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A one-pot chemoselective S-alkylation and acetylation of thiohydantoins using the alkyl orthoformate–$ZnCl_2$–Ac_2O reagent system

Ravi Kumar, Prem M. S. Chauhan *

Medicinal and Process Chemistry Division, Central Drug Research Institute†, Lucknow 226 001, India

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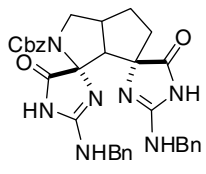
ABSTRACT

The chemoselective S-alkylation of 2-thiohydantoins is reported. The methodology involves the use of alkyl orthoformates (trimethyl and triethyl) as alkylating agents, which in the presence of Ac_2O and $ZnCl_2$ chemoselectively alkylate the thio group whilst other nucleophilic groups present in the thiohydantoins are acetylated simultaneously in moderate to high yields. A plausible mechanism for this reaction is delineated.

Thiohydantoins and their derivatives represent an important class of biologically active molecules having broad medicinal (anticancer,[1] anticonvulsant,[2] antidiabetic,[3] antimicrobial,[4] antiarrythmic,[5] hypolipidemic[6] and hypotensive[7]) and agrochemical[8] (herbicidal and fungicidal) applications. Furthermore, many thiohydantoins are responsible for inhibition of fatty acid hydrolases,[9] glycogen phosphorylases,[10] amylases[11] and serine proteases.[12]

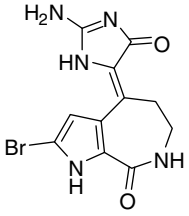
Thiohydantoins are useful synthons in natural product synthesis. Complex natural products such as the tetracyclic core of styloguanidine (**1**) and hymenialdisine (**2**), and bioactive heterocycles possesing a glycociamidine ring are commonly synthesized from their corresponding thiohydantoins. Conversion of 2-thiohydantoins to substituted glycociamidines is usually carried out in two steps; first thioalkyation of the thiohydantoin and then nucleophilic substitution of the thioalkyl group with a suitable nucleophile.[13–18] In general, thioalkylation is accomplished using alkyl halides which are toxic, dangerous, carcinogenic and nonselective.[19,20] Hence, there remains a need for an efficient protocol for chemoselective S-alkylation of 2-thiohydantoins using surrogate alkyl halide reagents (Fig. 1).

Orthoesters are commonly used in the preparation of ketals and acetals.[21–23] However, in recent years, increased interest has



1

Tetracyclic core of the complex hexacyclic bisguanidine alkaloid styloguanidine.[13]



2

Hymenialdisine[14b]

Figure 1. Structures of the tetracyclic core of styloguanidine (**1**) and hymenialdisine (**2**).

* Corresponding author. Tel.: +91 9415106859; fax: +91 522 2223405.
E-mail address: prem_chauhan_2000@yahoo.com (P. M. S. Chauhan).
† CDRI Communication No. 7501.

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Table 1
Chemoselective S-alkylation and acetylation of 2-thiohydantoins

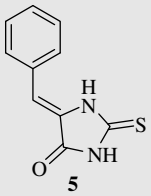
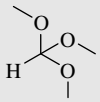
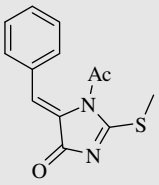
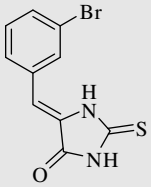
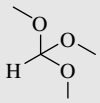
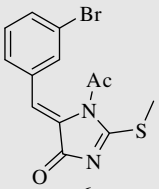
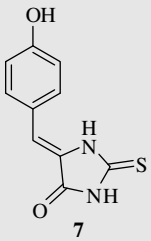
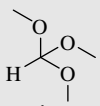
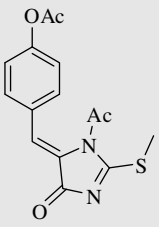
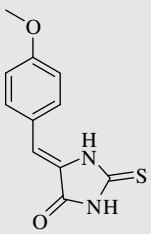
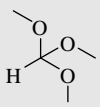
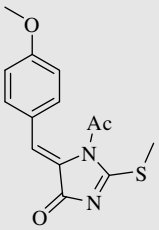
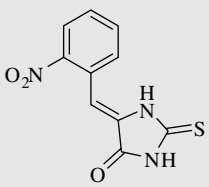
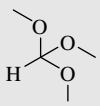
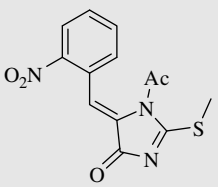
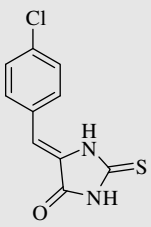
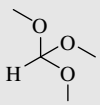
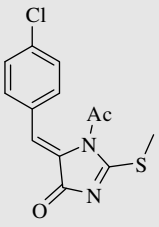
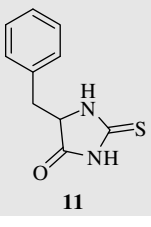
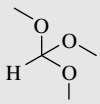
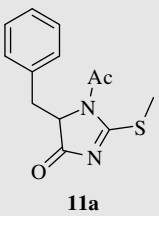
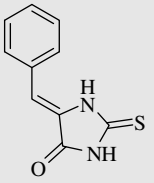
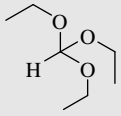
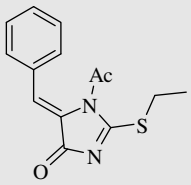
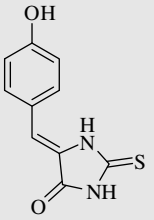
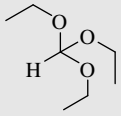
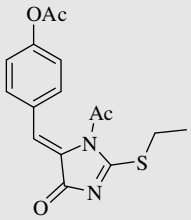
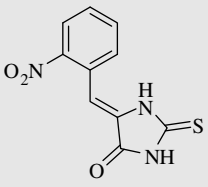
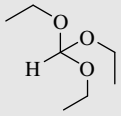
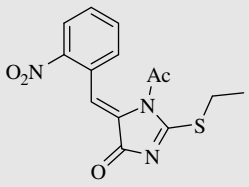
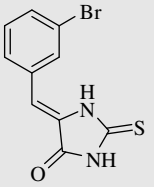
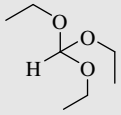
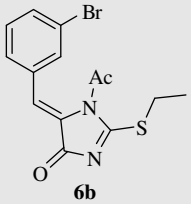
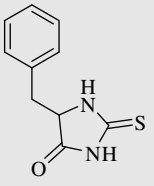
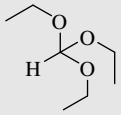
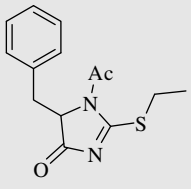
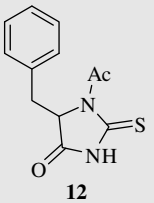
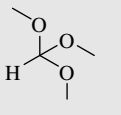
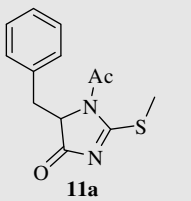
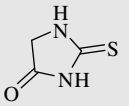
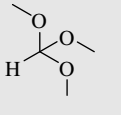
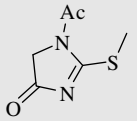
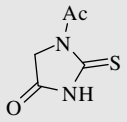
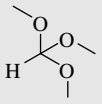
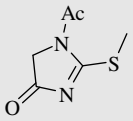
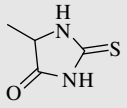
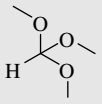
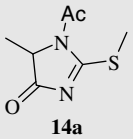
Entry	Substrate	Orthoformate	Product	Yield (%)	Time (h)
1	 **5**	 **4a**	 **5a**	78[a]	6
2	 **6**	 **4a**	 **6a**	72[b]	8
3	 **7**	 **4a**	 **7a**	69[b]	7
4	 **8**	 **4a**	 **8a**	71[a]	8
5	 **9**	 **4a**	 **9a**	88[a]	4
6	 **10**	 **4a**	 **10a**	65[a]	7
7	 **11**	 **4a**	 **11a**	82[b]	18

Table 1 (*continued*)

Entry	Substrate	Orthoformate	Product	Yield (%)	Time (h)
8	 **5**	 **4b**	 **5b**	81[a]	6
9	 **7**	 **4b**	 **7b**	72[b]	7
10	 **9**	 **4b**	 **9b**	90[a]	4
11	 **6**	 **4b**	 **6b**	74[b]	8
12	 **11**	 **4b**	 **11b**	83[b]	18
13	 **12**	 **4a**	 **11a**	82[b]	15
14	 **3**	 **4a**	 **3a**	65[a]	18

(*continued on next page*)

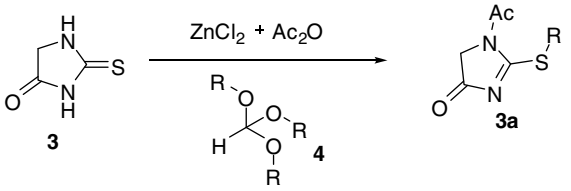
Table 1 (*continued*)

Entry	Substrate	Orthoformate	Product	Yield (%)	Time (h)
15	 **13**	 **4a**	 **3a**	67[a]	18
16	 **14**	 **4a**	 **14a**	40[b]	16

[a] Purified by filtration.
[b] Purified by column chromatography.

focused on alkyl orthoformates as alternative reagents to alkyl halides for safer and selective alkylation protocols. In particular, Selva's group recently developed a one-pot procedure for highly selective mono-C-methylation of arylacetonitrile using trimethyl orthoformate (TMOF) as the methylating agent.[24] Earlier, the same group reported that O-, S- and C-methylation of phenol, thiophenol and phenylacetonitrile, respectively, could be carried out using TMOF as the methylating agent.[25] Several TMOF-mediated N-methylations of aromatic amines and imidazole-like compounds have also been cited in the literature.[26–28]

In our endeavour to synthesize some key nitrogen heterocycles, it was observed that S-methylation and N-acetylation of 5-phenylmethylene-2-thiohydantoin (**5**) occurred on treatment with trimethyl orthoformate in Ac_2O and $ZnCl_2$ in one-pot. Herein, we report a one-pot chemoselective S-alkylation of 2-thiohydantoins and simultaneous acetylation of nucleophilic centres in the same molecule using alkyl orthoformates in Ac_2O and $ZnCl_2$. To the best of our knowledge, there have been no reports on this type of reaction.

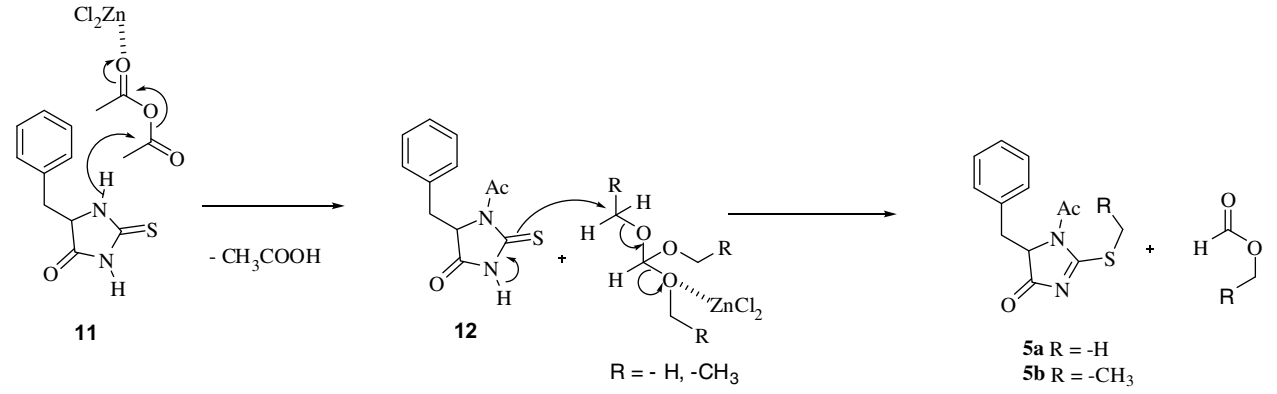


Scheme 1. General scheme for the chemoselective S-alkylation and acetylation of 2-thiohydantoins.

Initial investigations were focused on chemoselective S-alkylation of 5-substituted-2-thiohydantoins using 5-phenylmethylene-2-thiohydantoin (**5**) as the model substrate. At 100 °C, 1 equiv of $ZnCl_2$ was required for a 5:1 solution of trimethyl orthoformate (**4a**) and Ac_2O to convert completely 5-phenylmethylene-2-thiohydantoin (**5**) into its *S*-methyl *N*-acetyl derivative **5a**.

It was found that in the absence of either Ac_2O or $ZnCl_2$ the reaction failed to furnish the desired product. In order to explore whether substituents on the phenyl ring affected the reactivity of 5-phenylmethylene-2-thiohydantoins (PMHs), diversely phenyl substituted PMHs[29] were reacted with TMOF in Ac_2O and $ZnCl_2$. The results listed in Table 1 demonstrate that substituents on the phenyl ring do not affect the reactivity of PMHs towards S-alkylation. 5-(2-Nitrobenzylidene)-2-thioxoimidazolidin-4-one (**9**) reacted surprisingly rapidly with alkyl orthoformates to give the highest yields of products (Scheme 1).

To investigate the chemoselectivity of the reagent system, we carried out the reaction of 5-(4-hydroxybenzylidine)-2-thiooxoimidazolidin-4-one (**7**) with TMOF in Ac_2O and $ZnCl_2$ which resulted in N-, O-acetylated, S-methylated product **7a**. TLC analysis of the reaction of 5-benzyl-2-thiohydantoin with reference compound (**12**) provided an insight into the reaction mechanism indicating that acetylation precedes alkylation. Based on the above observation, we propose that $ZnCl_2$ mediated acetylation is followed by nucleophilic attack of the S-nucleophile of 1-acetylated 2-thiohydantoin at the alkoxy carbon (not the carboxylic carbon)



Scheme 2. Proposed mechanism for the S-alkylation and acetylation of 2-thiohydantoins.

of the orthoformate resulting in S-alkylation (Scheme 2). This was supported by the fact that when triethyl orthoformate (TEOF) was used instead of TMOF, S-ethylation took place along with N-acetylation (entries 8–12). 5-Benzyl (**11**) and 5-methyl-2-thiohydantoin (**14**) also gave the expected products (**11a**) and (**14a**), respectively, but were less reactive in comparison to their 5-methylene counterparts. Unsubstituted 2-thiohydantoin (**3**) yielded 1-acetyl-2-methylsulfanyl-4-imidazolidinone (**3a**) but the product of the reaction of 2-thiohyantoin (**3**) with TEOF in Ac_2O and $ZnCl_2$ was too unstable to be purified by column chromatography. 1-Methyl-2-thiohydantoin gave a complex mixture of products, whilst 1-acetyl-2-thiohydantoin (**13**) reacted smoothly to furnish 1-acetyl-2-methylsulfanyl-4-imidazolidinone (**3a**) in moderate yield. PMHs **5**–**10** gave better yields in comparison to 5-alkyl-2-thiohydantoins (**11**, **12** and **14**). Another interesting observation was that the active methylene group of 2-thiohydantoin (**3**) did not react with orthoformates, however, similar cyclopentendiones are known to react with orthoesters via their active methylene group.[30]

In conclusion, we have developed a highly chemoselective one-pot S-alkylation (methylation, ethylation) and acylation protocol of thiohydantoins.[31] This new protocol should help to expedite the overall synthetic process and reduce the labour involved in total syntheses of natural products. This method could be used for derivatization of natural products for medicinal chemistry purposes as it chemoselectively alkylates the thio group whilst any other nucleophilic groups are acetylated. It may also be useful for the alkyaltion of thiohydantoin molecules containing oxidation prone functional groups, in which case oxidative nucleophilic substitution[14a] of the thio group will not be possible.

General experimental procedure: $ZnCl_2$ (1.2 equiv, 1.2 mmol) was added to a mixture of 2 ml of acetic anhydride and 10 ml of trialkyl orthoformate at 100 °C. The resulting mixture was stirred for 5 min and then the 2-thiohydantoin (1 mmol) was added. The reaction was monitored by TLC analysis. After completion, the reaction mixture was cooled to room temperature and 20 ml of water was added. In most cases, a precipitate formed which was filtered and dried. In some cases (entries 2, 3, 11–13 and 16) a precipitate was not formed after addition of water. In these cases, the reaction mixture was neutralized with saturated sodium bicarbonate solution and extracted with DCM (15 ml × 3). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography using DCM as the eluent.

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31. *Representative analytical data for 1-acetyl-5-benzylidene-2-methylsufanyl-4-imidazolidinone* (**5a**): mp: 172–174 °C; Recrystallization solvent: Chloroform; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.18 (dd, 2H, J = 9.6 Hz, J' = 2 Hz), 7.46-7.43 (m, 3H), 7.00 (s, 1H), 2.67 (s, 3H), 2.64 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.74, 167.87, 163.17, 137.22, 134.27, 132.53, 130.80, 129.75, 129.55, 129.10, 126.04, 25.11, 14.89 ppm. IR (KBr) ν = 1747.6, 1712.0, 1706.5, 1634.4, 1597.4, 1495.9, 1371.0, 1291.5, 1215.7, 767.0 cm^{-1}. ESMS: m/z = 219 (M+1−Ac). Anal. Calcd for $C_{13}H_{12}N_2O_2S$ (260.06): C, 59.98; H, 4.65; N, 10.76. Found: C, 59.89; H, 4.60; N, 10.68.
Compound (**7a**): mp: 185–187 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.20 (d, 2H, J = 8.7 Hz), 7.18 (d, 2H, J = 9 Hz), 6.96 (s, 1H), 2.67 (s, 3H), 2.62 (s, 3H), 2.34 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 169.38, 169.32, 167.34, 162.95, 151.92, 136.72, 133.30, 131.62, 124.28, 121.87, 24.68, 21.01, 14.47 ppm. IR (KBr) ν = 1750.5, 1723.5, 1638.9, 1598.1, 1490.7, 1374.4, 1279.5, 1206.9, 1167.7, 918.7 cm^{-1}. ESMS: m/z = 277 (M+1−Ac). Anal. Calcd for $C_{15}H_{14}N_2O_4S$ (318.07): C, 56.59; H, 4.43; N, 8.80. Found: C, 56.52; H, 4.40; N, 8.73.
Compound (**7b**): mp: 178–180 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.19 (d, 2H, J = 9 Hz), 7.18 (d, 2H, J = 8.7 Hz), 6.95 (s, 1H), 3.25 (q, 2H, J = 7.4 Hz), 2.67 (s, 3H), 2.35 (s, 3H), 1.50 (t, 3H, J = 7.2 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.83, 166.88, 162.14, 151.73, 136.60, 132.90, 131.45, 123.59, 121.80, 95.80, 25.48, 24.59, 20.82, 13.03 ppm. IR (KBr) ν = 1751.6, 1727.2, 1638.6, 1598.1, 1487.4, 1372.5, 1272.5, 1206.2, 1167.8, 915.8 cm^{-1}. ESMS: m/z = 291 (M+1−Ac). Anal. Calcd for $C_{16}H_{16}N_2O_4S$ (332.08): C, 57.82; H, 4.85; N, 8.43. Found: C, 57.58; H, 4.68; N, 8.25.