N^3-(ARYLTHIO-, ARALKYLTHIO- AND ALKYLTHIO)-5,5-DIMETHYLHYDANTOINS: SULFENYL GROUP TRANSFER REACTIONS AND THEIR PROPERTIES[1]

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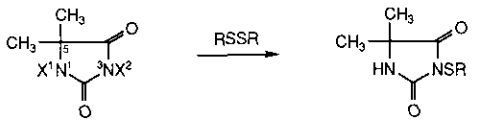
Abstract — Sulfenyl-transfer reactions toward a variety of nucleophiles were successfully carried out using N^3-sulfenyl-substituted 5,5-dimethylhydantoins (2a-c). During the course of the synthesis of 2 by the reaction of N^1-bromo-5,5-dimethylhydantoin (1c) with disulfides, the sulfenyl groups were found to be at the position of N^3 although the bromine was at N^1 in the starting monobromohydantoin (1c). Some mechanistic speculations were considered for the formation of 2 from 1c.

A variety of sulfenimides as sulfenyl-transfer reagents have hitherto been reported.[2] Surprisingly however, since Büchel and Conte[3] reported the synthesis of N^3-(arylthio- and aralkylthio)-5,5-dimethylhydantoins (2), no systematic investigation on sulfenyl-transfer reactions utilizing 2 has been published. To our knowledge, there is only the paper by Sosnovsky and Krogh[4] dealing with sulfenyl-transfer reactions to amines using 2a.

Our continuing interest in group transfer reactions mediated by 5,5-dimethyl-

Scheme 1



1 **a.** $X^1=X^2=H$
b. $X^1=H$, $X^2=Br$
c. $X^1=Br$, $X^2=H$

2 **a.** R=Ph
b. R=*p*-Cl-Ph
c. $R=PhCH_2$
d. R=Et

hydantoin derivatives[5] led us to study sulfenyl-transfer reactions using 2. N^3-(Arylthio-, aralkylthio- and alkylthio)-5,5-dimethylhydantoins (2) were conveniently prepared by the reaction of N-monobromo-5,5-dimethylhydantoin with the appropriate disulfides using a reported procedure[3] as shown in Scheme 1. The reaction of 2a-c with a variety of nucleophiles smoothly proceeded to give the corresponding sulfenylated compounds in good to excellent yields as seen in Table 1. Easy preparation of 2a-c and rapid completion of the sulfenyl group transfer reactions should lead to wide use of this system in organic syntheses.

Table 1. Products Derived from the Reaction of 2 with Nucleophiles

Sulfenimide	Nucleophile	Product[a]	Reaction Condition (Solv., Temp., Reaction time)	Mp(°C) or n_D (lit. mp or bp)	Yield (%)
2a	morpholine	PhSN⟨O⟩	CH_2Cl_2, rt, 16 h	33-35 (33-36)[6]	99.9
	piperazine	PhSN⟨NSPh⟩	CH_2Cl_2, rt, 4 h	162-164 (164-166)[6]	79
	aniline	PhSNHPh	C_2H_5OH, refl., 3.5 h	54.5-56.5 (57-59)[7]	86
	MBT[b]	PhSS-MBT	benzene, refl., 15 min	ca.30	93
	KCN	PhSCN	CH_2Cl_2-H_2O, rt, 1 h	n_D^{25} 1.5709 (66-67/3torr)[2b]	86
2b	morpholine	p-Cl-PhSN⟨O⟩	CH_2Cl_2, rt, 23.5 h	35-37	98.5
2c	morpholine	$PhCH_2SN$⟨O⟩	benzene, refl., 1 h	72-74 (72-74)[7]	91
	MBT[b]	$PhCH_2SS$-MBT	benzene, refl., 45 min	64.5-65.5	87-95
	$PhSO_2Na$	$PhCH_2SSO_2Ph$	CH_2Cl_2-H_2O, rt, 10 h	39-41	70.5

a. Satisfactory elemental analyses for C, H, N, S, and Cl were obtained within ±0.3% of the expected values.

b. 2-Mercaptobenzothiazole.

Although the position of the bromine of N-monobromo-5,5-dimethylhydantoin had been considered to be at N^3, the extensive work of Corral and Orazi[8] on the monobromination of 1a with an equivalent quantity of bromine in alkaline medium or with other bromination methods led to establishment of the structure as N^1-bromo-5,5-dimethyl-

hydantoin (1c). From this result, the structure of N-monobromo-5,5-dimethylhydantoin used in the preparation of 2 by Büchel and Conte[3] can be regarded as 1c. Interestingly, N^3-(arylthio-, aralkylthio- and alkylthio)-5,5-dimethylhydantoins (2) were nevertheless obtained by treatment of appropriate disulfides with 1c, in which a bromine atom was located at the N^1 position. The structures of 2a-d were readily characterized by examining the chemical shift of the amide NH's in the ^{1}H nmr at around δ 6.3-7.5[9] as shown in Table 2.

Table 2. Preparation of 5,5-Dimethylhydantoin Derivatives

Compound[a]	Mp(°C)(lit, mp)	Yield(%)	^{1}H Nmr (δ, ppm)[d] (lit. value)			
			N^1-H	N^3-H	N^1-CH_3	N^3-CH_3
2a	123-125[c](106-107)[3]	77	7.17-7.58[e]			
2b	145.5-148 (128-129)[3]	62	6.33			
2c	142-143[c](125-126)[3]	35-70	6.83			
2d	101-103	74	7.45			
3a[b]	oil	52 (from 2a)				3.10
3b	60-61.5	53				3.04
4b	92-93	36			2.83	
5a	121-123	59		9.55		
5b	149-151	66		9.17		
5c	160-162	44-86		9.13		
5d	79-81	45		9.17		
6[b]	157.5-159.5(160)[10]			9.55 (9.3)[9]	2.86 (2.85)[12]	
9[b]	146-147.5(148.5-149)[11]		6.98 (6.6)[9]			3.03 (3.00)[12]

a. Unless otherwise specified, satisfactory elemental analyses for C, H, N, S, and Cl were obtained within ±0.3% of the expected values.

b. Elemental analysis was not performed.

c. The mp occasionally varied probably due to the different crystal form caused by a different solvent composition [CH_2Cl_2-ether-(n-hexane)] used for recrystallization.

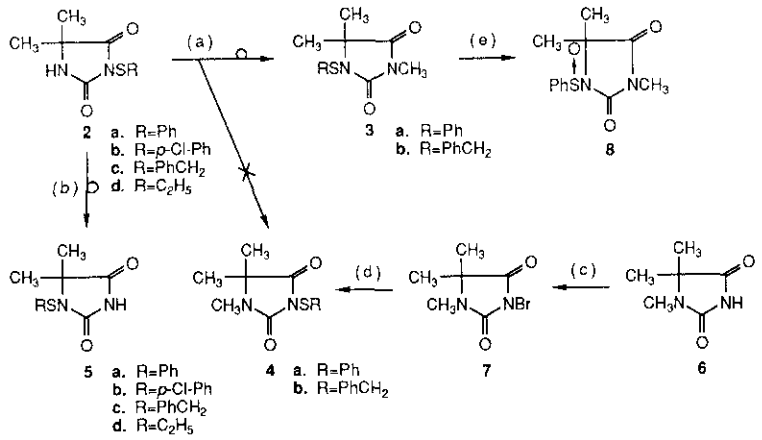
d. ^{1}H Nmr spectra were obtained in $CDCl_3$ using TMS as an internal standard.

e. The amide proton shows overlapping with aromatic protons, but the proton for 2a obtained in a different experiment was at δ 7.02.

This strongly suggests migration of bromine or some other rearrangement in the formation of 2. To confirm the structure of 2 by chemical transformations as shown

in Scheme 2, we tried methylation of 2a and 2c by treatment with an equimolar amount of sodium hydride (NaH) followed by reaction with dimethyl sulfate to obtain methylated compounds in 52 and 53% yields, respectively.

Scheme 2



(a) NaH/DMF, $(CH_3O)_2SO_2$, -20°C. (b) NaH/DMF, -20°C or rt.
(c) Br_2/aq. KOH. (d) $(PhCH_2S)_2$/benzene, refl. (e) m-CPBA/CH_2Cl_2.

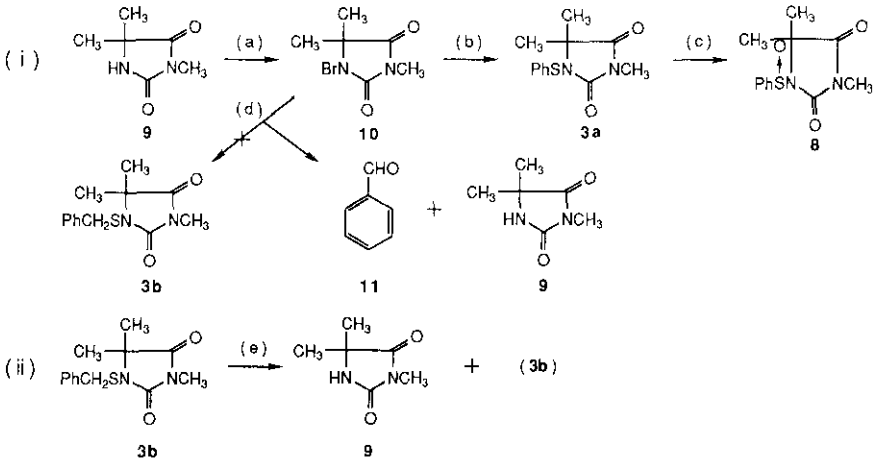
The signals of the methyl groups attached to nitrogen in the ^1H nmr at δ 3.10 and 3.04[12] suggested that the location of the methyl group is unexpectedly at N^3, indicating sulfenyl group migration from N^3 to N^1 during the methylation reaction. For comparison, compound 4b was unambiguously synthesized by the reaction of 7 with dibenzyl disulfide and this was shown to be not identical with the above obtained 3b, as expected (Table 2).

We thought it would be interesting to find in which stage of the two consecutive reactions (NaH treatment or the following methylation) the sulfenyl migration occurred. Treatment of 2a-d with NaH resulted in the formation of sulfenyl-migrated compounds, 5a-d, in 44 to 86% yields, the structures of which were confirmed by ^1H nmr spectra[9] (Table 2). This showed that sulfenyl migration occurred prior to the methylation reaction. Taking account of the acidity[13] of both amide (imide) NH's at positions 1 and 3, this fact may be explained by assuming that the nitrogen anion at position 1 generated by treatment of 2a-d with NaH is less thermodynamically stable than that at position 3 to lead to the formation of a more stable nitrogen anion at position 3, accompanied by simultaneous

sulfenyl migration from N^3 to N^1. However, at present, the mechanism of the sulfenyl migration is not clear.

In order to fully confirm the structures of the sulfenyl-migrated 3a and 3b, we next attempted to synthesize them by alternative routes as shown in Scheme 3. The reaction of N^1-bromo-3,5,5-trimethylhydantoin (10) with diphenyl disulfide afforded the desired 3a as an oil, which was subsequently converted to crystalline 8 (mp 139-141°C) by oxidation with m-CPBA. This was identical with the oxidation product of the sulfenyl-migrated product, 3a, as shown in Scheme 2. However, the reaction of 10 with dibenzyl disulfide did not afford the anticipated 3b, producing instead a small amount of benzaldehyde (11), identified as 2,4-dinitrophenylhydrazone, together with the debrominated 9 (38-43% yield). Next, treatment of 3b obtained as shown in Scheme 2 with morpholine in refluxing benzene for 48 h gave the desulfenylated 9 in a yield of 45.8%, and the unreacted starting 3b (~19%) was recovered. The structures of 3a and 3b were thus established by ^1H nmr spectra as well as by alternative synthesis of 3a or transformation of 3b to 9.

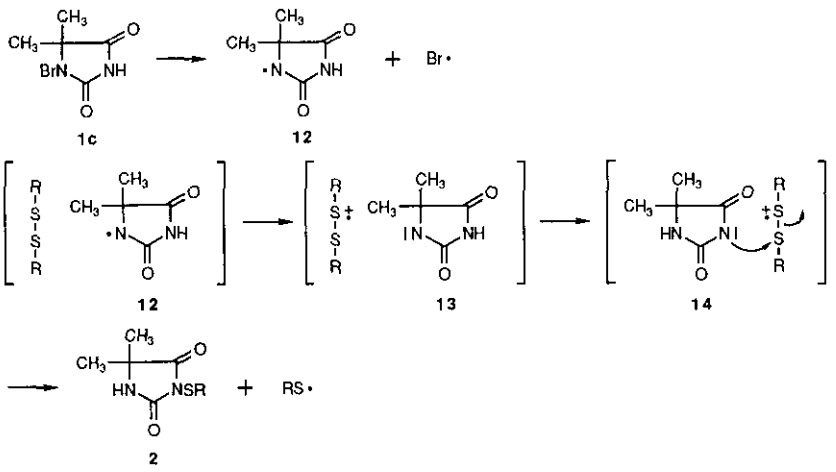
Scheme 3



(a) Br_2/aq.KOH. (b) $(PhS)_2$/benzene, refl. (c) m-CPBA/CH_2Cl_2.
(d) $(PhCH_2S)_2$/benzene, refl. (e) morpholine/benzene, refl.

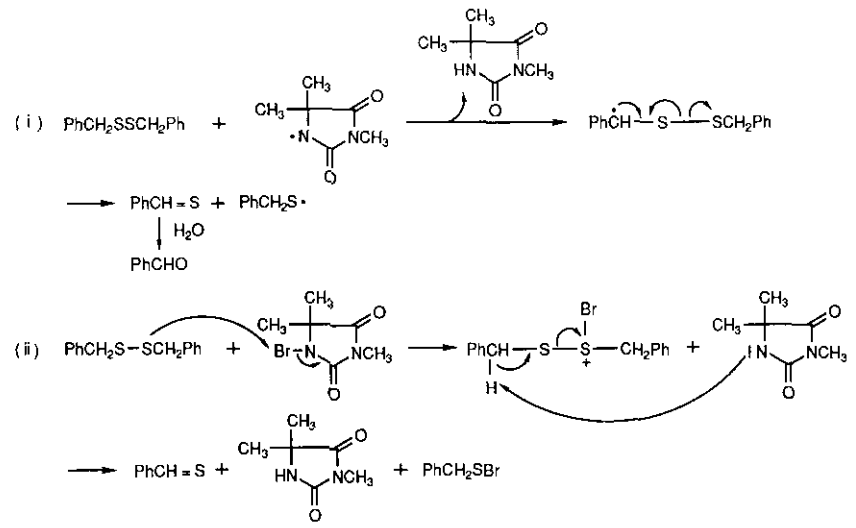
Some mechanistic speculations were then considered for the formation of N^3-sulfenylated hydantoin (2) from N^1-bromohydantoin (1c) and disulfides. The initial reaction is considered to proceed through a radical process[3] as shown in Scheme 4. The initially formed 12 is considered to be an electron-demanding

Scheme 4



radical and accordingly electron transfer from disulfide to 12 may occur to form 13 having a nitrogen anion at position 1. Here, the nitrogen anion at position 3 seems to be by far more stable than that at position 1 as already discussed above. A rapid prototropy from N^3 to N^1 is likely to occur, giving 14, which subsequently attacks the sulfur atom adjacent to the cation radical to give 2. With respect to the formation of benzaldehyde (11) in the reaction of 10 with dibenzyl disulfide, at least two alternative pathways seem to be possible as shown in Scheme 5. However, discrimination between the two routes would require further study.

Scheme 5



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