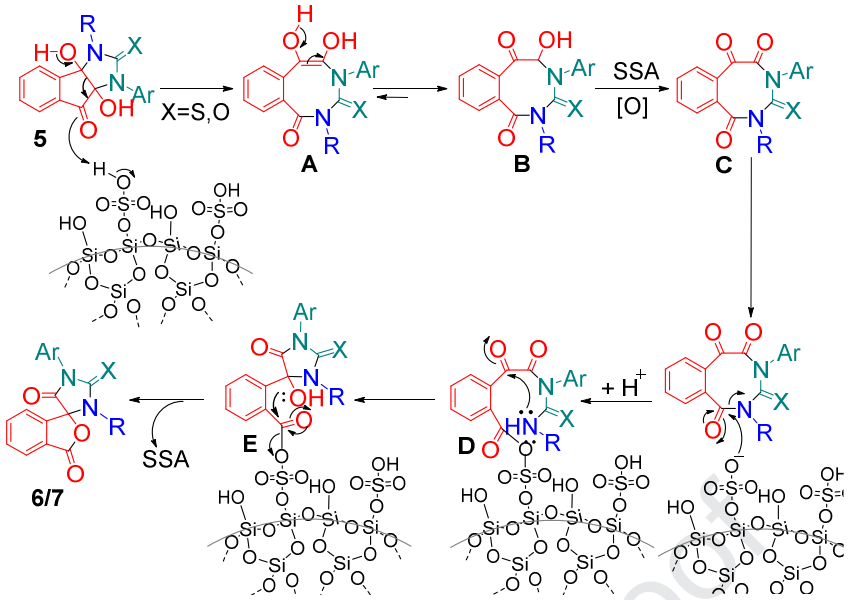


Fig. 2. ORTEP diagrams of compounds **6a** (CCDC 1858914) & **6c** (CCDC 1921631). Thermal ellipsoids are shown at 50% probability.

The surface of the heterogeneous SSA is embedded with a large number of active sites containing oxo-, -SO_3H and -OH functional groups. The sulfonic acid groups rapidly transfer protons for catalysis of the reaction and also act as a binding and activating group of the 1,2-diol intermediates **5**. The active sites of SSA are also responsible for carrying out oxidation at the intermediate stage of the reaction. A plausible mechanistic pathway has been depicted in Scheme 2 to rationalize the product formation, where the dual role of SSA has been emphasized in the oxidative rearrangement. At first the intermediate **5** gets protonated from the sulfonic acid group and consequently the central C-C bond is ruptured to furnish eight-membered amide intermediate **A** which readily tautomerizes to α-hydroxyketo intermediate **B**. Next, the intermediate **B** experiences SSA assisted oxidation to form eight-membered intermediate **C** with vicinal dicarbonyl groups. Thereafter, a nucleophilic attack of SiO_2-OSO_3^- causes the breakage of the cyclic amide linkage to produce a substructure **D**. Subsequently a facile intramolecular attack of the free NH group of **D** to one of the vicinal dicarbonyl groups produces thiohydantoin/hydantoin intermediate **E**. In the final step, the nucleophilic attack of the free hydroxyl group of **E** to the ester carbonyl produces spiro-fused thiohydantoins/hydantoins **6/7** with simultaneous regeneration of SSA. Therefore, several bond-breaking and bond-construction on the surface of SSA lead to the facile formation of spiro-fused *N*,*N*′-disubstituted thiohydantoins/hydantoins under mild and solvent-free conditions.



Scheme 2. A plausible mechanistic pathway for the formation of spiro-fused thiohydantoins/hydantoins **6**/**7** on the SSA surface.

As SSA has been implemented as solid-support in the synthesis, the ease of separation, as well as its scope of reusability was examined to assess the industrial viability of the method. In the present synthesis, the SSA particles were easily separated from the reaction mixture by sonication in ethylacetate followed by simple filtration. Then straightforward washing of SSA with ethylacetate made them suitable for application in the next catalytic cycle. This way the SSA was employed in the synthesis of **6a** for six catalytic cycles. Notably the yield of the product **6a** altered from 83% to 80% which showed an insignificant loss of the catalytic activity of SSA even after repeated applications (Fig. 3).

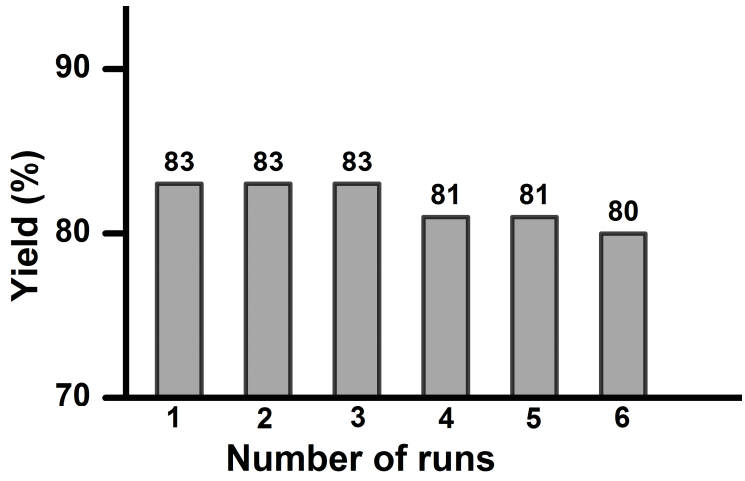


Fig. 3. Recyclability of SSA in the synthesis of **6a**.

3. Conclusions

In conclusion, we have developed a one-pot synthetic method for the construction of drug-like phthalidyl fused spiro thiohydantoin/hydantoin scaffolds from easily available starting materials within a short time. The cooperative acidic and oxidizing properties of SSA have been successfully exploited in the facile synthesis of spiro-fused thiohydantoins/hydantoins with diverse functionalities. Easy recyclability of SSA, good to excellent yield of the products, wider substrate scope, solvent-free two steps out of three and high atom economy make this method attractive and practicable. This multicomponent synthesis involving SSA represents an effective one-pot general approach to construct complex spiro-fused thiohydantoins/hydantoins with considerable diversity and variation from readily available substrates.

4. Experimental Section

4.1. General Information

The solvents and chemicals were procured from commercial chemical suppliers and used without further purification. Melting points were recorded in open capillary tubes and were uncorrected. Perkin-Elmer 782 spectrophotometer was used for FTIR spectra. Coloumn

chromatography was performed with neutral alumina (Merck) and using hexane/ethylacetate solvent system. ^{1}H (300 MHz & 500 MHz) and ^{13}C NMR (75 MHz & 126 MHz) spectra were recorded on Bruker instrument (300 MHz & 500 MHz) in $CDCl_3$ and DMSO-d_6. Some ^{1}H (400 MHz) and ^{13}C NMR (101 MHz) spectra were recorded on JEOL instrument (400 MHz) in $CDCl_3$. HRMS spectra were recorded using Xevo G2-S QTof instrument. Elemental analyses (C, H and N) were done in Perkin-Elmer 2400 elemental analyzer. The X-ray diffraction data for crystallized compounds were collected with MoK_α radiation at 296 K using the Bruker APEX-II CCD System.

4.2. General procedure for the synthesis of *N*,*N'*-disubstituted-3a,8a-dihydroxy-2-thioxo/oxo-2,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazol-8(1*H*)-ones (**5a-w/ 5a'-f'**)

At first, the synthesis of *N*,*N'*-disubstituted-thioureas/ureas (**3a-w/ 3a'-f'**) were carried out within 2-3 minutes by successive addition of substituted isothiocyanate/isocyanate **1/1'** (1.0 mmol) and primary amines **2** (1.0 mmol) under neat condition at 0 °C in a 100 mL round bottom flask. Then the crude thiourea/urea derivatives (**3a-w/ 3a'-f'**) were dissolved in 10 mL chloroform. To the above solution 178 mg (1.0 mmol) of ninhydrin **4** was added and the mixture was subjected to reflux for 15 minutes. Completion of the reaction was monitored by TLC. Thereafter, chloroform was removed under reduced pressure. Instead of tedious work-up procedure and chromatographic purification the crude mixture was kept in high vacuum till solid crystalline intermediate **5** appeared. The resulting solid product **5** was characterized by ^{1}H and ^{13}C NMR spectroscopy. Presence of two characteristic carbon peaks at ~ δ 90.0 in ^{13}C NMR spectra suggested the formation of 1,2-diol intermediates (**5a-w/ 5a'-f')**.

4.3. Spectroscopic data of some representative intermediates **5**

4.3.1. 3-benzyl-3a,8a-dihydroxy-1-phenyl-2-thioxo-2,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazol-8(1*H*)-one (**5a**)

Yield 386 mg (~ 96%) as yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} = 7.82 (d, *J* = 7.5 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 1H;), 7.54 (t, *J* = 7.5 Hz, 1H), 7.44-7.42 (m, 2H), 7.40-7.37 (m, 5H), 7.28-7.22 (m, 6H), 5.30-5.22 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ_{ppm} = 193.8, 181.5, 147.8, 137.6, 137.1, 135.6, 132.5, 131.2, 130.5, 129.18, 129.12, 128.5, 127.6, 127.4, 125.4, 125.1, 92.0, 89.7, 46.9.

4.3.2. 3-(4-fluorobenzyl)-3a,8a-dihydroxy-1-phenyl-2-thioxo-2,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazol-8(1*H*)-one (**5d**)

Yield 410 mg (~ 98%) as yellow solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ_{ppm} = 7.81-7.75 (m, 2H), 7.70 (s, 1H), 7.63-7.57 (m, 3H), 7.41-7.33 (m, 3H), 7.26-7.22 (m, 4H), 7.09-6.98 (m, 2H), 5.22 (d, *J* = 16.5 Hz, 1H), 5.00 (d, *J* = 16.5 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ_{ppm} = 194.5, 180.1, 161.3 (d, *J* = 240.52 Hz), 159.7, 149.0, 137.3, 136.8, 134.5, 132.9, 131.3, 131.1, 130.9, 129.5 (d, *J* = 4.12 Hz), 128.6, 128.1, 126.2, 124.4, 114.9 (d, *J* = 20.92 Hz), 92.0, 91.6, 45.6.

4.3.3. 3-cyclopropyl-3a,8a-dihydroxy-1-phenyl-2-thioxo-2,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazol-8(1*H*)-one (**5f**)

Yield 335 mg (~ 95%) as white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ_{ppm} = 8.06 (d, *J* = 6.3 Hz, 1H), 7.91-7.86 (m, 1H), 7.77 (d, *J* = 6.3 Hz, 1H), 7.66-7.55 (m, 2H), 7.29-7.26 (m, 4H), 7.05-7.03 (m, 2H), 1.91-1.81 (m, 1H), 0.90-0.88 (m, 2H), 0.71-0.68 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ_{ppm} = 194.8, 181.8, 148.6, 137.4, 137.2, 133.1, 131.5, 131.1, 128.8, 128.2, 126.4, 124.6, 92.3, 90.9, 27.4, 9.2, 5.3.

4.3.4. 3-butyl-3a,8a-dihydroxy-1-phenyl-2-thioxo-2,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazol-8(1*H*)-one (**5i**)

Yield 364 mg (~ 99%) as yellow solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ_{ppm} = 7.90 (d, *J* = 6.9 Hz, 1H), 7.75-7.68 (m, 4H), 7.47-7.40 (m, 3H), 7.23 (s, 2H), 6.72 (d, *J* = 6.6 Hz, 1H), 3.79-3.74 (m, 2H), 1.87-1.77 (m, 1H), 1.74-1.66 (m, 1H), 1.40-1.30 (m, 2H), 0.95 (t, *J* =

7.1 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ_{ppm} = 196.2, 179.0, 148.9, 137.0, 136.8, 132.7, 131.3, 131.2, 128.7, 128.3, 125.7, 124.4, 92.1, 90.1, 43.2, 30.4, 20.2, 14.1.

4.3.5. 3-allyl-3a,8a-dihydroxy-1-phenyl-2-thioxo-2,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazol-8(1*H*)-one (**5j**)

Yield 340 mg (~ 97%) as yellow solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ_{ppm} = 8.01 (d, *J* = 7.8 Hz, 1H), 7.90 (t, *J* = 7.5 Hz, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.71-7.60 (m, 3H), 7.43-7.35 (m, 3H), 7.22-7.19 (m, 2H), 5.91-5.79 (m, 1H), 5.16 (d, *J* = 17.4 Hz, 1H), 5.05 (d, *J* = 10.2 Hz, 1H), 4.57-4.52 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ_{ppm} = 194.2, 179.0, 148.8, 137.0, 136.9, 134.4, 132.7, 131.1, 130.8, 130.6, 128.3, 127.7, 126.2, 124.1, 116.8, 91.7, 91.1, 45.2.

4.3.6. 3a,8a-dihydroxy-3-(2-hydroxyethyl)-1-phenyl-2-thioxo-2,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazol-8(1*H*)-one (**5k**)

Yield 348 mg (~ 98%) as white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ_{ppm} = 8.08-8.04 (m, 1H), 7.99-7.94 (m, 1H), 7.84-7.79 (m, 1H), 7.74-7.59 (m, 3H), 7.39-7.37 (m, 3H), 7.19-7.18 (m, 2H), 4.95 (s, 1H), 4.04-3.93 (m, 1H), 3.85-3.77 (m, 2H), 3.63-3.53 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ_{ppm} = 194.3, 179.1, 149.2, 137.4, 137.1, 133.0, 131.5, 130.8, 128.6, 128.0, 125.7, 124.5, 91.6, 91.2, 58.7, 45.3.

4.3.7. 3a,8a-dihydroxy-1-(4-methoxyphenyl)-3-(pyridin-3-ylmethyl)-2-thioxo-2,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazol-8(1*H*)-one (**5p**)

Yield 425 mg (~ 98%) as yellow solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ_{ppm} = 8.43-8.30 (m, 2H), 7.70-7.56 (m, 7H), 7.16-7.07 (m, 3H), 6.89 (s, 2H), 5.16-5.07 (m, 2H), 3.72 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ_{ppm} = 194.5, 180.2, 159.1, 149.1, 148.0, 137.1, 135.4, 134.1, 133.1, 132.0, 131.5, 129.8, 126.1, 124.6, 123.3, 114.0, 91.9, 91.4, 55.7, 44.2.

4.3.8. 3a,8a-dihydroxy-1-(2-methoxyphenyl)-3-(4-methylbenzyl)-2-thioxo-2,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazol-8(1*H*)-one (**5r**)

Yield 440 mg (~ 98%) as yellow solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ_{ppm} = 7.68-7.65 (m, 1H), 7.50-7.49 (m, 3H), 7.38 (d, *J* = 9.0 Hz, 2H), 7.31-7.22 (m, 2H), 7.05-7.03 (m, 2H), 6.93-6.91 (m, 4H), 5.12 (d, *J* = 16.2 Hz, 1H), 4.91 (d, *J* = 16.8 Hz, 1H), 3.36 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ_{ppm} = 193.5, 180.2, 156.1, 148.5, 135.9, 135.4, 135.2, 133.4, 132.1, 130.8, 129.8, 128.4, 127.3, 125.9, 125.8, 123.4, 120.2, 112.4, 92.0, 90.3, 55.4, 45.7, 20.8.

4.4. General procedure for the synthesis of *N,N'*-disubstituted-2-thioxo-3'*H*-spiro[imidazolidine-4,1'-isobenzofuran]-3',5-diones (**6a-w**) and *N,N'*-disubstituted-3'*H*-spiro[imidazolidine-4,1'-isobenzofuran]-2,3',5-triones (**7a-f**)

The synthesized intermediates (**5a-w/ 5a'-f'**, 1.0 mmol) in 100 mL round bottom flask (as described earlier) was dissolved in minimum volume of chloroform and then 600 mg of SSA was added. The mixture was stirred for 5 minutes at room temperature and then dried under vacuum. These way intermediates **5** were absorbed on the surface of SSA which was then subjected to heating at 65 °C on an oil bath. After 2 h continuous heating the maximum conversion of the intermediates was observed (as monitored by TLC). After cooling at room temperature ethylacetate was added to the mass which was sonicated and then filtered through Whatman-42 filter paper followed by washing with ethylacetate (4 × 5 ml) to separate out organic compounds from SSA surface. Then ethylacetate was removed from the filtrate under vacuum to collect the crude product which was purified over neutral alumina coloumn chromatography using 20% ethylacetate in hexane as solvent system. The purified solid products **6/7** were characterized by ^{1}H and ^{13}C NMR spectroscopy. Presence of three characteristic carbon peaks at δ ~ 166.6, 166.0 & 91.0 in ^{13}C NMR spectra indicates the lactone carbonyl carbon, amide carbonyl carbon of thiohydantoin ring and spiro carbon respectively. In addition HRMS values strongly suggested the formation of the desired spiro derivatives **6/7**.

4.4.1. 3-benzyl-1-phenyl-2-thioxo-3'*H*-spiro[imidazolidine-4,1'-isobenzofuran]-3',5-dione (**6a**)

R_f=0.50 (Hexane/Ethyl acetate 7:3); Yield 332 mg (~ 83%) as white solid; m.p. 120 °C. IR (KBr): 3100 (Ar-H), 2980 (aliphatic C-H), 1760 (lactone C=O), 1600 (amide C=O), 1150 (C=S) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 7.83 (d, *J* = 7.8 Hz, 1H), 7.50-7.36 (m, 5H), 7.33-7.27 (m, 2H), 7.04-6.91 (m, 6H), 5.08 (d, *J* = 15.3 Hz, 1H), 4.50 (d, *J* = 15.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 183.5, 166.6, 166.0, 141.0, 135.2, 134.8, 132.7, 131.8, 129.6, 129.2, 128.4, 128.36, 128.34, 128.0, 126.8, 126.2, 123.0, 91.7, 47.4. HRMS (ESI-TOF): *m/z* calcd for $C_{23}H_{16}N_2O_3S + H^+$: 401.0960 $[M + H]^+$; found: 401.0992.

4.4.2. 1-phenyl-3-(pyridin-3-ylmethyl)-2-thioxo-3'*H*-spiro[imidazolidine-4,1'-isobenzofuran]-3',5-dione (**6b**)

R_f=0.38 (Hexane/Ethyl acetate 4:6); Yield 320 mg (~ 80%) as white solid; m.p. 160 °C. IR (KBr): 3130 (Ar-H), 2988 (aliphatic C-H), 1755 (lactone C=O), 1590 (amide C=O), 1145 (C=S) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ_{ppm} = 8.43 (d, *J* = 4.0 Hz, 1H), 8.21 (s, 1H), 8.00 (d, *J* = 7.5 Hz, 1H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.59-7.48 (m, 5H), 7.39 (d, *J* = 7.0 Hz, 2H), 7.17 (d, *J* = 7.6 Hz, 1H), 7.13-7.10 (m, 1H), 5.10 (d, *J* = 15.5 Hz, 1H), 4.66 (d, *J* = 15.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ_{ppm} = 183.4, 166.3, 165.8, 149.5, 149.3, 140.7, 136.0, 135.2, 132.5, 132.4, 131.1, 129.8, 129.3, 128.2, 126.8, 126.6, 123.3, 122.9, 91.6, 44.7. Elemental analysis calcd (%) for $C_{22}H_{15}N_3O_3S$: C 65.82, H 3.77, N 10.47; found: C 65.78, H 3.80, N 10.40.

4.4.3. 3-phenethyl-1-phenyl-2-thioxo-3'*H*-spiro[imidazolidine-4,1'-isobenzofuran]-3',5-dione (**6c**)

R_f=0.46 (Hexane/Ethyl acetate 7:3); Yield 364 mg (~ 88%) as white solid; m.p. 180 °C. IR (KBr): 3132 (Ar-H), 2970 (aliphatic C-H), 1762 (lactone C=O), 1607 (amide C=O), 1158 (C=S) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 7.99 (d, *J* = 7.2 Hz, 1H), 7.73-7.65 (m,

2H), 7.48-7.44 (m, 3H), 7.41-7.37 (m, 1H), 7.34-7.31 (m, 2H), 7.17-7.11 (m, 3H), 7.00-6.97 (m, 2H), 3.85-3.75 (m, 1H), 3.44-3.34 (m, 1H), 2.93 (t, *J* = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 182.7, 166.5, 166.0, 140.9, 137.4, 135.5, 132.4, 129.6, 129.2, 128.6, 128.3, 127.2, 126.7, 126.6, 122.7, 92.3, 45.8, 34.2. HRMS (ESI-TOF): *m/z* calcd for $C_{24}H_{18}N_2O_3S$ + H^+: 415.1116 $[M + H]^+$; found: 415.1113.

4.4.4. 3-(4-fluorobenzyl)-1-phenyl-2-thioxo-3'*H*-spiro[imidazolidine-4,1'-isobenzofuran]-3',5-dione (**6d**).

R_f=0.48 (Hexane/Ethyl acetate 7:3); Yield 334 mg (~ 80%) as white solid; m.p. 152 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 7.90 (d, *J* = 7.8 Hz, 1H), 7.59-7.54 (m, 1H), 7.50-7.43 (m, 4H), 7.34-7.31 (m, 2H), 7.05-6.93 (m, 3H), 6.77-6.69 (m, 2H), 5.06 (d, *J* = 15.3 Hz, 1H), 4.53 (d, *J* = 15.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 183.5, 166.5, 166.0, 162.3 (d, *J* = 246.00 Hz), 141.0, 135.0, 132.6, 132.0, 131.2, 130.3 (d, *J* = 8.55 Hz), 129.7, 129.3, 128.3, 126.9, 126.4, 122.9, 115.3 (d, *J* = 21.75 Hz), 91.7, 46.6. HRMS (ESI-TOF): *m/z* calcd for $C_{23}H_{15}FN_2O_3S$ + H^+: 419.0865 $[M + H]^+$; found: 419.0877.

4.4.5. 3-(4-methylbenzyl)-1-phenyl-2-thioxo-3'*H*-spiro[imidazolidine-4,1'-isobenzofuran]-3',5-dione (**6e**)

R_f=0.51 (Hexane/Ethyl acetate 7:3); Yield 350 mg (~ 85%) as white solid; m.p. 110 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 7.95 (d, *J* = 7.5 Hz, 1H), 7.64-7.59 (m, 1H), 7.54-7.48 (m, 4H), 7.42-7.39 (m, 2H), 7.12 (d, *J* = 7.8 Hz, 1H), 6.92 (s, 4H), 5.09 (d, *J* = 15.0 Hz, 1H), 4.63 (d, *J* = 15.3 Hz, 1H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_c = 183.4, 166.7, 166.0, 141.1, 137.7, 134.8, 132.7, 132.1, 131.7, 129.6, 129.2, 129.0, 128.4, 128.3, 126.9, 126.2, 123.0, 91.8, 47.2, 21.0. HRMS (ESI-TOF): *m/z* calcd for $C_{24}H_{18}N_2O_3S$ + H^+: 415.1116 $[M + H]^+$; found: 415.1196.

4.4.6. 3-cyclopropyl-1-phenyl-2-thioxo-3'*H*-spiro[imidazolidine-4,1'-isobenzofuran]-3',5-dione (**6f**)

R_f=0.48 (Hexane/Ethyl acetate 7:3); Yield 240 mg (~ 68%) as white solid; m.p. 194 °C. IR (KBr): 3090 (Ar-H), 2980 (aliphatic C-H), 1750 (lactone C=O), 1590 (amide C=O), 1140 (C=S) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm} = 8.05-8.01 (m, 1H), 7.83-7.79 (m, 1H), 7.75-7.72 (m, 1H), 7.52-7.48 (m, 4H), 7.35-7.33 (m, 2H), 2.59 (s, 1H) , 0.92 (s, 1H), 0.80-0.77 (m, 1H), 0.62 (s, 1H) , 0.54-0.50 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_{ppm} = 184.2, 166.5, 166.4, 141.7, 135.4, 132.4, 132.1, 129.6, 129.2, 128.2, 127.2, 126.7, 122.1, 93.0, 27.0, 6.6, 5.0. Elemental analysis calcd (%) for $C_{19}H_{14}N_2O_3S$: C 65.13, H 4.03, N 8.00; found: C 65.11, H 4.09, N 7.92.

4.4.7. 3-cyclohexyl-1-phenyl-2-thioxo-3'*H*-spiro[imidazolidine-4,1'-isobenzofuran]-3',5-dione (**6g**)

R_f=0.55 (Hexane/Ethyl acetate 7:3); Yield 275 mg (~ 70%) as white solid; m.p. 126 °C. IR (KBr): 3110 (Ar-H), 2986 (aliphatic C-H), 1755 (lactone C=O), 1592 (amide C=O), 1135 (C=S) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 8.06 (d, *J* = 6.9 Hz, 1H), 7.85-7.73 (m, 2H), 7.60-7.50 (m, 4H), 7.40-7.36 (m, 2H), 4.38 (s, 1H), 2.07 (d, *J* = 10.8 Hz, 1H), 1.78-1.53 (m, 5H), 1.34-1.17 (m, 3H), 0.99-0.87 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 182.3, 166.8, 166.2, 142.4, 135.1, 132.6, 132.0, 129.4, 129.1, 128.4, 127.2, 126.5, 122.9, 92.3, 58.6, 30.9, 30.4, 26.0, 25.9, 24.9. Elemental analysis calcd (%) for $C_{22}H_{20}N_2O_3S$: C 67.33, H 5.14, N 7.14; found: C 67.24, H 5.21, N 7.10.

4.4.8. 1-phenyl-3-propyl-2-thioxo-3'*H*-spiro[imidazolidine-4,1'-isobenzofuran]-3',5-dione (**6h**)

R_f=0.54 (Hexane/Ethyl acetate 7:3); Yield 296 mg (~ 84%) as white solid; m.p. 110 °C. IR (KBr): 3090 (Ar-H), 2972 (aliphatic C-H), 1766 (lactone C=O), 1603 (amide C=O), 1150 (C=S) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 8.08 (d, *J* = 7.8 Hz, 1H), 7.90-7.76 (m, 2H), 7.58-7.49 (m, 4H), 7.47-7.39 (m, 2H), 3.76-3.66 (m, 1H), 3.31- 3.21 (m, 1H), 1.78-1.54 (m, 2H), 0.84 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 182.8, 166.6, 166.1,

141.1, 135.4, 132.5, 132.3, 129.5, 129.1, 128.3, 127.2, 126.6, 122.6, 92.2, 46.0, 21.5, 11.1. HRMS (ESI-TOF): *m/z* calcd for $C_{19}H_{16}N_2O_3S + H^+$: 353.0960 $[M + H]^+$; found: 353.1010.

4.4.9. 3-butyl-1-phenyl-2-thioxo-3'*H*-spiro[imidazolidine-4,1'-isobenzofuran]-3',5-dione (**6i**).

R_f=0.54 (Hexane/Ethyl acetate 7:3); Yield 310 mg (~ 84%) as white solid; m.p. 116 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 7.98 (d, *J*= 7.5 Hz, 1H), 7.78-7.63 (m, 2H), 7.54-7.40 (m, 4H), 7.31-7.29 (m, 1H), 7.22-7.18 (m, 1H), 3.70-3.60 (m, 1H), 3.26-3.16 (m, 1H), 1.52-1.32 (m, 2H), 1.21-1.12 (m, 2H), 0.74 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 182.8, 166.6, 166.1, 141.1, 135.5, 132.4, 129.5, 129.4, 129.2, 128.3, 127.3, 126.7, 122.7, 92.3, 44.2, 30.2, 19.9, 13.4. HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{18}N_2O_3S + H^+$: 367.1116 $[M + H]^+$; found: 367.1194.

4.4.10. 3-allyl-1-phenyl-2-thioxo-3'*H*-spiro[imidazolidine-4,1'-isobenzofuran]-3',5-dione (**6j**)

R_f=0.56 (Hexane/Ethyl acetate 7:3); Yield 274 mg (~ 78%) as white solid; m.p. 120 °C. IR (KBr): 3130 (Ar-H), 1750 (lactone C=O), 1600 (amide C=O), 1155 (C=S) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 7.92 (d, *J* = 7.5 Hz, 1H), 7.73-7.61 (m, 2H), 7.45-7.37 (m, 4H), 7.30-7.27 (m, 2H), 5.72-5.59 (m, 1H), 4.91 (d, *J* = 10.2 Hz, 1H), 4.80 (d, *J* = 17.1 Hz, 1H), 4.28 (dd, *J* = 15.0, 7.0 Hz, 1H), 3.98 (dd, *J* = 16.4, 6.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 182.6, 166.5, 166.0, 140.9, 135.2, 132.5, 132.3, 130.8, 129.5, 129.2, 128.2, 127.3, 126.4, 123.0, 119.4, 91.9, 46.7. HRMS (ESI-TOF): *m/z* calcd for $C_{19}H_{14}N_2O_3S + H^+$: 351.0803 $[M + H]^+$; found: 351.0812.

4.4.11. 3-(2-hydroxyethyl)-1-phenyl-2-thioxo-3'*H*-spiro[imidazolidine-4,1'-isobenzofuran]-3',5-dione (**6k**)

R_f=0.44 (Hexane/Ethyl acetate 7:3); Yield 265 mg (~ 75%) as white solid; m.p. 110 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ_{ppm} = 8.05 (d, *J* = 7.5 Hz, 1H), 7.84 (t, *J* = 7.4 Hz, 1H), 7.77 (t, *J* = 7.5 Hz, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.54-7.47 (m, 3H), 7.38 (d, *J* = 7.0 Hz, 2H),

4.00 (dt, *J* = 14.7, 5.0 Hz, 1H), 3.80-3.71 (m, 2H), 3.53-3.48 (m, 1H), 1.88 (br s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_{ppm} = 184.0, 166.6, 166.1, 140.7, 135.7, 132.6, 132.5, 129.8, 129.4, 128.3, 127.4, 126.8, 122.9, 92.1, 60.4, 46.6. Elemental analysis calcd (%) for $C_{18}H_{14}N_2O_4S$: C 61.01, H 3.98, N 7.91; found: C 60.96, H 4.05, N 7.81.

4.4.12. 3-(4-chlorobenzyl)-2-thioxo-1-(p-tolyl)-3'*H*-spiro[imidazolidine-4,1'-isobenzofuran]-3',5-dione (**6l**)

R_f=0.49 (Hexane/Ethyl acetate 7:3); Yield 370 mg (~ 82%) as white solid; m.p. 178 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 7.98 (d, *J* = 7.5 Hz, 1H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.37-7.28 (m, 4H), 7.16-7.10 (m, 3H), 7.04-7.01 (m, 2H), 5.11 (d, *J* = 15.3 Hz, 1H), 4.61 (d, *J* = 15.3 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 183.6, 166.5, 166.1, 140.8, 139.9, 135.0, 133.9, 133.7, 131.9, 129.9, 129.7, 128.5, 127.9, 126.7, 126.3, 122.9, 91.6, 46.5, 21.3. Elemental analysis calcd (%) for $C_{24}H_{17}ClN_2O_3S$: C 64.21, H 3.82, N 6.24; found: C 64.24, H 3.89, N 6.19.

4.4.13. 3-(4-methylbenzyl)-2-thioxo-1-(*p*-tolyl)-3'*H*-spiro[imidazolidine-4,1'-isobenzofuran]-3',5-dione (**6m**)

R_f=0.56 (Hexane/Ethyl acetate 7:3); Yield 364 mg (~ 85%) as white solid; m.p. 160 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 7.96 (d, *J* = 7.8 Hz, 1H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.37-7.28 (m, 4H), 7.14 (d, *J* = 7.5 Hz, 1H), 6.94 (s, 4H), 5.10 (d, *J* = 14.7 Hz, 1H), 4.65 (d, *J* = 15.0 Hz, 1H), 2.44 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 183.5, 166.6, 166.0, 141.0, 139.7, 137.6, 134.7, 132.0, 131.6, 129.9, 129.8, 128.9, 128.3, 127.9, 126.8, 126.0, 122.9, 91.7, 47.1, 21.2, 20.9. Elemental analysis calcd (%) for $C_{25}H_{20}N_2O_3S$: C 70.07, H 4.70, N 6.54; found: C 70.01, H 4.75, N 6.58.

4.4.14. 3-allyl-2-thioxo-1-(*p*-tolyl)-3'*H*-spiro[imidazolidine-4,1'-isobenzofuran]-3',5-dione (**6n**)

R_f=0.53 (Hexane/Ethyl acetate 7:3); Yield 288 mg (~ 79%) as white solid; m.p. 140 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 8.04 (d, *J* = 7.2 Hz, 1H), 7.85- 7.73 (m, 2H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.36-7.26 (m, 4H), 5.84-5.71 (m, 1H), 5.03 (d, *J* = 10.2 Hz, 1H), 4.92 (d, *J* = 16.8 Hz, 1H), 4.40 (dd, *J* = 15.5, 6.7 Hz, 1H), 4.10 (dd, *J* = 15.3, 6.2 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 182.9, 166.6, 166.1, 140.9, 139.8, 135.2, 132.3, 130.9, 129.9, 127.9, 127.4, 126.4, 123.0, 119.3, 92.0, 46.7, 21.2. Elemental analysis calcd (%) for $C_{20}H_{16}N_2O_3S$: C 65.92, H 4.43, N 7.69; found: C 65.90, H 4.38, N 7.76.

4.4.15. 1-(4-methoxyphenyl)-3-propyl-2-thioxo-3'*H*-spiro[imidazolidine-4,1'-isobenzofuran]-3',5-dione (**6o**)

R_f=0.49 (Hexane/Ethyl acetate 7:3); Yield 330 mg (~ 86%) as white solid; m.p. 100 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 7.98 (d, *J* = 7.2 Hz, 1H), 7.78-7.66 (m, 2H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.22-7.18 (m, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 3.77 (s, 3H), 3.66-3.56 (m, 1H), 3.21-3.11 (m, 1H), 1.66-1.47 (m, 2H), 0.74 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 183.3, 166.8, 166.1, 160.2, 141.2, 135.4, 132.3, 129.4, 127.3, 126.6, 125.0, 122.6, 114.5, 92.2, 55.4, 46.0, 21.6, 11.2. HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{18}N_2O_4S + H^+$: 383.1065 $[M + H]^+$; found: 383.1076.

4.4.16. 1-(4-methoxyphenyl)-3-(pyridin-3-ylmethyl)-2-thioxo-3'*H*-spiro[imidazolidine-4,1'-isobenzofuran]-3',5-dione (**6p**)

R_f=0.36 (Hexane/Ethyl acetate 4:6); Yield 360 mg (~ 84%) as white solid; m.p. 172 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ_{ppm} = 8.43 (s, 1H), 8.21 (s, 1H), 7.99 (d, *J* = 7.5 Hz, 1H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.58-7.53 (m, 2H), 7.29 (d, *J* = 9.0 Hz, 2H), 7.16 (d, *J* = 7.5 Hz, 1H), 7.12 (s, 1H), 7.02 (d, *J* = 8.5 Hz, 2H), 5.08 (d, *J* = 15.5 Hz, 1H), 4.65 (d, *J* = 15.5 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ_{ppm} = 183.9, 166.5, 165.8, 160.3, 149.5, 149.3, 140.7, 136.0, 135.2, 132.3, 131.2, 129.4, 126.8, 126.6, 124.9, 123.3, 122.9, 114.6, 91.6, 55.5,

44.8. Elemental analysis calcd (%) for $C_{23}H_{17}N_3O_4S$: C 64.03, H 3.97, N 9.74; found: C 64.09, H 3.95, N 9.80.

4.4.17. 3-(4-fluorobenzyl)-1-(2-methoxyphenyl)-2-thioxo-3'*H*-spiro[imidazolidine-4,1'-isobenzofuran]-3',5-dione (**6q**)

R_f=0.46 (Hexane/Ethyl acetate 7:3); Yield 367 mg (~ 82%) as white solid; m.p. 184 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 7.88 (d, *J* = 6.6 Hz, 1H), 7.58-7.53 (m, 1H), 7.51-7.46 (m, 1H), 7.44-7.39 (m, 1H), 7.31-7.28 (m, 1H), 7.09-7.07 (m, 1H), 7.05-6.98 (m, 4H), 6.74 (t, *J* = 8.7 Hz, 2H), 4.97 (d, *J* = 15.9 Hz, 1H), 4.57 (d, *J* = 15.3 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 183.6, 166.3, 166.1, 162.2 (d, *J* = 245.85 Hz), 154.8, 141.7, 134.9, 131.8, 131.5, 130.6, 130.2 (d, *J* = 8.10 Hz), 130.1, 126.6, 126.1, 122.9, 121.5, 121.1, 115.3 (d, *J* = 21.67 Hz), 112.2, 91.8, 56.1, 46.6. HRMS (ESI-TOF): *m/z* calcd for $C_{24}H_{17}FN_2O_4S + H^+$: 449.0971 $[M + H]^+$; found: 449.0977.

4.4.18. 1-(2-methoxyphenyl)-3-(4-methylbenzyl)-2-thioxo-3'*H*-spiro[imidazolidine-4,1'-isobenzofuran]-3',5-dione (**6r**)

R_f=0.49 (Hexane/Ethyl acetate 7:3); Yield 385 mg (~ 87%) as white solid; m.p. 176 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 7.94 (d, *J* = 7.5 Hz, 1H), 7.64-7.47 (m, 3H), 7.38 (d, *J* = 6.3 Hz, 1H), 7.20-7.06 (m, 3H), 7.00-6.93 (m, 4H), 5.00 (d, *J* = 15.0 Hz, 1H), 4.70 (d, *J* = 15.3 Hz, 1H), 3.86 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 183.6, 166.5, 166.3, 154.9, 141.8, 137.6, 134.8, 132.2, 131.6, 131.5, 130.7, 129.0, 128.3, 126.7, 126.0, 123.0, 121.7, 121.1, 112.2, 92.0, 56.1, 47.3, 21.0. HRMS (ESI-TOF): *m/z* calcd for $C_{25}H_{20}N_2O_4S + H^+$: 445.1222 $[M + H]^+$; found: 445.1253.

4.4.19. 1-(4-fluorophenyl)-3-(4-methylbenzyl)-2-thioxo-3'*H*-spiro[imidazolidine-4,1'-isobenzofuran]-3',5-dione (**6s**)

R_f=0.48 (Hexane/Ethyl acetate 7:3); Yield 390 mg (~ 90%) as white solid; m.p. 160 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 7.97 (d, *J* = 7.8 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H),

7.53 (t, *J* = 7.5 Hz, 1H), 7.43-7.39 (m, 2H), 7.27-7.20 (m, 2H), 7.13 (d, *J* = 7.2 Hz, 1H), 6.94 (s, 4H), 5.10 (d, *J* = 15.0 Hz, 1H), 4.64 (d, *J*= 15.3 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 183.3, 166.7, 166.0, 162.8 (d, *J* = 248.32 Hz), 140.9, 137.8, 134.9, 132.0, 131.8, 130.3, 130.2, 129.1, 128.5, 126.9, 126.3, 123.0, 116.4 (d, *J* = 22.8 Hz), 91.8, 47.3, 21.0. Elemental analysis calcd (%) for $C_{24}H_{17}FN_2O_3S$: C 66.66, H 3.96, N 6.48; found: C 66.64, H 4.03, N 6.40.

4.4.20. 3-allyl-1-(4-fluorophenyl)-2-thioxo-3'*H*-spiro[imidazolidine-4,1'-isobenzofuran]-3',5-dione (**6t**)

R_f=0.48 (Hexane/Ethyl acetate 7:3); Yield 324 mg (~ 88%) as white solid; m.p. 148 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 8.05 (d, *J* = 6.9 Hz, 1H), 7.85-7.74 (m, 2H), 7.56-7.54 (m, 1H), 7.41-7.37 (m, 2H), 7.27-7.19 (m, 2H), 5.82-5.69 (m, 1H), 5.03 (d, *J* = 9.9 Hz, 1H), 4.91 (d, *J*= 16.8 Hz, 1H), 4.42-4.35 (m, 1H), 4.12-4.05 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 182.5, 166.5, 166.0, 162.8 (d, *J* = 248.47 Hz), 140.7, 135.3, 132.4, 130.7, 130.2 (d, *J* = 9.15 Hz), 128.3, 127.3, 126.5, 123.0, 119.5, 116.3 (d, *J* = 22.87 Hz), 91.9, 46.8. Elemental analysis calcd (%) for $C_{19}H_{13}FN_2O_3S$: C 61.95, H 3.56, N 7.60; found: C 61.87, H 3.66, N 7.68.

4.4.21. 3-cyclopropyl-1-(2,4-dichlorophenyl)-2-thioxo-3'*H*-spiro[imidazolidine-4,1'-isobenzofuran]-3',5-dione (**6u**)

R_f=0.40 (Hexane/Ethyl acetate 7:3); Yield 293 mg (~ 70%) as white solid; m.p. 140 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 8.07 (d, *J* = 7.5 Hz, 1H), 7.86-7.74 (m, 2H), 7.59-7.54 (m, 2H), 7.42-7.30 (m, 2H), 2.63-2.60 (m, 1H), 0.94-0.77 (m, 2H), 0.72-0.51 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ_{ppm} = 183.2, 166.7, 166.2, 155.7, 141.0, 136.7, 136.3, 133.8, 133.2, 130.1, 129.7, 129.0, 127.9, 126.5, 124.9, 93.4, 27.1, 6.6, 5.0. Elemental analysis calcd (%) for $C_{19}H_{12}Cl_2N_2O_3S$: C 54.43, H 2.88, N 6.68; found: C 54.52, H 2.95, N 6.62.

4.4.22. 1-(2,4-dichlorophenyl)-3-propyl-2-thioxo-3'*H*-spiro[imidazolidine-4,1'-isobenzofuran]-3',5-dione (**6v**)

R_f=0.47 (Hexane/Ethyl acetate 7:3); Yield 360 mg (~ 85%) as white solid; m.p. 150 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 7.98 (d, *J* = 7.2 Hz, 1H), 7.79-7.67 (m, 2H), 7.51-7.47 (m, 2H), 7.34-7.24 (m, 2H), 3.67-3.57 (m, 1H), 3.21-3.11 (m, 1H), 1.68-1.42 (m, 2H), 0.75 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 181.4, 165.9, 165.8, 140.6, 136.8, 135.4, 134.4, 132.4, 131.7, 130.4, 129.1, 127.9, 127.2, 126.6, 122.6, 92.3, 45.9, 21.5, 11.0. Elemental analysis calcd (%) for $C_{19}H_{14}Cl_2N_2O_3S$: C 54.17, H 3.35, N 6.65; found: C 54.10, H 3.43, N 6.59.

4.4.23. 3-butyl-1-(2,4-dichlorophenyl)-2-thioxo-3'*H*-spiro[imidazolidine-4,1'-isobenzofuran]-3',5-dione (**6w**)

R_f=0.52 (Hexane/Ethyl acetate 7:3); Yield 375 mg (~ 86%) as white solid; m.p. 164 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 8.08 (d, *J* = 7.5 Hz, 1H), 7.88-7.76 (m, 2H), 7.61-7.56 (m, 2H), 7.44-7.33 (m, 2H), 3.78-3.68 (m, 1H), 3.34-3.24 (m, 1H), 1.71-1.59 (m, 2H), 1.31-1.19 (m, 2H), 0.83 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 181.5, 166.0, 165.9, 140.7, 136.9, 135.5, 134.5, 132.5, 131.8, 130.5, 129.2, 128.0, 127.3, 126.7, 122.7, 92.4, 44.3, 30.1, 19.8, 13.4. Elemental analysis calcd (%) for $C_{20}H_{16}Cl_2N_2O_3S$: C 55.18, H 3.70, N 6.44; found: C 55.13, H 3.77, N 6.35.

4.4.24. 3-(4-methylbenzyl)-1-phenyl-3'*H*-spiro[imidazolidine-4,1'-isobenzofuran]-2,3',5-trione (**7a**)

R_f=0.45 (Hexane/Ethyl acetate 7:3); Yield 350 mg (~ 88%) as white solid; m.p. 134 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 7.97 (d, *J* = 7.5 Hz, 1H), 7.66-7.41 (m, 7H), 7.13 (d, *J* = 8.4 Hz, 1H), 6.97-6.86 (m, 4H), 4.59 (d, *J* = 15.0 Hz, 1H), 4.28 (d, *J* = 15.0 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 166.3, 165.7, 154.4, 141.0, 137.7, 134.7, 132.2,

131.6, 130.9, 129.2, 129.1, 128.6, 128.5, 127.4, 126.0, 125.7, 122.9, 91.8, 43.8, 20.9. HRMS (ESI-TOF): *m/z* calcd for $C_{24}H_{18}N_2O_4 + H^+$: 399.1345 $[M + H]^+$; found: 399.1374.

4.4.25. 1-phenyl-3-(pyridin-3-ylmethyl)-3'*H*-spiro[imidazolidine-4,1'-isobenzofuran]-2,3',5-trione (**7b**)

R_f=0.35 (Hexane/Ethyl acetate 7:3); Yield 327 mg (~ 85%) as yellow solid; m.p. 144 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 8.45 (s, 1H), 8.15 (s, 1H), 8.00 (d, *J* = 7.5 Hz, 1H), 7.67 (t, *J* = 7.2 Hz, 1H), 7.59 (t, *J* = 8.4 Hz, 1H), 7.51-7.49 (m, 4H), 7.47-7.40 (m, 2H), 7.15 (d, *J* = 7.7 Hz, 2H), 4.62 (d, *J* = 15.6 Hz, 1H), 4.31 (d, *J* = 15.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 166.2, 165.6, 154.7, 149.4, 149.5, 140.8, 136.6, 135.3, 132.4, 130.8, 129.7, 129.4, 129.0, 127.5, 127.4, 126.7, 125.9, 123.0, 91.7, 41.7. HRMS (ESI-TOF): *m/z* calcd for $C_{22}H_{15}N_3O_4 + H^+$: 386.1141 $[M + H]^+$; found: 386.1154.

4.4.26. 3-cyclohexyl-1-phenyl-3'H-spiro[imidazolidine-4,1'-isobenzofuran]-2,3',5-trione (**7c**)

R_f=0.45 (Hexane/Ethyl acetate 7:3); Yield 270 mg (~ 72%) as white solid; m.p. 98 °C. IR (KBr): 3180 (Ar-H), 2930 (aliphatic C-H), 1740 (lactone C=O), 1640 (amide C=O), 1560 (amide -N-(C=O)-N-) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 8.04 (d, *J* = 7.2 Hz, 1H), 7.83-7.71 (m, 2H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.48-7.46 (m, 4H), 7.41-7.35 (m, 1H), 3.12-3.01 (m, 1H), 1.95-1.54 (m, 8H), 1.07-1.00 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ_{ppm} = 166.6, 165.7, 153.4, 141.9, 135.2, 132.0, 130.9, 129.1, 128.5, 127.8, 126.4, 125.8, 122.6, 92.6, 54.6, 31.1, 30.8, 25.9, 25.8, 24.8. Elemental analysis calcd (%) for $C_{22}H_{20}N_2O_4$: C 70.20, H 5.36, N 7.44; found: C 70.10, H 5.42, N 7.40.

4.4.27. 3-(4-chlorobenzyl)-1-(*p*-tolyl)-3'*H*-spiro[imidazolidine-4,1'-isobenzofuran]-2,3',5-trione (**7d**).

R_f=0.42 (Hexane/Ethyl acetate 7:3); Yield 364 mg (~ 84%) as white solid; m.p. 120 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ_{ppm} = 7.96 (d, *J* = 8.0 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 7.12-7.10 (m, 3H),

6.92 (d, *J* = 8.5 Hz, 2H), 4.57 (d, *J* = 15.5 Hz, 1H), 4.23 (d, *J* = 15.5 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ_{ppm} = 166.3, 165.6, 154.6, 141.0, 138.9, 134.9, 134.1, 134.0, 131.9, 130.0, 129.9, 128.7, 128.1, 127.3, 126.2, 125.6, 122.9, 91.7, 43.3, 21.2. Elemental analysis calcd (%) for $C_{24}H_{17}ClN_2O_4$: C 66.60, H 3.96, N 6.47; found: C 66.54, H 4.05, N 6.42.

4.4.28. 3-cyclopropyl-1-(*p*-tolyl)-3'*H*-spiro[imidazolidine-4,1'-isobenzofuran]-2,3',5-trione (**7e**)

R_f=0.45 (Hexane/Ethyl acetate 7:3); Yield 226 mg (~ 65%) as white solid; m.p. 158 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm} = 8.03 (d, *J* = 7.6 Hz, 1H), 7.79 (t, *J* = 7.4 Hz, 1H), 7.72 (t, *J* = 7.6 Hz, 1H), 7.50 (d, *J*= 7.6 Hz, 1H), 7.32-7.24 (m, 4H), 2.37 (s, 3H), 2.36- 2.33 (m, 1H), 0.92-0.86 (m, 1H), 0.69- 0.57 (m, 2H), 0.55-0.47 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_{ppm} = 166.8, 165.6, 154.9, 141.8, 138.9, 135.3, 132.0, 129.9, 128.2, 127.7, 126.6, 125.8, 122.3, 92.9, 22.3, 21.3, 5.1, 4.3. Elemental analysis calcd (%) for $C_{20}H_{16}N_2O_4$: C 68.96, H 4.63, N 8.04; found: C, 68.89, H 4.60, N 7.99.

4.4.29. 3-hexyl-1-(*p*-tolyl)-3'*H*-spiro[imidazolidine-4,1'-isobenzofuran]-2,3',5-trione (**7f**)

R_f=0.62 (Hexane/Ethyl acetate 7:3); Yield 330 mg (~ 84%) as white solid; m.p. 150 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 8.04 (d, *J* = 7.2 Hz, 1H), 7.84-7.71 (m, 2H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.36-7.25 (m, 4H), 3.36 (ddd, *J* = 15.4, 8.8, 6.7 Hz, 1H), 3.03 (ddd, *J* = 14.6, 8.7, 6.4 Hz, 1H), 2.38 (s, 3H), 1.51-1.39 (m, 2H), 1.25-1.14 (m, 6H), 0.82 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ_{ppm} = 166.5, 165.8, 154.5, 141.3, 138.7, 135.2, 132.1, 129.8, 128.2, 127.7, 126.5, 125.6, 122.6, 92.4, 40.8, 31.0, 28.9, 26.2, 22.3, 21.2, 13.9. Elemental analysis calcd (%) for $C_{23}H_{24}N_2O_4$: C 70.39, H 6.16, N 7.14; found: C 70.34, H 6.22, N 7.08.

4.5. Single crystal X-ray Data

4.5.1. Single crystal X-ray structure analysis of **6a** (**CCDC 1858914**)

colourless block, triclinic, Cell volume 976.0(6), Space group P-1, a = 7.400(3) Å, b = 9.871(4) Å, c = 14.468(5) Å, α = 74.553(4)°, β = 87.932(5)°, γ = 73.530(5)°, Z = 2, λ (MoK_α) = 0.71073 Å, ρ = 1.363 g. cm^{-3}, μ (MoK_α) = 0.193 mm^{-1}, F(000) = 416, Cell measurement temperature T = 296(2), Total reflections = 6945, 1.460° < θ < 25.100°, R_1 & wR_2 [$I > 2\sigma(I)$] = 0.0396 (2692) & 0.0897 (3425), R_1 & wR_2 (for all data) = 0.0514 & 0.0834, Goodness-of-fit on F^2 = 1.017, Data completeness = 0.986.

4.5.2. Single crystal X-ray structure analysis of **6c** (**CCDC 1921631**)

colourless block, orthorhombic, Cell volume 4061.5(19), Space group P b c a, a = 14.569(4) Å, b = 13.780(4) Å, c = 20.229(5) Å, α = 90°, β = 90°, γ = 90°, Z = 8, λ (MoK_α) = 0.71073 Å, ρ = 1.356 g. cm^{-3}, μ (MoK_α) = 0.188 mm^{-1}, F(000) = 1728, Cell measurement temperature T = 296(2), Total reflections = 45121, 2.013° < θ < 25.574°, R_1 & wR_2 [$I > 2\sigma(I)$] = 0.0363 (3211) & 0.1103 (3800), R_1 & wR_2 (for all data) = 0.0444 & 0.1019, Goodness-of-fit on F^2 = 1.023, Data completeness = 0.996.

Acknowledgements

S. M. thanks University Grants Commission (UGC), New Delhi, India for offering Senior Research Fellowship (SRF). Authors acknowledge DST-FIST; India funded Single-Crystal Diffractometer facility, DST-PURSE, India funded HRMS facility, Centre of Advanced Study (CAS-V, UGC, New Delhi) at Department of Chemistry, University of Calcutta for instrumental and financial assistance and also thankful to Central Instrument Facility (CIF), Bose Institute, for NMR facility.

Appendix A. Electronic Supplementary Information

Supplementary data regarding this article can be found in a separate file.

References

[1] M. E. Jung, S. Ouk, D. Yoo, C. L. Sawyers, C. Chen, C. Tran, J. Wongvipat, *J. Med. Chem. 53* (**2010)** 2779.

[2] G. L. Khatik, J. Kaur, V. Kumar, K. Tikoo, P. Venugopalan, V. A. Nair, *Eur. J. Med. Chem. 46* (**2011)** 3291.

[3] K. Tachibana, I. Imaoka, T. Shiraishi, H. Yoshino, M. Nakamura, M. Ohta, H. Kawata, K. Taniguchi, N. Ishikura, T. Tsunenari, H. Saito, M. Nagamuta, T. Nakagawa, K. Takanashi, E. Onuma, H. Sato, *Chem. Pharm. Bull. 56* (**2008)** 1555.

[4] K. K. Kononowicz, E. Szymanska, *Il Farmaco 57* (**2002)** 909.

[5] Y. S. Bae, S. Choi, J. J. Park, J. H. Joo, M. Cui, H. Cho, W. J. Lee, S. H. Lee, *Bioorg. Med. Chem. 24* (**2016)** 4144.

[6] M. C. P. A. Albuquerque, T. G. Silva, M. G. R. Pitta, A. C. A. Silva, P. G. Silva, E. Malagueno, J. V. Santana, A. G. Wanderley, M. C. A. Lima, S. L. Galdino, J. Barbe, I. R. Pitta, *Pharmazie 60* (**2005)** 13.

[7] D. L. Boger, M. A. Labroli, T. H. Marsilje, Q. Jin, M. P. Hedrick, S. J. Baker, J. Hoon Shim, S. J. Benkovic, *Bioorg. Med. Chem. 8* (**2000)** 1075.

[8] A. Takahashi, H. Matsuoka, K. Yamada, Y. Uda, *Food Chem. Toxicol. 43* (**2005)** 521.

[9] D. Blanco-Ania, P. H. H. Hermkens, L. A. J. M. Sliedregt, H. W. Scheeren, F. P. J. T. Rutjes, *J. Comb. Chem. 11* (**2009)** 527.

[10] T. Docsa, K. Czifrak, C. Huse, L. Somsak, P. Gergely, *Mol. Med. Rep. 4* (**2011)** 477.

[11] A. Leon, M. Del-Angel, J. L. A. Vila, G. Delgado, *Prog. Chem. Org. Nat. Prod. 104* (**2017)** 127.

[12] B. Jiang, T. Rajale, W. Wever, S-J. Tu, G. Li, *Chem. Asian J. 5* (**2010**) 2318.

[13] Preeti, K. N. Singh, *Org. Biomol. Chem. 16* (**2018)** 9084.

[14] M. M. Manzari, M. H. Ghahremani, T. Sedaghat, F. Shayan, M. A. Faramarzi, *Eur. J. Org. Chem.* (**2019)**, 1741.

[15] D. Das, *ChemistrySelect 1* (**2016)** 1959.

[16] M. A. Zolfigol, *Tetrahedron 57* (**2001)** 9509.

[17] K. Debnath, S. Pathak, A. Pramanik, *Tetrahedron Lett. 55* (**2014)** 1743.

[18] A. Kundu, A. Pramanik, *Mol. Diversity 19* (**2015)** 459.

[19] R. Guo, C. Zhu, Z. Sheng, Y. Li, W. Yin, C. Chu, *Tetrahedron Lett. 56* (**2015)** 6223.

[20] S. V. Shelar, N. P. Argade, *Org. Biomol. Chem. 17* (**2019)** 6671.

[21] H. J. Patel, J. Sarra, F. Caruso, M. Rossi, U. Doshia, R. A. Stephani, *Bioorg. Med. Chem. Lett. 16* (**2006)** 4644.

Facile synthesis of phthalidyl fused spiro thiohydantoins through silica sulfuric acid induced oxidative rearrangement of ninhydrin adducts of thioureas

Subhro Mandal[a], Animesh Pramanik[a,*]

[a]*Department of Chemistry, University of Calcutta, 92, A. P. C. Road, Kolkata-700 009, India*

Fax: +91-33-2351-9755; Tel: +91 9830107470

E-mail: pramanikanimesh61@gmail.com

Highlights:

- Synthesis of spiro-fused thiohydantoin through SSA induced oxidative rearrangement
- Easy recyclability of SSA, good to excellent yield of products, wider substrate scope
- Shorter reaction time and high atom economy
- Spiro-fusion of two biologically active heterocycles, thiohydantoin and phthalide

Declaration of Interest Statement

There are no conflicts of interest.