5,5-Diaryl and 5-Alkyl-3-phenyl-4-imidazolidones: A Novel Synthesis

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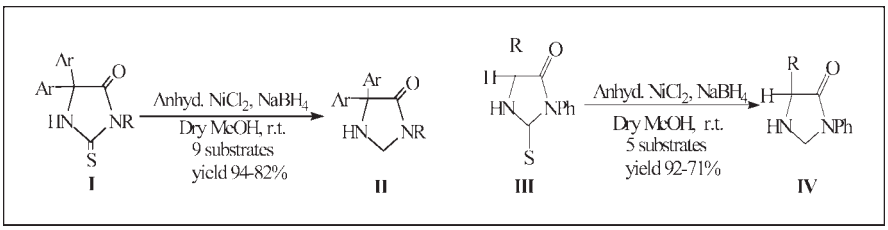
Received October 14, 2008
DOI 10.1002/jhet.165
Published online 2 September 2009 in Wiley InterScience (www.interscience.wiley.com).



Synthesis of 5,5-diaryl and 5-alkyl-3-phenyl-4-imidazolidones has been reported by reductive desulfurization of 5,5-diaryl and 5-alkyl-3-phenyl-2-thiohydantoins with nickel boride.

J. Heterocyclic Chem., **46**, 1007 (2009).

INTRODUCTION

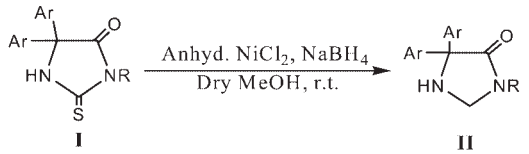
Compounds containing an imidazole ring are well-known in living systems. A number of 4-imidazolidone derivatives display a wide range of biological properties including anti-convulsant [1], anti-depressant [2], anti-inflammatory [3], anti-viral [4], anti-tumor [5], etc. 4-imidazolidones can be prepared by multistep synthesis involving reagents which are difficult to handle [6]. Although sodium and amyl alcohol [7], sodium amalgam [8], H_2 pressure on Pd-charcoal catalyst [9], and Raney nickel [10] have been reported as dethiating agents for 2-thiohydantoins, the yields range from low to moderate. However, the synthesis of 4-imidazolidones by reductive desulfurization of 2-thiohydantoins has not received attention. Reductive desulfurization of 2-thiohydantoins would obviously provide an alternate and convenient method of synthesis of 4-imidazolidones.

Nickel boride [11] has been reported as a convenient and efficient reagent for reductive desulfurization of benzimidazoline-2-thiones, 2-thiobarbituric acids [12], 2-thioxo-4-3*H*-quinazolinones [13], and 2-thioxo-5*H*-pyrano[23-*d*]pyrimidines [14]. In view of its versatility and ease of handling, we decided to explore its application for the desulfurization of 5,5-diaryl, 5-alkyl-3-phenyl and 5-alkyl-2-thiohydantoins.

RESULTS AND DISCUSSION

In this article, we report a convenient synthesis of 5,5-diaryl and 5-alkyl-3-phenyl-4-imidazolidones by reductive desulfurization of 5,5-diaryl-2-thiohydantoins (**Ia–i**) and 5-alkyl-3-phenyl-2-thiohydantoins (**IIIa–e**) with nickel boride in dry methanol at ambient temperature. The nickel boride was prepared *in situ* from anhydrous nickel chloride and sodium borohydride. Reactions were carried out under varying conditions by changing solvents and molar ratio of substrate to nickel boride to optimize conditions for quantitative desulfurization.

The 5,5-diaryl-2-thiohydantoins underwent complete reductive desulfurization to give the corresponding 5,5-diaryl-4-imidazolidones in high yields [Eq. (1)] and were identified by their spectral data. The sulfur by-product of these reactions is hydrogen sulfide gas. A number of new 4-imidazolidones have been synthesized in this manner. All the 4-imidazolidones showed a distinct peak at δ 4.4–4.5 for two protons due to —NH—CH_2—NR— group. IR showed a peak at ∼1680–1750 cm^{-1} due to —CO—NR group. No 4-imidazolidinones (double bond between 1-2 positions or 2-3 positions) were formed under these conditions. These results are listed in Table 1.



(1)

a:	Ar = C_6H_5, R = H	b:	Ar = p-$MeOC_6H_4$, R = H
c:	Ar = p-MeC_6H_4, R = H	d:	Ar = o-MeC_6H_4, R = H
e:	Ar = p-ClC_6H_4, R = H	f:	Ar = o-ClC_6H_4, R = H
g:	Ar = p-BrC_6H_4, R = H	h:	Ar = m-BrC_6H_4, R = H
i:	Ar = C_6H_5, R = C_6H_5		

The reactions carried out in ethanol, THF, and DMF were sluggish and showed the formation of

Table 1

Reactions of 5,5-diaryl-2-thiohydantoin with nickel boride in dry methanol[a] at ambient temperature.

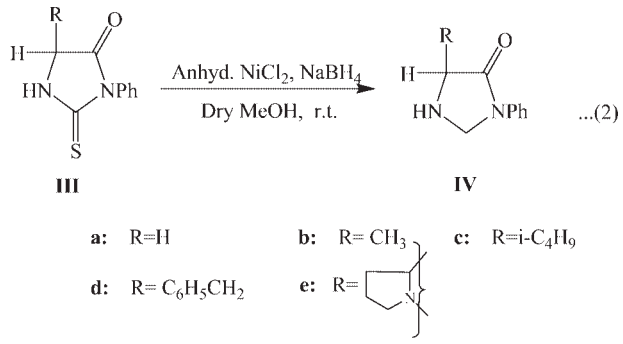
Run	Substrate (S)	Molar ratio S:$NiCl_2$:$NaBH_4$	Reaction time (min)	Product (P)	Yield (%)
1.	**Ia**	1:8:8	5	5,5-diphenyl-4-imidazolidone (**IIa**)	94 [15]
2.	**Ib**	1:8:8	15	5,5-di(*p*-anisyl)-4-imidazolidone (**IIb**)	89 [10a]
3.	**Ic**	1:10:10	30	5,5-di(*p*-tolyl)-4-imidazolidone (**IIc**)	89
4.	**Id**	1:5:5	45	5,5-di(*o*-tolyl)-4-imidazolidone (**IId**)	88
5.	**Ie**	1:6:6	120	5,5-di(*p*-chlorophenyl)-4-imidaolidone (**IIe**)	89
6.	**If**	1:6:6	150	5,5-di(*o*-chlorophenyl)-4-imidazolidone (**IIf**)	86
7.	**Ig**	1:10:10	5	5,5-di(*p*-bromophenyl)-4-imidazolidone (**IIg**)	87
8.	**Ih**	1:8:8	10	5,5-di(*m*-bromophenyl)-4-imidazolidone (**IIh**)	84
9.	**Ih**	1:10:10	5	5,5-di(*m*-bromophenyl)-4-imidazolidone (**IIh**)	86
10.	**Ih**	1:15:15	5	5,5-di(*m*-bromophenyl)-4-imidazolidone (**IIh**)	82
11.	**Ii**	1:20:20[b]	6 h	–	–[c]

[a] 5 mL of dry methanol was used for 0.1 g of substrate.
[b] Reaction started with 1:10:10 molar ratio of S:$NiCl_2$:$NaBH_4$ and another lot of 10:10 $NiCl_2$:$NaBH_4$ was added after 2 h.
[c] Incomplete reaction.

complex mixture of products, unlike the reactions in dry methanol. Therefore, dry methanol was the solvent of choice in these reactions. Reaction of 5,5-diphenyl-2-thiohydantoin (**Ia**) with sodium borohydride alone in 1:8 molar ratio yielded a mixture of products, whereas starting material was recovered on reaction with nickel chloride alone (molar ratio 1:8) under these conditions. This confirms that the reductive desulfurizations are proceeding due to nickel boride generated *in situ*.

Nickel boride showed high selectivity toward desulfurization because it did not affect the carbonyl group and also no dehalogenated products were obtained in the reactions of **Ie–h**. Reaction of 5,5-di(*m*-bromophenyl)-2-thiohydantoin (**Ih**) in high-molar ratios also did not show any debromination (Table 1) as only 82 and 86% of 5,5-di(*m*-bromophenyl)-4-imidazolidone (IIh) was isolated in runs 9 and 10, respectively. 3,5,5-Triphenyl-2-thiohydantoin (**Ii**) did not undergo any reaction and starting material was recovered unchanged even after using high-molar ratios (run 11). This could be due to steric hindrance of the 3-phenyl groups, which prevents reaction on the surface of catalyst.

Reactions of 5-alkyl-3-phenyl-2-thiohydantoins (**IIIa–d**) also yielded corresponding 5-alkyl-3-phenyl-4-imidazolidones (**IVa–d**) in high yields with nickel boride [Eq. (2)]. Desulfurization of 2-phenyl-1*H*-pyrrolo[1,2-*c*]imidazol-3-thio-1-one (**IIIe**) with nickel boride yielded 2-phenyl-1*H*-pyrrolo[1,2-*c*]imidazol-1-one (**IVe**) with 89% yield. Synthesis of **IVe** has been reported by multistep synthesis [16]. Reactions of 2-thiohydantoin (**Va**), 5-methyl-2-thiohydantoin (**Vb**), and 5-isopropyl-2-thiohydantoin (**Vc**) were not clear and mixtures of products were obtained. All the results are listed in Table 2.



Therefore, we conclude that nickel boride is an efficient reagent for the reductive desulfurization of 5,5-diaryl-2-thiohydantoins (**I**) and 5-alkyl-3-phenyl-2-thiohydantoins (**III**) and provides a convenient route for synthesis of 4-imidazolidones (**II** and **IV**) in high yields.

EXPERIMENTAL

Starting materials. Methanol (S.D. Fine) was used after drying by the reported procedure [17]. Nickel (II) chloride hexahydrate (Thomas Baker Chemicals) was dried by heating in a crucible till golden yellow, it was then allowed to cool at room temperature and stored over calcium chloride in a dessiccator. Sodium borohydride (E. Merck) was used in all the reactions. Thiourea (S.D. Fine) was used as such for the preparation of starting materials. Benzils were prepared from the corresponding hydrobenzoins by oxidation with NBS [18]. Glycine, alanine, isoleucine, phenylalanine, and proline were obtained from commercial sources. 5,5-Diaryl-2-thiohydantoins were prepared by the condensation of thiourea and benzils in the presence of potassium hydroxide [19]. 5-Alkyl-3-phenyl-2-thiohydantoins were prepared by the reaction of corresponding amino acids with aniline, triethyl amine, carbon disulphide, and methyl iodide [20] and 5-alkyl-2-thiohydantoins were

Table 2

Reactions of 5-alkyl-3-phenyl-2-thiohydantoins and 5-alkyl-2-thiohydantoin with nickel boride in dry methanol at ambient temperature.

Run	Substrate (S)	Molar ratio S:$NiCl_2$:$NaBH_4$	Reaction time (min)	Product (P)	Yield (%)
12.	**IIIa**	1:10:10	5	3-phenyl-4-imidazolidone (**IVa**)	72
13.	**IIIb**	1:10:10	5	5-methyl-3-phenyl-4-imidazolidone (**IVb**)	92
14.	**IIIc**	1:10:10	10	5-isobutyl-3-phenyl-4-imidazolidone (**IVc**)	71
15.	**IIId**	1:5:5	10	5-benzyl-3-phenyl-4-imidazolidone (**IVd**)	85
16.	**IIIe**	1:10:10	15	2-phenyl-1*H*-pyrrolo[1,2-c]imidazol-1-one (**IVe**)	89 [16]
17.	**Va**	1:5:5[a]	150	–	–[b]
18.	**Va**	1:3:9	5	–	–[b]
19.	**Vb**	1:5:5	60	–	–[b]
20.	**Vc**	1:5:5	15	–	–[b]
21.	**Vc**	1:10:10	5	–	–[b]

[a] Reaction started with 1:3:3 molar ratio of S:$NiCl_2$:$NaBH_4$ and second lot of $NiCl_2$:$NaBH_4$ was added after 60 min.
[b] Starting material disappeared but number of spots were observed on TLC.

prepared by reaction of amino acids with potassium thiocyanate in acetic anhydride [21].

Reactions of 2-thiohydantoins. In a typical procedure, 5,5-diphenyl-2-thiohydantoin (**Ia**) (0.1 g, 0.37315 mmol), anhydrous nickel chloride (0.3851 g, 2.9851 mmol), and dry methanol (5 mL) were placed in a 50 mL round-bottomed flask fitted with a condenser and a $CaCl_2$ guard tube. The flask was mounted over a magnetic stirrer. Sodium borohydride (0.1135 g, 2.9851 mmol) was added very cautiously while stirring the solution vigorously. The progress of the reaction was monitored by TLC using petroleum ether-ethyl acetate as eluent. After disappearance of the starting material, the reaction mixture was filtered through a celite pad (~1 inch) and washed with methanol (1 × 15 mL). The combined filtrate was diluted with water (~50 mL) and extracted with ethyl acetate (3 × 10 mL). The combined extract was dried over anhydrous $MgSO_4$, filtered, and concentrated on a rotary evaporator to give a new product, which was purified by recrystallization from ethanol and analyzed by mp, IR, NMR, and mass spectra as 5,5-diphenyl-4-imidazolidone (**IIa**) (0.0825 g, 94%) mp 182–183°C (lit. mp 183°C) [15]. All other products were synthesized similarly from the corresponding 2-thiohydantoins. The spectroscopic data of newly synthesized 4-imidazolidones is listed as follows.

IIc: (0.08 g, 89%), mp 170°C; IR: NH 3185, C=O 1699 cm^{-1}; ^1H NMR: δ 2.32–2.35 (2× CH_3, 6H), 4.39 (s, 2H, H-2), 7.12–7.50 (m, 8H, Ar′—H, Ar′′—H); MS ES+ for $C_{17}H_{18}N_2O$ (266): 267 (M^+ +1). Anal. Calcd. for $C_{17}H_{18}N_2O$: C, 76.72; H, 6.82; N, 10.53. Found: C, 76.73; H, 6.82; N, 10.52.

IId: (0.078 g, 88%), mp 150°C; IR: NH 3216, C=O 1710 cm^{-1}; ^1H NMR: δ 1.99 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 4.55 (s, 2H, H-2), 7.11–7.36 (m, 8H, Ar—H); MS ES+ for $C_{17}H_{18}N_2O$ (266): 267 (M^+ +1). Anal. Calcd. for $C_{17}H_{18}N_2O$: C, 76.72; H, 6.82; N, 10.53. Found: C, 76.72; H, 6.83; N, 10.52.

IIe: (0.082 g, 89%), mp 140°C; IR: NH 3308, C—O 1683 cm^{-1}; ^1H NMR: δ 4.43 (s, 2H, H-2), 7.29–7.36 (m, 4H, 2′, 6′, 2′′ and 6′′-H), 7.49–7.52 (d, J = 8.68 Hz, 2H, 3" and 5"-H), 7.56–7.59 (d, J = 8.44 Hz, 2H, 3′ and 5′-H); MS ES+ for $C_{15}H_{12}N_2Cl_2O$ (306): 307 (M^+ +1). Anal. Calcd. for $C_{15}H_{12}N_2Cl_2O$: C, 58.87; H, 3.95; N, 9.15. Found: C, 58.87; H, 3.96; N, 9.15.

IIf: (0.078 g, 86%), mp 142–145°C; IR: NH 3409, C=O 1708 cm^{-1}; ^1H NMR: δ 4.43–4.50 (t, 2H, H-2), 7.26–7.59 (m, 8H, Ar—H); MS ES+ for $C_{15}H_{12}N_2Cl_2O$ (306): 329 (M^+ + Na). Anal. Calcd. for $C_{15}H_{12}N_2Cl_2O$: C, 58.87; H, 3.95; N, 9.15. Found: C, 58.88; H, 3.95; N, 9.14.

IIg: (0.08 g, 87%), mp 176°C; IR: NH 3409, C=O 1708 cm^{-1}; ^1H NMR: δ 4.42 (s, 2H, H-2), 7.26–7.59 (m, 8H, Ar—H); MS ES+ for $C_{15}H_{12}N_2Br_2O$ (394): 395 (M^+ +1). Anal. Calcd. for $C_{15}H_{12}N_2Br_2O$: C, 45.74; H, 3.07; N, 7.11. Found: C, 45.72; H, 3.08; N, 7.10.

IIh: (0.0796 g, 84%), mp 110–112°C; IR: NH 3173, C=O 1686 cm^{-1}; ^1H NMR: δ −4.43 (s, 2H, H-2), 7.18–7.84 (m, 8H, Ar—H); MS ES+ for $C_{15}H_{12}N_2Br_2O$ (394): 395 (M^+ +1). Anal. Calcd. for $C_{15}H_{12}N_2Br_2O$: C, 45.74; H, 3.07; N, 7.11. Found: C, 45.72; H, 3.08; N, 7.11.

IVa: (0.0610 g, 72%), mp 154°C; IR: NH 3155, C=O 1766 cm^{-1}; ^1H NMR: δ 3.60–3.62 (d, 2H, H-4), 4.74 (s, 2H, H-2), 7.16–7.57 (m, 5H, Ar—H); MS ES+ for $C_9H_{10}N_2O$ (162): 162 (M^+). Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.69; H, 6.22; N, 17.26. Found: C, 66.70; H, 6.22; N, 17.25.

IVb: (0.0786 g, 92%); IR: NH 3292, C=O 1714 cm^{-1}; ^1H NMR: δ 1.44–1.46 (d, 3H, 5-CH_3), 3.63–3.70 (q, 1H, H-5), 4.80 (s, 2H, H-2), 7.1644–7.5828 (m, 5H, Ar—H); MS ES+ for $C_{10}H_{12}N_2O$ (176): 177 (M^+ +1). Anal. Calcd. for $C_{10}H_{12}N_2O$: C, 68.21; H, 6.87; N, 15.91. Found: C, 68.21; H, 6.88; N, 15.90.

IVc: (0.0624 g, 71%), mp 113°C; IR: NH 3284, C—O 1689 cm^{-1}; ^1H NMR: δ 0.98–1.02 (t, 6H, H-γ), 1.47–1.50 (m, 1H, H-β), 1.85–1.90 (m, 2H, H-α), 3.60–3.63 (d, 1H, H-4), 4.79 (s, 2H, H-2), 7.35–7.57 (m, 5H, Ar—H); MS ES+ for $C_{13}H_{18}N_2O$ (218): 219 (M^+ +1). Anal. Calcd. for $C_{13}H_{18}N_2O$: C, 71.58; H, 8.32; N, 12.84. Found: C, 71.58; H, 8.33; N, 12.82.

IVd: (0.0750 g, 85%), mp 140°C; IR: NH 3283, C—O 1682 cm^{-1}; ^1H NMR: δ 3.08–3.24 (m, 2H, —CH_2Ph), 3.89 (s, 1H, H-5), 4.53–4.71 (dd, J = 7.2 Hz, 2H, H-2), 7.13–7.52 (m, 10H, Ar—H); MS ES+ for $C_{16}H_{16}N_2O$ (252): 253 (M^+ +1). Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.22; H, 6.40; N, 11.11. Found: C, 76.23; H, 6.40; N, 11.10.

IVe: (0.0775 g, 89%), mp 90°C; IR: C=O 1692 cm^{-1}; ^1H NMR: δ 1.82–1.91 (m, 2H, H-6), 2.18–2.25 (q, 2H, H-7), 2.66–2.74 (q, 1H, H-8), 3.24–3.31 (m, 1H, H-8), 3.91–3.95 (t, 1H, H-5), 4.56–4.59 (d, J = 8.29 Hz, 1H, H-2), 4.99–5.02 (d,

J = 8.29, 1H, H-2), 7.14–7.59 (m, 5H, Ar—H); MS ES+ for $C_{12}H_{14}N_2O$ (202): 203 (M^+ +1). Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.31; H, 6.98; N, 13.86. Found: C, 71.31; H, 6.98; N, 13.86.

Acknowledgments. A. Agrawal is grateful to CSIR, New Delhi, India for the award of senior research fellowship.

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