Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2022, **32**, 126–128

Mendeleev Communications

A convenient synthesis of 3-aryl-5-methylidene-2-thiohydantoins

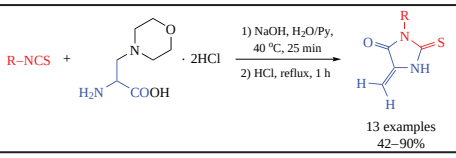
Maxim E. Kukushkin,[a,b] Nikita A. Karpov,[a] Dmitry E. Shybanov,[a] Nikolai V. Zyk[a] and Elena K. Beloglazkina*[a]

[a] *Department of Chemistry, M. V. Lomonosov Moscow State University, 119991 Moscow, Russian Federation. E-mail: beloglazki@mail.ru*

[b] *National University of Science and Technology 'MISIS", 119049 Moscow, Russian Federation*

DOI: 10.1016/j.mencom.2022.01.041

3-Aryl-5-methylidene-2-thiohydantoins were constructed in one-pot reaction of aryl isothiocyanates and 3-morpholinoalanine in alkaline medium with the subsequent treatment with boiling hydrochloric acid.



Keywords: 2-thiohydantoins, exocyclic C=C bond, heterocyclization, isothiocyanates, amino acids.

Hydantoins and thiohydantoins are well-known heterocyclic compounds which have found application in synthetic chemistry and in the development of substances with various types of biological activity, (see, for example, recent reviews).[1,2] The introduction of exocyclic double C=C bond into position 5 of (thio)hydantoin ring makes the molecules suitable for electrophilic and nucleophilic addition,[3–6] 1,3-dipolar cycloaddition[7,8] and Diels–Alder reaction.[9] The preparation of thiohydantoins with exocyclic arylidene or alkylidene substituent at the C^5 atom is well developed based on the olefination with aldehydes/ketones resulting in the formation of tri-[10–12] or tetra-substituted[13,14] exocyclic C=C bonds. However, approaches to thiohydantoins containing exocyclic methylidene (CH_2=) fragment are rather scarce. At the same time, double bond of such a substitution pattern is sterically not hindered and looks more suitable for various chemical transformations in comparison with the corresponding arylidene and alkylidene derivatives.

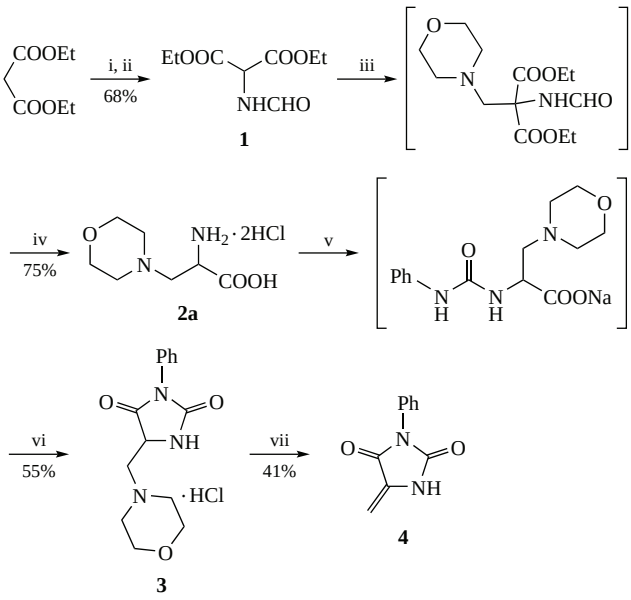
It should be noted, that for hydantoins some general methods for the preparation of 5-methylidene derivatives are known,[15–18] whereas for 5-methylidenethiohydantoins, we did not find in literature general procedures allowing one to vary substituents at their nitrogen atoms. Despite the seeming simplicity of the structure, just a few examples of the preparation of 5-methylidenethiohydantoins are documented. The reaction of benzyl isothiocyanate with methyl serinate and its variations[19] are limited to thiohydantoin derivatives containing benzyl moieties at positions 1 and 3. The prolonged retro-Michael decay of 5-(thiomorpholinomethyl)thiohydantoin in water[20] was realized only once and seems inconvenient.

The approach we propose is based on the modified one-pot reaction procedure described by Fujisaki for the synthesis of 2-oxo analogues of 5-methylidenethiohydantoins.[15] Our procedure does not require preliminary isolation of 5-(morpholinomethyl)thiohidantoin formed *in situ* and provides ample opportunities to vary the substituents in the position 3 of the resulting thiohydantoins.

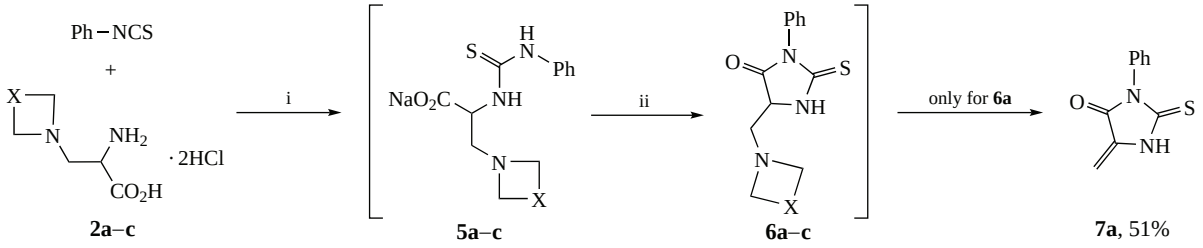
Fujisaki[15] proposed an access (Scheme 1) to 5-methylidene-3-phenylhydantoin **4** based on the reaction of phenylisothiocyanate with β-morpholinoalanine **2a**. Our attempts to reproduce this reaction for isothiocyanates were not so successful giving product **4** in low yields.

We reasoned that compound **4** could form a dimer in acidic medium[20] as a result of the Michael reaction between two molecules of **4**. To minimize this unwanted reaction, we adjusted pH value of the reaction mixture to ~4 by adding triethylamine, which improved the yield from 24%[15] to 41%. However, our attempt to extend such optimized procedure for the synthesis of similar thioxo derivatives resulted in partial or complete desulfurization of the target compounds with the formation of the corresponding hydantoins or their dimers. The key to the success of the synthesis (Scheme 2) was realizing the process without isolation of intermediate morpholine derivative **6**. As a result, an universal preparative technique for the synthesis of 5-methylidene-2-thiohydantoins, the key point of which was the *in situ* preparation of 5-(aminomethyl)-substituted thiohydantoins **6**, was developed. The latter were then readily converted into target products **7a**–**m** (Schemes 2, 3).

Optimizing the reported[22] reaction conditions, we synthesized the series of β-aminoalanines **2a**–**c** which were reacted with



Scheme 1 *Reagents and conditions*: i, $NaNO_2$, AcOH; ii, Zn, HCO_2H (ref. 21); iii, morpholine, CH_2O, 5 min; iv, HCl, 4 days; v, Ph–NCO, NaOH, H_2O; vi, HCl, 18 h; vii, H_2O, 2 days.



2a–c

a X = CH_2OCH_2
b X = $(CH_2)_2$
c X = $(CH_2)_3$

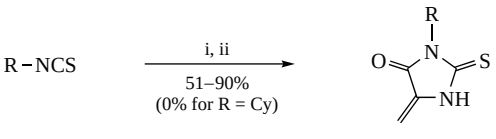
5a–c **6a–c** **7a**, 51%

Scheme 2 *Reagents and conditions*: i, Ph–NCS, NaOH, Py, H_2O (pH 9–10), 40 °C, 25 min; ii, HCl (10% aq., pH 1–2), reflux, 1 h.

isocyanates in a Py/H_2O mixture at pH 9–10 and then with boiled 1 N HCl by Edman method[23] (see Scheme 2) to form thiohydantoins. This approach suggests boiling for 2 h, but we found that reducing the reaction time to 1 h has no effect on product yield. It was revealed that in the case of substrate **2a**, in contrast to **2b**,**c**, the intermediate 5-morpholinomethylhydantoin **6a** spontaneously eliminated amine, and the target methylidenethiohydantoin **7a** was isolated as almost pure precipitate. In the cases of substrates **2b**,**c** the formation of precipitate **7a** did not occur. Therefore, amino acid **2a** was selected for further optimization.

We also varied the reaction time of amino acid **2a** and PhNCS in an alkaline medium. According to reported data,[24] this parameter might critically affect the amount of impurities formed during the reaction, as at basic pH the polymerization of the intermediate thiourea could occur. We carried out two similar reactions of PhNCS with **2a**; the first for 25 min, the second for 50 min of stirring at pH 9–10 and further boiling in an acidic medium for 1 h. In the second reaction, although the yield of the crude product was somewhat higher (54%), significant amounts of by-products were formed compared to the first reaction (51%). To raise the product yield, we also tried to increase the boiling time in hydrochloric acid at the stage of obtaining thiohydantoin from compound **2a** and PhNCS from 1 to 10 h. However, this experiment brought about a desulfurized product, hydantion **4**.

Thus, the optimal conditions for the preparation of methylidenethiohydantoin **7a** are those as outlined in Scheme 2 (for details, see Online Supplementary Materials). This protocol was successfully applied to the synthesis of a series of 3-substituted 5-methylidenethiohydantoins **7a**–**m** (Scheme 3). Regarding the yields of products **7**, we may conclude that in case of the starting isothiocyanates with the donor substituents, the yields of products are higher. Nevertheless, it is worth noting the wide scope of the proposed method.



7a–m

a R = Ph, 51%
b R = 2-FC_6H_4, 73%
c R = 3-FC_6H_4, 56%
d R = 4-FC_6H_4, 68%
e R = 2-ClC_6H_4, 66%
f R = 3-ClC_6H_4, 57%
g R = 4-ClC_6H_4, 60%
h R = 3-Cl-4-FC_6H_3, 56%
i R = 3-MeC_6H_4, 68%
j R = 4-MeC_6H_4, 72%
k R = 3-$MeOC_6H_4$, 89%
l R = 4-$MeOC_6H_4$, 90%
m R = 4-$O_2NC_6H_4$, 73%

Scheme 3 *Reagents and conditions*: i, **2a**, NaOH, Py, H_2O (pH 9–10), 40 °C, 25 min; ii, HCl (10% aq., pH 1–2), reflux, 1 h.

Since alkyl substituents are electron donors inherently, we also tested cyclohexyl isothiocyanate in this reaction, however the formation of the desired methylidenethiohydantoin was not observed. Thus, the scope of the proposed method appears to be limited to aryl isothiocyanates.

In summary, a convenient universal preparative procedure for the synthesis of 3-aryl-5-methylidene-2-thiohydantoins has been developed. The proposed synthesis is very facile to implement, versatile and does not require the use of expensive reagents.

This work was supported by the Russian Science Foundation (grant no. 20-73-00234). This work in part of NMR and X-ray study was supported by the M. V. Lomonosov Moscow State University Program of Development.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.01.041.

References

1 S. Cho, S.-H. Kim and D. Shin, *Eur. J. Med. Chem.*, 2019, **164**, 517.
2 L. Konnert, F. Lamaty, J. Martinez and E. Colacino, *Chem. Rev.*, 2017, **117**, 13757.
3 D. A. Hahn, M. J. McLean and H. T. Murphy, *J. Am. Chem. Soc.*, 1938, **60**, 1927.
4 R. L. McKee and H. R. Hense, *J. Am. Chem. Soc.*, 1944, **66**, 2020.
5 A. Litzinger, *J. Am. Chem. Soc.*, 1934, **56**, 673.
6 R. L. Antipin, E. K. Beloglazkina, A. G. Magouga, A. N. Chernysheva and N. V. Zyk, *Chem. Heterocycl. Compd.*, 2008, **44**, 1135 (*Khim. Geterotsikl. Soedin.*, 2008, 1406).
7 H. M. Hassaneen, H. A. Daboun, H. A. Abdelhadi and N. A. Abdel-reheim, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1995, **107**, 269.
8 M. E. Kukushkin, A. A. Kondratyeva, N. V. Zyk, A. G. Majouga and E. K. Beloglazkina, *Russ. Chem. Bull., Int. Ed.*, 2019, **68**, 2088 (*Izv. Akad. Nauk, Ser. Khim.*, 2019, 2088).
9 D. E. Shybanov, M. E. Kukushkin, V. A. Tafeenko, N. V. Zyk, Yu. K. Grishin, V. A. Roznyatovsky and E. K. Beloglazkina, *Mendeleev Commun.*, 2021, **31**, 246.
10 O. Yu. Kuznetsova, R. L. Antipin, A. V. Udina, O. O. Krasnovskaya, E. K. Beloglazkina, V. I. Terenin, V. E. Koteliansky, N. V. Zyk and A. G. Majouga, *J. Heterocycl. Chem.*, 2016, **53**, 1570.
11 M.-W. Ding, Y. Sun, X.-P. Liu and Z.-J. Liu, *Org. Prep. Proced. Int.*, 2003, **35**, 391.
12 A. I. Khodair, *Carbohydr. Res.*, 2001, **331**, 445.
13 M. E. Kukushkin, D. A. Skvortsov, M. A. Kalinina, V. A. Tafeenko, V. V. Burmistrov, G. M. Butov, N. V. Zyk, A. G. Majouga and E. K. Beloglazkina, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2020, **195**, 544.
14 N. M. Evdokimov, I. V. Magedov, D. McBrayer and A. Kornienko, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 1558.
15 F. Fujisaki, K. Shoji and K. Sumoto, *Heterocycles*, 2009, **78**, 213.
16 A. M. Said and G. P. Savage, *J. Org. Chem.*, 2011, **76**, 6946.
17 H. W. Shih and W. C. Cheng, *Tetrahedron Lett.*, 2008, **49**, 1008.

18 F. Fujisaki, H. Aki, A. Naito, E. Fukami, N. Kashige, F. Miake and K. Sumoto, *Chem. Pharm. Bull*., 2014, **62**, 429.
19 T. A. Cernak and J. L. Gleason, *Heterocycles*, 2007, **71**, 117.
20 F. Fujisaki, K. Shoji and K. Sumoto, *Chem. Pharm. Bull*., 2009, **57**, 1415.
21 A. B. Galun, *J. Chem. Eng. Data*, 1976, **21**, 241.
22 N. Abe, F. Fujisaki and K. Sumoto, *Chem. Pharm. Bull*., 1998, **46**, 142.
23 P. Edman, *Acta Chem. Scand*., 1950, **4**, 277.
24 A. V. Yakusheva, S. S. Galibeev, R. R. Spiridonova, Ya. D. Samuilov and A. M. Kochnev, *Polym. Sci., Ser. B*, 2008, **50**, 321 (*Vysokomol. Soedin*., 2008, **50**, 2042).

Received: 8th June 2021; Com. 21/6581