Reactions of α-Aminoacetonitriles with Isothiocyanates. Synthesis of 1,3-Disubstituted 5-Imino-2-thiohydantoins

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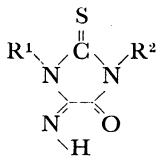
(Received April 24, 1979)

The reactions of α-aminoacetonitriles with isothiocyanates gave 1-cyanomethyl-1,3-disubstituted thioureas or 1,3-disubstituted 4-amino-4-imidazoline-2-thiones depending upon the reaction conditions. In the presence of polar organic solvents such as methanol the former products were easily cyclized to the latter. 1,3-Disubstituted 4-amino-4-imidazoline-2-thiones were autoxidized in methanol affording 1,3-disubstituted 5-imino-2-thiohydantoins.

A number of reports have been published concerning the synthesis of 1,3-disubstituted 5-iminohydantoins.[1-3] However, no synthetic study on 1,3-disubstituted 5-imino-2-thiohydantoins seems to have been reported except for the work of Kinoshita *et al.*[4] In a previous paper,[5] a report was given on the crystal structure of 1,3-dimethyl-5-imino-2-thiohydantoin prepared by the reaction of methylaminoacetonitrile with methyl isothiocyanate in the presence of atmospheric oxygen. This paper deals with the synthesis of 1,3-disubstituted 5-imino-2-thiohydantoins and the mechanism of the reaction of isothiocyanates with α-aminoacetonitriles.

Results and Discussion

Various types of isothiocyanates were allowed to react with α-aminoacetonitriles. The most basic compounds for this reaction are methyl isothiocyanate and equimolar quantities of methylaminoacetonitrile, which gave compound **1a** in methanol solution (85% yield). The structure of **1a** was confirmed to be 1,3-dimethyl-5-imino-2-thiohydantoin by the spectra data.

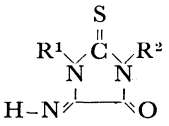


1, **a**: $R^1=R^2=CH_3$

The structure of the ring system has been established by X-ray analysis of **1a**.[5] However, the above reaction was carried out using benzene as a solvent to give compound **2a** (77% yield). The structure of **2a** was determined to be 1-cyanomethyl-1,3-dimethylthiourea by the spectral data.

When the reaction was undertaken using toluene as a solvent, compound **3a** was quantitatively precipitated (91% yield). However, when phenyl isothiocyanate

TABLE 1. YIELDS AND ANALYTICAL DATA OF 1,3-DISUBSTITUTED 5-IMINO-2-THIOHIDANTOINS (**1**)



Compd	R^1	R^2	Yield[a] %	Mp °C	Molecular[b] formula	Found (Calcd) C%	H%	N%	S%
1a	CH_3	CH_3	85	112	$C_5H_7N_3OS$	38.21 (38.21	4.52 4.49	26.62 26.73	20.52 20.40)
1b	C_6H_5	CH_3	75	170	$C_{10}H_5N_3OS$	54.85 (54.78	4.19 4.14	19.08 19.16	14.76 14.62)
1c	$C_6H_5CH_2$	CH_3	88	113	$C_{11}H_{11}N_3OS$	56.59 (56.63	4.71 4.75	18.13 18.01	13.62 13.74)
1d	$CH_3(CH_2)_3$	CH_3CH_2	40	78	$C_9H_{15}N_3OS$	50.46 (50.68	6.93 7.09	19.55 19.70	15.12 15.03)
1e	$C_6H_5CH_2$	CH_3CH_2	58	115	$C_{12}H_{13}N_3OS$	58.53 (58.28	5.16 5.30	16.88 16.77	13.24 13.28)
1f	$C_6H_5CH_2$	$CH_3CH_2CH_2$	42	67	$C_{13}H_{15}N_3OS$	59.49 (59.75	5.59 5.79	16.12 16.08	12.42 12.27)
1g	$C_6H_5CH_2$	$CH_3(CH_2)_3$	35	75	$C_{14}H_{17}N_3OS$	60.95 (61.06	6.03 6.22	15.29 15.26	11.72 11.64)
1h	$C_6H_5CH_2$	C_6H_5	14	196	$C_{16}H_{13}N_3OS$	64.94 (65.07	4.36 4.44	14.32 14.23	11.00 10.85)
1i	CH_3	$C_6H_5CH_2$	34	103	$C_{11}H_{11}N_3OS$	56.45 (56.63	4.61 4.75	18.04 18.01	13.83 13.74)
1j	$CH_3(CH_2)_3$	$C_6H_5CH_2$	70	73	$C_{14}H_{17}N_3OS$	61.07 (61.06	6.25 6.22	15.22 15.26	11.41 11.64)

a) Isolated yields. b) Determined by high resolution mass spectrometry.

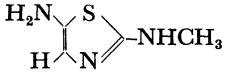
Table 2. Physical properties of 1,3-disubstituted 5-imino-2-thiohydantoins (**1**)

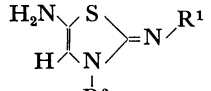
Compd	IR[a] ν/cm^{-1} C=N	C=O	N-H	UV[b] $\lambda_{max}(\varepsilon)$/nm	^{1}H NMR[c] of N-H, N-CH_2, and N-CH_3 (δ/ppm)
1a	1680	1755	3250	309 (11400)	3.23 (s, 3H, CH_3), 3.37 (s, 3H, CH_3), 10.10 (s, 1H, NH)
1b	1680	1745	3260	300 (14600)	3.30 (s, 3H, CH_3), 10.01 (s, 1H, NH)
1c	1680	1745 1754*	3260	308.5 (15600)	3.30 (s, 3H, CH_3), 5.19 (s, 2H, CH_2), 9.09 (s, 1H, NH)
1d	1678	1748	3260	312 (16000)	3.95 (q, J=7 Hz, 2H, CH_2), 4.03 (t, J=7 Hz, 2H, CH_2) 8.93 (s, 1H, NH)
1e	1680	1745	3250	309 (15700)	3.95 (q, J=7 Hz, 2H, CH_2), 5.19 (s, 2H, CH_2), 9.03 (s, 1H, NH)
1f	1680	1745	3250	309.5 (15800)	3.82 (t, J=7 Hz, 2H, CH_2), 5.16 (s, 2H, CH_2), 9.04 (s, 1H, NH)
1g	1680	1750	3250	310 (15200)	3.85 (t, J=7 Hz, 2H, CH_2), 5.16 (s, 2H, CH_2), 9.04 (s, 1H, NH)
1h	1678	1753	3260	310 (15800)	5.30 (s, 2H, CH_2), 9.17 (s, 1H, NH)
1i	1678	1750	3260	310 (15900)	3.43 (s, 3H, CH_3), 5.00 (s, 2H, CH_2), 8.99 (s, 1H, NH)
1j	1678	1745	3270	314 (14900)	4.01 (t, J=7 Hz, 2H, CH_2), 4.98 (s, 2H, CH_2), 8.97 (s, 1H, NH)

a) Measured in Nujol mulls (* shoulder). b) Observed in EtOH. c) Observed in DMSO-d_6 (**1** and **1b**), and CCl_4 (**1c**—**j**).

was used instead of methyl isothiocyanate, **2b** was not isolated even in a nonpolar solvent (benzene), **3b** being obtained in 88% yield. Whether the reaction gives **2** or **3** seems to depend upon the subtle difference in the overall polarity of the reaction system. Actually **2** was easily cyclized to **3** in a polar solvent. The structure of **3** was deduced to be 1,3-disubstituted 4-amino-4-imidazoline-2-thione by the spectral data.

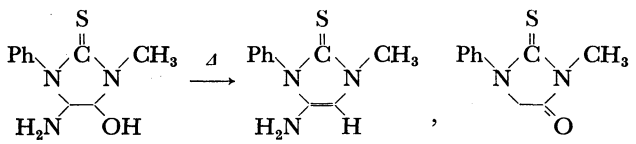
In 1948, Cook *et al.*[6] examined the reaction of aminoacetonitrile with methyl isothiocyanate to give 5-amino-2-(methylamino)thiazole (**4**). It appears that the isomer **5** is also possible as the structure of **3**.

$H_2NCH_2CN + CH_3NCS \longrightarrow$  **4**



5, **a**: $R^1=R^2=CH_3$
b: $R^1=C_6H_5$, $R^2=CH_3$

However, convincing proof for the structure of **3** could be given by the pyrolysis of **6** prepared by the reduction of **1b** with $LiAlH_4$. The main products derived from the pyrolysis of **6** at the injection port of a gas chromatograph were determined to be a dehydration compound, 1-methyl-3-phenyl-4-amino-4-imidazoline-2-thione and a deamination compound, 1-phenyl-3-methyl-2-thiohydantoin by gas chromatography mass spectrometry (Fig. 1).



6 (*cis*/*trans*)

The retention time and the mass spectrum of the dehydration peak 2 in Fig. 1 were identical with those of **3b** (Fig. 2). Compound **3b** underwent no ring-isomerization,[7] the starting material being recovered after heating at 230 °C. The structure of **3** should be similar to that of the dehydration compound of **6**, but not that of **5**. However, we have found no definite evidence for

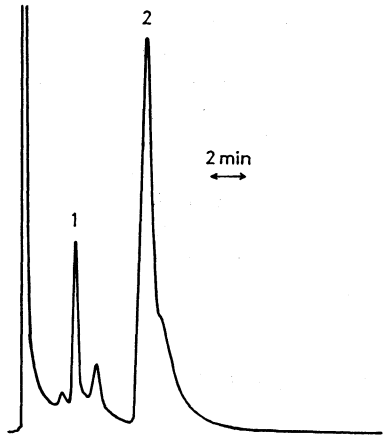


Fig. 1. Gas chromatogram of the products derived from the pyrolysis of *cis*-**6** taken by total ion current of GC-MS. Column of 2% Silicone OV-17 on Gas Chrom Q, 1 m×2 mm i.d. glass column, col. temp: 200 °C, inj. temp: 230 °C, flow rate: 23 ml/min He.

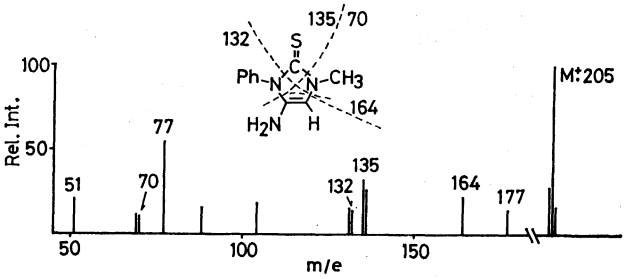


Fig. 2. Mass spectrum of peak 2 in Fig. 1.

the isomerization of **5** to **3** not occurring in the reaction process.

Even the solid of **3** is labile and turns dark-red on exposure to air producing a dimeric compound (**7**) which is insoluble in benzene, toluene, or cold methanol. Compound **7** is slightly soluble in hot methanol and is autoxidized to give **1**. Figure 3 shows the gas chromatogram derived from the autoxidation of **3a** in methanol solution. From the mass spectrum of GLC peak 2

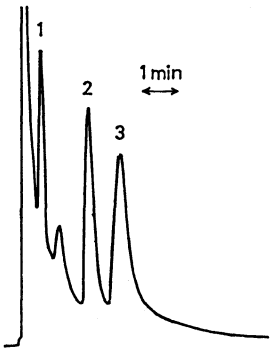
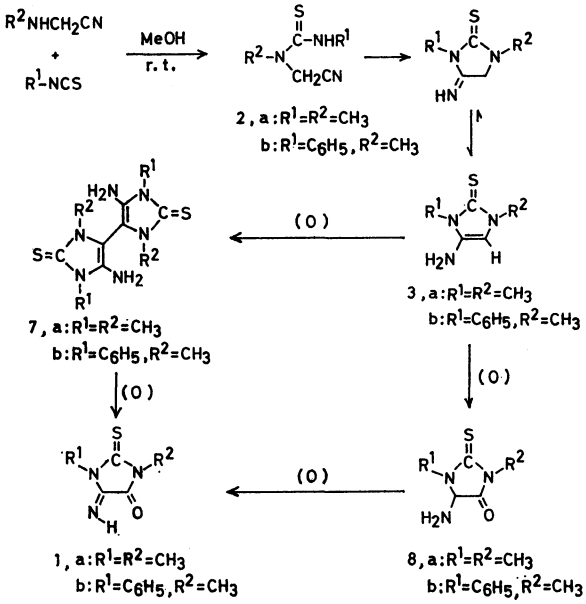


Fig. 3. Gas chromatogram of the products derived from the methanol solution of **3a** (after stirring 35 min at room temperature). Column of 2% Silicone OV-17 on Gas Chrom Q, 1 m×2 mm i.d. glass column, col. temp: 170 °C, inj. temp: 230 °C, flow rate: 32 ml/min He.

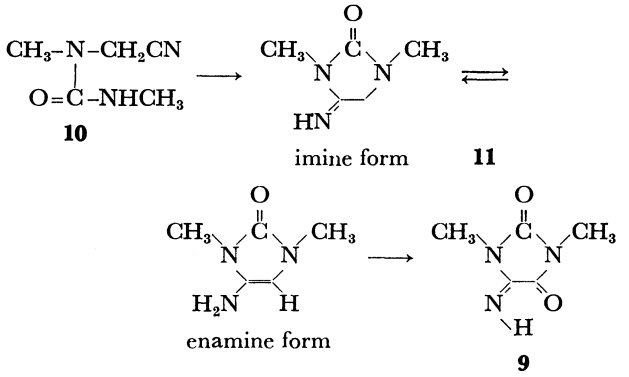
shown in Fig. 3, it was found that the peak is due to a new intermediate compound (**8a**). Attempts to isolate **8a** were unsuccessful. However, the intermediate **8b** could be isolated from the methanol solution of **3b**. In the presence of atmospheric oxygen **8b** was converted into **1b** quantitatively in a methanol solution at room temperature. The structure of **8b** was determined to be 5-amino-3-methyl-1-phenyl-2-thiohydantoin.

A plausible mechanism of the reaction of α-amino-acetonitriles with isothiocyanates in methanol is given in Scheme 1. 5-Imino-2-thiohydantoins (**1**) can be prepared from the autoxidation of two intermediate compounds (**7** and **8**) derived from the autoxidation of **3**.



Scheme 1.

The above reaction is applicable to the synthesis of 5-iminohydantoin derivatives such as 1,3-dimethyl-5-iminohydantoin (**9**) obtained by the reaction of methyl-aminoacetonitrile with methyl isocyanate. However, the reaction was extremely slow under conditions similar to those for the reaction in the preparation of **1**.



It was found that the cyclization reaction of **10** to **11** requires some kind of catalytic base such as pyridine or triethylamine, and the autoxidation of **11** to **9** requires a long period of time (*ca.* two weeks). The low reactivity of **11** toward atmospheric oxygen can be attributed to the fact that the equilibrium of **11** lies toward the imine form, whereas that of **3** lies toward the enamine form. Information on these tautomers was obtained from NMR spectra.

Experimental

All melting points are uncorrected. IR spectra were obtained on a JASCO IRA-2 spectrometer, UV spectra on a Cary 14 spectrometer, NMR spectra on a Varian A-60D spectrometer using tetramethylsilane as an internal standard, and high resolution mass spectra on a JEOL JMS-01SG mass spectrometer using a direct insertion probe and an ionization energy of 75 eV. GLC analyses were carried out on a JEOL JGC-20KFP gas chromatograph and GC-MS analyses on a JEOL JMS D-100 gas chromatograph mass spectrometer.

Materials. Commercial methyl, ethyl, butyl, phenyl, benzyl isothiocyanates, methyl isocyanate, methylaminoacetonitrile, and amines of reagent grade were used. α-Aminoacetonitriles were prepared according to the reported method.[8]

*Preparation of 1-Cyanomethyl-1,3-dimethylthiourea (**2a**).* A solution of methyl isothiocyanate (1.46 g, 20 mmol) in benzene (30 ml) was added dropwise to a solution of methylaminoacetonitrile (1.4 g, 20 mmol) in benzene (30 ml) at 5—10 °C, and the reaction mixture was stirred at 5—10 °C for 15 min and then filtered to give a colorless crystalline product (**2a**) (2.2 g, 77%); mp 75°C; MS, M. W. obsd=143.051, M. W. calcd=143.052 for $C_5H_9N_3S$; IR (Nujol), 3400 (N-H), 2270 (C≡N), 1542 (-NHCSN<) cm^{-1}; NMR (δ, ppm, DMSO-d_6), 7.91 (broad, 1H), 4.95 (s, 2H), 3.13 (s, 3H), 2.95 (d, J=4.5 Hz, 3H). Found: C, 42.09; H, 6.35; N, 29.31; S, 22.17%. Calcd for $C_5H_9N_3S$: C, 41.94; H, 6.33; N, 29.34; S, 22.39%.

*Preparation of 1,3-Dimethyl-4-amino-4-imidazoline-2-thione (**3a**).* A solution of methyl isothiocyanate (1.46 g, 20 mmol) in toluene (30 ml) was added dropwise to a solution of methyl-aminoacetonitrile (1.4 g, 20 mmol) in toluene (30 ml) at room temperature, and the reaction mixture was stirred at room temperature for 30 min and then filtered to give colorless needles (**3a**) (2.6 g, 91%); mp 96 °C; MS, M. W. obsd=143.050, M. W. calcd=143.052 for $C_5H_9N_3S$; IR (Nujol), 3320, 1645 cm^{-1}; UV (EtOH), λ_{max} 266.5 nm; NMR (δ, ppm, DMSO-d_6), 6.16 (s, 1H), 4.73 (broad, 2H), 3.38 (s, 3H), 3.33 (s, 3H); Found: C, 41.89; H, 6.47; N, 29.23; S, 22.28%. Calcd for $C_5H_9N_3S$: C, 41.94; H, 6.33; N, 29.34

S, 22.39%. In another experiment run exactly as above, except that benzene–triethylamine (27: 3) was used in place of toluene, the yield of **3a** was 2.5 g (88%).

Preparation of 1-Methyl-3-phenyl-4-amino-4-imidazoline-2-thione (3b). A solution of phenyl isothiocyanate (2.7 g, 20 mmol) in benzene (30 ml) was added dropwise to a solution of methylaminoacetonitrile (1.4 g, 20 mmol) in benzene (30 ml) at room temperature, and the reaction mixture was stirred at room temperature for 30 min and then filtered to give a pale yellow product (**3b**) (3.6 g, 88%); mp 113 °C; MS, M. W. obsd=205.067, M. W. calcd=205.068 for $C_{10}H_{11}N_3S$; IR (Nujol), 3350, 3260, 1645 cm^{-1}: NMR (δ, ppm, DMSO-d_6), 7.43 (5H, C_6H_5), 6.31 (1H, =CH–), 4.40 (2H, NH_2), 3.43 (3H, CH_3); Found: C, 58.73; H, 5.40; N, 20.23; S, 15.42%. Calcd for $C_{10}H_{11}N_3S$: C, 58.51; H, 5.40; N, 20.47; S, 15.62%.

Preparation of 1,3-Disubstituted 5-Imino-2-thiohydantoins (1). The following procedure illustrates the general method. A solution of methyl isothiocyanate (1.46 g, 20 mmol) in MeOH (30 ml) was added dropwise to a solution of methylaminoacetonitrile (1.82 g, 26 mmol) in MeOH (30 ml) at room temperature, and the reaction mixture was stirred at room temperature for 48 h in the presence of atmospheric oxygen. The solvent was evaporated *in vacuo*, and the residue was dissolved in hot ethanol, and filtered to remove the insoluble dimer (**7a**). The filtrate was then cooled to *ca.* 10 °C and filtered to give **1a** (2.67 g). An analytical sample was recrystallized from ethanol. Analytical data and physical properties of **1a** are summarized in Tables 1 and 2, respectively, along with the other derivatives (**1b—j**).

Isolation of the Intermediary Compound 7a. A solution of **3a** (1.5 g) in MeOH (40 ml) was stirred at room temperature for 4 h, and the solution was filtered to give a grayish product (**7a**) (230 mg, 15%); mp 246—248 °C (dec); MS, M. W. obsd=284.086, M. W. calcd=284.088 for $C_{10}H_{16}N_6S_2$; IR (Nujol), 3300, 3170, 1680, 1640 cm^{-1}; UV (EtOH), 288 nm; NMR (δ, ppm, DMSO-d_6), 5.05 (s, 4H), 3.42 (s, 6H), 3.20 (s, 6H); Found: C, 42.14; H, 5.75; N, 29.51; S, 22.47%. Calcd for $C_{10}H_{16}N_6S_2$: C, 42.23; H, 5.67; N, 29.55; S, 22.55%.

Isolation of the Intermediary Compound 8b. A solution of **3b** (0.5 g) in MeOH (20 ml) was stirred at room temperature for 4 h, and the solvent was evaporated *in vacuo*. The residue was subjected to preparative TLC on silica gel eluting with petroleum ether–benzene–ethanol (12: 4: 3) to give 5-amino-3-methyl-1-phenyl-2-thiohydantoin (**8b**) (60 mg, 11%); colorless plastic solid; MS, M. W. obsd=221.063, M. W. calcd=221.062 for $C_{10}H_{11}N_3OS$; IR (Nujol), 3390, 3310, 1747 cm^{-1}; NMR (δ, ppm, CCl_4), 7.24 (s, 5H), 4.82 (s, 1H), 3.18 (s, 3H), 1.76 (broad, 2H), Found: C, 54.08; H, 5.10; N, 18.87; S, 14.41%. Calcd for $C_{10}H_{11}N_3OS$: C, 54.28; H, 5.01; N, 18.99; S, 14.49%.

Reduction of 1b. A solution of **1b** (1.31 g, 6 mmol) in dry THF (40 ml) was added dropwise to a suspension of lithium aluminum hydride (0.5 g, 13 mmol) in dry THF (40 ml) at a rate such as to produce gentle reflux. After completing the addition, sufficient water was added dropwise with ice–water cooling to decompose the excess hydride. The reaction mixture was filtered and extracted with CH_2Cl_2, and the solution was dried over sodium sulfate and concentrated under reduced pressure. The residue was chromatographed on silica gel ($CHCl_3$–EtOH, 40: 1) to give 240 mg of *cis*-4-amino-5-hydroxy-1-methyl-3-phenylimidazolidine-2-thione(*cis*-**6**) and 20 mg of *trans*-**6**.

cis-**6**: Mp 102—103.5 °C; MS, M. W. obsd=223.079, M. W. calcd=223.078 for $C_{10}H_{13}N_3OS$; IR ($CHCl_3$), 3400, 3340 cm^{-1}; NMR (δ, ppm, DMSO-d_6), 7.35 (5H, C_6H_5), 5.12 (d, J=6 Hz, 1H, CH), 5.05 (d, J=6 Hz, 1H, CH), 3.5—3.0 (broad, 3H), 3.11 (s, 3H, CH_3). Found: C, 53.81; H, 5.66; N, 18.77; S, 14.30%. Calcd for $C_{10}H_{13}N_3OS$: C, 53.79; H, 5.87; N, 18.82; S, 14.36%.

trans-**6**: Mp 145.5—146.5 °C; MS, M^+ 223; IR ($CHCl_3$), 3380, 3330 cm^{-1}; NMR (δ, ppm, DMSO-d_6), 7.40 (5H, C_6H_5), 4.85 (d, J=3 Hz, 1H, CH), 4.63 (d, J=3 Hz, 1H, CH), 3.4—3.0 (broad, 3H), 3.08 (s, 3H, CH_3). Found: C, 53.62; H, 5.94; N, 18.71; S, 14.27%. Calcd for $C_{10}H_{13}N_3OS$: C, 53.79; H, 5.87; N, 18.82; S, 14.36%.

The assignments of *cis*/*trans*-**6** were carried out according to the reported method.[9]

Reaction of Methylaminoacetonitrile with Methyl Isocyanate. A solution of methyl isocyanate (1.6 g, 28 mmol) in benzene (30 ml) was added dropwise to a solution of methylaminoacetonitrile (2 g, 28.6 mmol) at 5—10 °C, and the reaction mixture was stirred at 5—10 °C for 10 min and then filtered to give 1-cyanomethyl-1,3-dimethylurea (**10**) (2.8 g, 78%); mp 83—83.5 °C; MS, M^+ 127; IR (Nujol), 3370 (N–H), 2250 (C≡N), 1640, 1550 cm^{-1}; NMR (δ, ppm, DMSO-d_6) 6.58 (broad, 1H, NH), 4.28 (s, 2H, CH_2), 2.84 (s, 3H, CH_3), 2.61 (d, J=4.5 Hz, 3H, CH_3). Found: C, 47.30; H, 7.09; N, 33.01%. Calcd for $C_5H_9N_3O$: C, 47.23; H, 7.13; N, 33.05%. A solution of **10** (2.54 g, 20 mmol) in methanol–triethylamine (50 ml: 5 ml) was stirred at room temperature for 24 h, and the solvent was evaporated *in vacuo* to give 1,3-dimethyl-4-iminoimidazolidine-2-one (**11**) (2.3 g, 91%); mp 35—37 °C; MS, M^+ 127; IR (Nujol), 3290 (N–H), 1740, 1716, 1668 cm^{-1}; NMR (δ, ppm, DMSO-d_6), 4.26 (s, 1H, NH), 3.92 (s, 2H, CH_2), 2.84 (s, 3H, CH_3), 2.79 (s, 3H, CH_3). Found: C, 47.18; H, 7.25; N, 33.00%. Calcd for $C_5H_9N_3O$: C, 47.23; H, 7.13; N, 33.05%. A solution of **11** (0.5 g, 4 mmol) in pyridine (20 ml) was stirred at room temperature for two weeks and separated by column chromatography (silica gel) to give 1,3-dimethyl-5-iminohydantoin (**9**) (110 mg, 20%); mp 117—118 °C (lit,[1] 119—120 °C); IR (Nujol), 3255 (N–H), 1735 (C=O), 1730 (C=O), 1665 (C=N) cm^{-1}; NMR (δ, ppm, $CDCl_3$), 8.85 (s, 1H, NH), 3.22 (s, 3H, CH_3), 3.12 (s, 3H, CH_3). Found: C, 42.49; H, 5.05; N, 29.86%. Calcd for $C_5H_7N_3O_2$: C, 42.55; H, 5.00; N, 29.77%.

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