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Synthesis of 5-methylidene-2-thio- and 2-selenohydantoins from isothiocyanates or isoselenocyanates and L-serine

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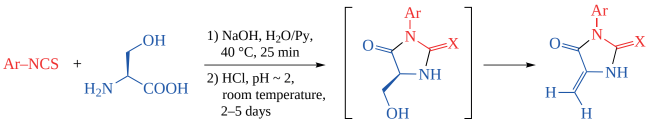
3-Aryl-5-methylidenethiohydantoins and 3-aryl-5-methylidene-selenohydantoins were obtained by one-pot reaction of aryl isothiocyanates or isoselenocyanates with L-serine in NaOH–H$_2$O–Py mixture followed by room temperature HCl-promoted dehydration.



X = S, 5 examples, 34–78%
X = Se, 1 example, 34%

Keywords: 2-thiohydantoins, 2-selenohydantoins, exocyclic C=C bond, dehydration, isothiocyanates, isoselenocyanates, L-serine.

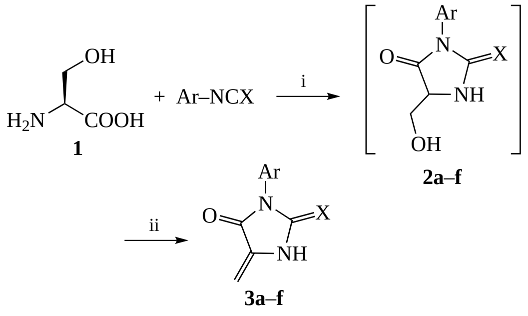
Thiohydantoins are heterocyclic compounds with wide range of biological activity[1,2] including antitumor activity on various cancer cell lines.[2–7] Along with their oxygen analogues, hydantoins, they represent a structural moiety in some pharmaceuticals.[8,9] Organoselenium compounds are known to possess antioxidant,[10] antimicrobial,[11] antitumor[12] and anti-inflammatory[13] properties. Several organoselenium compounds, including ebselen and Se-methylselenocystein, are being evaluated as promising neuroprotectors and antioxidants as well as anticancer drugs.[14,15]

The presence of an exocyclic C=C double bond in position 5 of thio- or selenohydantoins expands the ability of the compounds to various chemical transformations.[16] In particular, cycloaddition reactions at such bonds[17,18] allow one to significantly complicate the skeleton of the molecules by adding spiro junctions to their structures. At the same time, although some methods have been described for the preparation of 5-arylidene-[19–21] and 5-indolidene[22,23] thio- and selenohydantoin derivatives, the analogues containing an exocyclic methylidene double bond C=CH$_2$ are much less presented in the literature. Preparation of 5-methylidenehydantoins from 5-(hydroxymethyl)hydantoins under the action of triphenylphosphine and DIAD[24] or trifluoroacetic anhydride[25] were reported. Recently, 5-methylidenethiohydantoins[16] were prepared in good yields by elimination of morpholine from 5-(morpholinomethyl)-thiohydantoins which were in turn synthesized from morpholinomethylglycine. However, the preparation of the starting morpholinomethylglycine was not easy.

In this work, we demonstrate the possibility to use commercially available L-serine **1** instead of morpholinomethylglycine for the synthesis of 5-methylidene-2-thiohydantoins and their selenium analogues. The proposed technique is the reaction of aryl isothiocyanate or isoselenocyanate with L-serine in NaOH–H$_2$O–Py mixture followed by room temperature dehydration (Scheme 1).

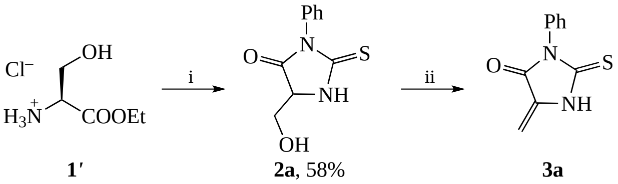
Optimization of the reaction conditions was carried out for the synthesis of 5-methylidene-3-phenyl-2-thiohydantoin **3a** (Scheme 2, Table 1). Initial 5-(hydroxymethyl)thiohydantoin **2a** was obtained from phenyl isothiocyanate and serine ethyl ester hydrochloride **1′** synthesized from L-serine **1** and thionyl chloride in ethanol.[26] In attempted dehydration, procedures for the synthesis of similar compounds using triphenylphosphine and DIAD[24] (entry 1), DCC and CuCl[27] (entry 2), (COCl)$_2$[28] (entry 3), SOCl$_2$[29] (entry 4), TsCl[30] (entry 5), triphosgene[31] (entry 6), or CDI[32] (entry 7) did not afford the target product **3a** in significant amounts. At the same time, acid dehydration of compound **2a** (entries 8, 9) gave practically pure 5-methylidene-3-phenylthiohydantoin **3a** by simply stirring a suspension of compound **2a** in aqueous hydrochloric acid at room temperature at pH 2–4 for one week. The reaction proceeded more effectively at pH ~ 2 (entry 9).

Examples of polyfunctional compound dehydration under mild conditions, for example, by using Burgess' reagent or Martin's



a Ar = Ph, X = S, 78%
b Ar = 4-MeC$_6$H$_4$, X = S, 63%
c Ar = 3-MeC$_6$H$_4$, X = S, 48%
d Ar = 4-ClC$_6$H$_4$, X = S, 60%
e Ar = 4-MeOC$_6$H$_4$, X = S, 34%
f Ar = 4-MeC$_6$H$_4$, X = Se, 42%

Scheme 1 *Reagents and conditions*: i, Py–H$_2$O, 1 M NaOH, pH 9–10, 40 °C, 25 min, then HCl–H$_2$O, pH ~ 2, room temperature, 2 days; ii, HCl–H$_2$O, pH ~ 2, room temperature, 2–12 days.



Scheme 2 *Reagents and conditions*: i, PhNCS, Et$_3$N, CHCl$_3$, room temperature, 3 days; ii, various conditions (see Table 1).

Table 1 Optimization of dehydration of alcohol **2a** into 5-methylidene-3-phenyl-2-thiohydantoin **3a**.

Entry	Reagent	Reaction conditions	Yield of **3a**
1	Ph_3P, DIAD	Et_3N, THF	–
2	DCC	CuCl	–
3	$(COCl)_2$	Et_3N, THF	traces
4	$SOCl_2$	Py, THF	–
5	TsCl	DMAP, Et_3N	–
6	Triphosgene	Py, CH_2Cl_2	traces
7	CDI	Py, CH_2Cl_2	–
8	HCl–H_2O	pH ~ 4, room temperature, 10 days, [**2**] = 5.5 mg ml^{-1}	56%
9	HCl–H_2O	pH ~ 2, room temperature, 5 days, [**2**] = 5.5 mg ml^{-1}	68%

sulfurane, as well as dehydration under the action of acids, including Lewis acids, such as $BF_3{\cdot}Et_2O$ are documented.[33] However, all of these methods require some specific conditions, such as an anhydrous environment. The technique developed in the present work makes it possible to carry out dehydration in an aqueous solution of HCl without application of expensive reagents.

Taking into account the obtained results, we also demonstrated the possibility of 5-methylidenethiohydantoin preparation from isothiocyanates and L-serine without isolating intermediate hydroxymethyl derivatives **2**. At the first stage, a mixture of L-serine, pyridine and water was alkalized with 1 M NaOH to pH ~ 9–10, heated to 40 °C, then isothiocyanate was added, stirred for 25 min and washed with toluene to extract pyridine and residual isothiocyanate. After that the reaction mixture was diluted with water, concentrated hydrochloric acid was added dropwise to achieve pH ~ 2, and then it was left on stirring at room temperature for 3–4 days. The precipitate formed was filtered off. In the case of phenyl isothiocaynate **2a**, product **3a** was obtained in 78% yield after three days of stirring. However, in the case of other isothiocyanates the precipitates obtained after 4 day processing were the mixtures of hydroxymethyl intermediates **2b–e** with the desired methylidene products **3b–e**. To finalize the dehydration, these mixtures were again suspended in much water, acidified to pH ~ 2 and left on prolonged stirring.

We also tested the developed method for the preparation of 5-methylideneselenohydantoins on the example of the reaction between L-serine **1** and *p*-tolyl isoselenocyanate. As a result, 5-methylidene-3-(*p*-tolyl)selenohydantoin **3f** was obtained in 42% yield (see Scheme 1). However, the substance precipitated from this reaction mixture required additional purification by column chromatography. This can be explained by the lower stability of the selenoxo group under acidic conditions compared to the thioxo group.

To conclude, we have proposed a new effective method for the preparation of 3-aryl-5-methylidenethio- and seleno-hydantoins based on available commercial reagents, L-serine and isothiocyanates. The procedure can be extended toward accessible[34] isoselenocyanates, which enables preparation of 5-methylidene-substituted selenohydantoins, a previously unreported chemotype of organic compounds.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.11.020.

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