IMPROVED SYNTHESIS OF 5-ARYL-2-THIOXOIMIDAZOLIDIN-4-ONES FROM ARYLGLYOXAL HYDRATES

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A new kind of 5-aryl-2-thioxoimidazolidin-4-ones synthesis by condensation of arylglyoxal hydrates with thiourea in acetic acid solution at room temperatures has been developed.

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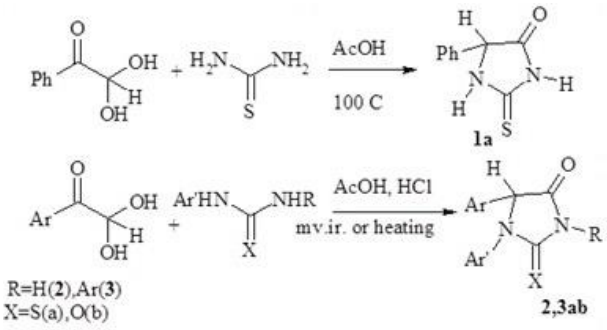
INTRODUCTION

Firstly 5-phenyl-2-thioxoimidazolidin-4-one (**1a)** had been synthesized from phenylglyoxal hydrate by interaction with thiourea in aqueous solution at room temperatures.[1] But in this work 5-phenyl-2-thiohydantoin (**1a)** structure of the condensation product no had been established by the author, only it has relevant of the data of the elemental analysis.[1] Only recently the strictly evidence that phenylglyoxal hydrate interaction with thiourea acetic acid solution at 100ºC yielded **1a** had been done[2] (Scheme 1). A structure of compound **1a** is consistent with data of ^{1}H and ^{13}C NMR spectra and mass-spectrum.[2] Also, it was shown that phenylglyoxal hydrate condensed with N-arylthioureas and N-arylureas yielding 1-aryl-5-phenylthiohydantoins (**2a)** and 1-aryl-5-phenylhydantoins (**2b)** (1,5-diarylimidazolidine-2,4-diones),[3,4] respectively, in the presence of polyphosphoric acid at microwave irradiation in the absence of solvent (Scheme 1). But this method needs using of large amounts of polyphosphoric acid (or "polyphosphoric ester"[3]) and is appreciable only for synthesis of small amounts of 1-aryl-5-phenylthiohydantoins.

It must be noted that arylglyoxals hydrates condense with N-arylthioureas (boiling acetic acid, 4 h) and N,N'-bisarylthioureas (boiling acetic acid, 6 h) in hydrochloric acid presence yielding 1,5-diarylthiohydantoins (**2a)** and 1,3,5-triarylthiohydantoins (**3a),**[4,5] respectively (Scheme 1).

In the same conditions, arylglyoxals react with N-arylureas and N,N'-bisarylureas yielding 1,5-diarylhydantoins (**2b)** and 1,3,5-triarylhydantoins (**3b),**[5] respectively.

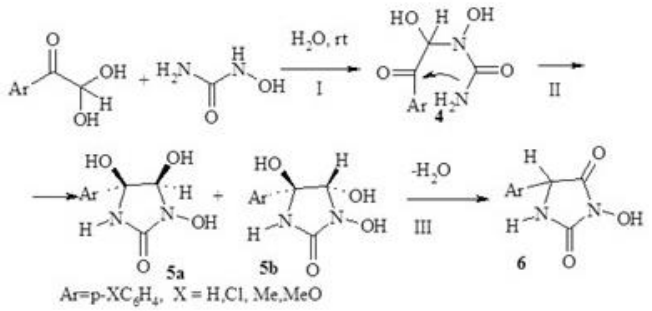


Scheme 1.

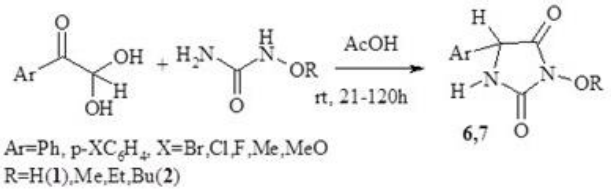
Also, it must be noted that 1,5-diarylhydantoins (**2b)** had also been prepared by arylglyoxals condensation with N-arylureas in the presence of hydrochloric acid and acetic acid in boiling ethanol for 4 h.[6]

It is obviously that 1-aryl-5-arylthiohydantoins formation from arylglyoxals hydrates and thiourea takes place in the presence of strong acid[3-5] or in boiling acetic acid solution.[2] But the course of this reaction in acetic acid media at room temperatures has not been studied.

Recently we had shown that arylglyoxals hydrates reacted with N-hydroxyurea in neutral aqueous solution in three stages (Scheme 2) yielding 3-hydroxy-5-arylimidazolidine-2,4-diones (**6)** as final products.[7] Some intermediate products, **4** and **5a-5b** of stages I and II had also been isolated. But in acetic acid media arylglyoxals condense with N-hydroxyurea and N-alkoxyureas selectively forming 5-aryl-3-hydroxyimidazolidine-2,4-diones (**6)** and 3-alkoxy-5-arylimidazolidine-2,4-diones (**7),** respectively at room temperatures[8] (Scheme 3).

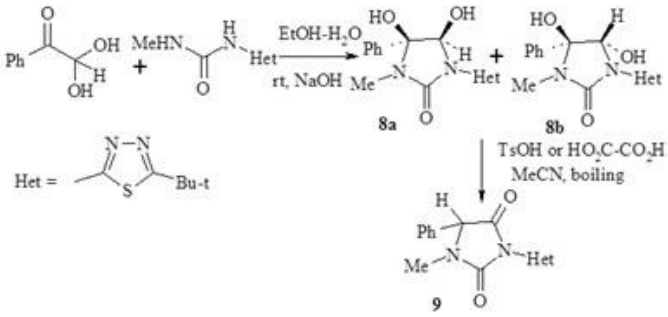


Scheme 2.



Scheme 3.

Phenylglyoxal hydrate reacts with N-tert-butyl-thiadiazol-2-yl-N'-metylurea in EtOH–H_2O solution in the presence of NaOH yielding cis- and trans-diastereomer 4,5-dihydroxyimidazolidin-2-ones (**8a,b**)[9] (Scheme 4). In the presence of TsOH or oxalic acid compounds **8a,b** transform in hydantoin **9** in boiling MeCN.



Scheme 4.

It might be possible that arylglyoxals hydrates could react with thiourea yielding proper 5-aryl-2-thioxoimidazolidin-4-one (5-aryl-2-thiohydantoins) in mild conditions. Heating of reaction mixture, the presence of strong acids or microwave irradiation are not conditions for 5-aryl-2-thiohydantoins forming from arylglyoxals hydrates and thiourea.

This work aim is devoted to further exploration of arylglyoxals hydrates interaction with thiourea in media of acetic acid at room temperatures.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on VARIAN JEMINI 400 spectrometer (400 and 100 MHz, respectively); solvent: $(CD_3)_2SO$, with TMS as internal standard. Mass spectra were recorded on VG 70-70EQ mass spectrometer in fast atom bombardment (FAB) mode. The solvents were purified and dried according to standard procedures. Used acetic acid was glacial.

5-Phenyl-2-thioxoimidazolidin-4-one (1a).

A mixture of phenylglyoxal hydrate (405 mg, 2.661 mmol), thiourea (253 mg, 3.326 mmol) and AcOH (10 mL) was stirred at 18-19°C for 10 min, maintained 18-19°C for 112 h, then formed crystal precipitate was filtered off, washed by AcOH (3 mL) and dried under vacuum 3 Torr, yielding (198 mg, 38.7%) 5-phenyl-2-thioxoimidazolidin-4-one (**1a)**, white crystals, m.p. 217 – 219 °C, after crystallization m.p. 218 – 219 °C (THF – C_6H_{14})(cf. m.p. 225°C (EtOH)[1], 188 – 189[2]). ^{1}H NMR spectrum, 400 MHz, $(CD_3)_2SO$, δ, ppm, (*J*, Hz): δ = 5.40 (1H, s, CH); 7.28 (2H, d, ^3J = 7.2, $H^{2,6}$ Ph); 7.36 – 7.40 (1H, m, H^4Ph); 7.41 – 7.45 (2H, m, $H^{3,5}$Ph); 10.51 (1H, s, NH); 11.88 (1H, s, NHC(O)), cf.[2]. ^{13}C NMR spectrum, 100 MHz, $(CD_3)_2SO$, δ, ppm: δ = 63.8 (CH Hydantoin); 126.6 (C-3, C-5 Ph); 128.5 (C-4 Ph) 128.8 (C-2, C-6 Ph); 134.4 (C-1, Ph); 174.7 (C=O); 182.8 (C=S) cf.[2]. Mass spectrum, *m/z*, (I_{rel}%): 193 $[M+H]^+$ (100). Anal. Calcd. for $C_9H_8N_2OS$ in %: C 56.23, H 4.19 , N 14.57. Found: C 56.08, H 4.32, N 14.37. Combined AcOH-filtrate was evaporated under vacuum 4 Torr at 25-30 °C, the residue was washed by cold water (8 ml), crystallized from THF – C_6H_{14}, dried under vacuum 4 Torr at 15 °C, additionally yielding (257 mg, 50.2%) **1a**.

5-(4'-Bromophenyl)-2-thioxoimidazolidin-4-one (1b).

A solution of 4-bromophenylglyoxal hydrate (352 mg, 1.522 mmol) in AcOH (15 mL) was added to mixture of thiourea (145 mg, 1.902 mmol) and AcOH (10 mL) at 18°C, the reaction mixture was stirred 1 h, then it was maintained at 18°C for 20 h, the solvent was evaporated under vacuum 3 Torr at 25–30 °C. The residue was washed by cold water (10 mL), dried under vacuum 3 Torr, yielding (365 mg, 88%) 5-(4'-bromophenyl)-2-thioxoimidazolidin-4-one (**1b)**, white crystals, mp. 204 – 205 °C (THF–C_6H_{14}). ^{1}H NMR spectrum, 400 MHz, $(CD_3)_2SO$, δ, ppm, (*J*, Hz): δ = 5.42 (1H, s, CH); 7.24 (2H, d, ^3J = 8.4, $H^{2,6}C_6H_4$); 7.64 (2H, d, ^3J = 8.4, $H^{3,5}C_6H_4$); 10.51 (1H, s, NH); 11.91 (1H, s, NHC(O)). ^{13}C NMR (100 MHz, $(CD_3)_2SO$,) δ = 63.2 (CH Hydantoin), 121.7 (C-4, C_6H_4Br), 128.7, 131.7 (C-2, C-6, C-3, C-5, C_6H_4Br), 133.8 (C-1, C_6H_4Br), 174.3 (C=O), 182.9 (C=S). Mass spectrum, *m/z*, (I_{rel}, %): 273 $[M+H]^+$ (57), 271 $[M+H]^+$ (53), 91 (69), 72 (100). Anal. Calcd. for $C_9H_7BrN_2OS$ in %: C 39.87, H 2.60 , N 10.33. Found: C 39.89, H 2.95, N 10.24.

5-(4'-Chlorophenyl)-2-thioxoimidazolidin-4-one (1c)

A solution of 4-chlorophenylglyoxal hydrate (158 mg, 0.846 mmol) in AcOH (12 mL) was added to mixture of thiourea (80 mg, 1.048 mmol) and AcOH (5 mL) at 17°C, the reaction mixture was stirred for 30 min, then it was maintained at 17°C for 46 h, the solvent was evaporated under vacuum 3 Torr at 25 – 27°C. The residue was washed by cold water (8 mL), dried under vacuum 3 Torr, yielding (180 mg, 94%) 5-(4'-chlorophenyl)-2-thioxoimidazolidin-4-one (**1c)**, yellow crystals, m.p. 209 – 211 °C (with decomp.) (THF – C_6H_{14}). ^{1}H NMR spectrum, 400 MHz, $(CD_3)_2SO$, δ, ppm, (*J*, Hz): δ = 5.44 (1H, s, CH); 7.30 (2H, d, ^3J = 8.4,

$H^{2,6}C_6H_4$); 7.51 (2H, d, ^3J = 8.4, $H^{3,5}C_6H_4$); 10.51 (1H, s, NH); 11.91 (1H, s, NHC(O)). ^{13}C NMR (100 MHz, $(CD_3)_2SO$,) δ = 63.2 (CH Hydantoin), 128.5, 128.8 (C-2, C-6, C-3, C-5, C_6H_4Cl), 133.1, 133.4 (C-1, C-4, C_6H_4Cl), 174.3 (C=O), 182.9 (C=S). Mass spectrum, *m/z*, (I_{rel}%): 229 $[M+H]^+$ (34), 227 $[M+H]^+$ (100). Anal. Calcd. for $C_9H_7ClN_2OS$ in %: C 40.53, H 2.65 , N 10.50. Found: C 40.46 , H 2.87, N 10.25 .

5-(4'-Fluorophenyl)-2-thioxoimidazolidin-4-one (1d)

A mixture of 4-fluorophenylglyoxal hydrate (164 mg, 0.962 mmol), thiourea (92 mg, 1.202 mmol) and AcOH (9 mL) was stirred at 19°C for 10 min, maintained 18-19°C for 111 h, then the solvent was evaporated under vacuum 4 Torr at 15°C, the residue was washed by cold water (5 ml), dried under vacuum 4 Torr at 16°C, yielding (181 mg, 89%) 5-(4'-fluorophenyl)-2-thioxoimidazolidin-4-one (**1d)**, white crystals, m.p. 169 – 171°C (with decomp.).^{1}H NMR spectrum, 400 MHz, $(CD_3)_2SO$, δ, ppm, (*J*, Hz): δ = 5.42 (1H, s, CH); 7.24 – 7.29 (2H, m, $H^{2,6}C_6H_4F$); 7.29 – 7.34 (2H, m, C_6H_4F); 10.49 (1H, s, NH); 11.88 (1H, s, NHC(O)). ^{13}C NMR (100 MHz, $(CD_3)_2SO$, (*J*, Hz)) δ = 63.15 (CH Hydantoin); 115.59 and 115.81, d, ^{C-F}J = 22 (C-3, C-5, C_6H_4F); 128.72 and 128.81, d, ^{C-F}J = 9 (C-2, C-6 C_6H_4F); 130.65 (C-1, C_6H_4F); 160.73 and 163.17, d, ^{C-F}J = 244 (C-4, C_6H_4F); 174.56 (C=O), 182.76 (C=S). Mass spectrum, *m/z*, (I_{rel}%): 211 $[M+H]^+$ (100), 166(14), 152 (16), 124 (64), 95 (14). Anal. Calcd. for $C_9H_7FN_2OS$: C 51.42, H 3.36 , N 13.33. Found: C 51.36, H 3.24, N 13.45.

5-(4'-Nitrophenyl)-2-thioxoimidazolidin-4-one (1e)

A mixture of 4-nitrophenylglyoxal hydrate (146 mg, 1.463 mmol), thiourea (71 mg, 0.928 mmol) and AcOH (6 mL) was stirred at 15°C for 10 min, maintained 18-19°C for 161 h, then the solvent was evaporated under vacuum 4 Torr at 25-30°C, the residue was washed by cold water (8 ml), dried under vacuum 4 Torr at 16°C, yielding (163 mg, 92%) 5-(4'-nitrophenyl)-2-thioxoimidazolidin-4-one (**1e)**, yellow crystals, m.decomp. 245 – 246°C (THF – PhH – C_6H_{14}).^{1}H NMR spectrum, 400 MHz, $(CD_3)_2SO$, δ, ppm, (*J*, Hz): δ = 5.66 (1H, s, CH); 7.58 (2H, d, ^3J = 8.4, $H^{2,6}C_6H_4$); 8.30 (2H, d, ^3J = 8.4 $H^{3,5}C_6H_4$); 10.64 (1H, s, NH); 12.03 (1H, s, NHC(O)). Mass spectrum, *m/z*, (I_{rel}%): 238 $[M+H]^+$ (40), 222 (11), 91 (100).). Anal. Calcd. for $C_9H_7N_3O_3S$: C 45.57, H 2.97, N 17.71. Found: C 45.22, H 3.12, N 17.43.

5-(4'-Methylphenyl)-2-thioxoimidazolidin-4-one (1f)

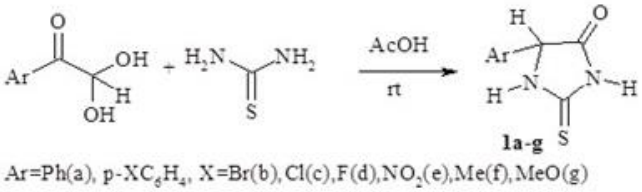
A mixture of 4-methylphenylglyoxal hydrate (256 mg, 1.542 mmol), thiourea (147 mg, 1.928 mmol) and AcOH (14 mL) was stirred at 15°C for 15 min, maintained 20°C for 65 h, then the solvent was evaporated under vacuum 4 Torr at 25-30°C, the residue was washed by cold water (11 ml), dried under vacuum 4 Torr at 15°C, yielding (310 mg, 97%) 5-(4'-methylphenyl)-2-thioxoimidazolidin-4-one 1f, white crystals, m.p. 226 – 228°C (with decomp.).^{1}H NMR spectrum, 400 MHz, $(CD_3)_2SO$, δ, ppm, (*J*, Hz): δ = 2.31 (3H, s, Me); 5.33 (1H, s, CH); 7.15 (2H, d, ^3J = 8.0, $H^{2,6}C_6H_4$); 7.23 (2H, d, ^3J = 8.0, $H^{3,5}C_6H_4$); 10.43 (1H, s, NH); 11.80 (1H, s, NHC(O)). Mass spectrum, *m/z*, (I_{rel}%): 207 $[M+H]^+$ (90), 119 (100). Anal. Calcd. for $C_{10}H_{10}N_2OS$ in %: C 58.23, H 4.89 , N 13.58. Found: C 58.35. , H 5.11, N .13.46.

5-(4'-Methoxylphenyl)-2-thioxoimidazolidin-4-one (1g).

A mixture of 4-methoxyphenylglyoxal hydrate (259 mg, 1.421 mmol), thiourea (119 mg, 1.563 mmol) and AcOH (14 mL) was stirred at 21– 23°C for 1 h, maintained at 19°C for 47 h, then the solvent was evaporated under vacuum 3 Torr at 20°C. The residue was extracted by CH_2Cl_2 (15 mL), the white precipitate was filtered off, washed by water (5 mL), dried under vacuum 4 Torr yielding (103 mg, 32.7%) 5-(4'-methoxylphenyl)-2-thioxoimidazolidin-4-one (**1g)**, white crystals, mp. 220 – 221°C (with decomp). ^{1}H NMR spectrum (400 MHz, $(CD_3)_2SO$, δ, ppm, (*J*, Hz): δ = 3.75 (3H, s, OMe); 5.32 (1H, s, CH); 6.98 (2H, d, ^3J = 8.4, $H^{3,5}C_6H_4$); 7.18 (2H, d, ^3J = 8.4, $H^{2,6}C_6H_4$); 10.43 (1H, s, NH); 11.80 (1H, s, NHC(O)). ^{13}C NMR (100 MHz, $(CD_3)_2SO$,) δ = 55.2 (OMe), 63.5 (CH Hydantoin), 114.2 (C-3, C-5 , C_6H_4O), 126.3 (C-1, C_6H_4O), 128.0 (C-2, C-6, C_6H_4O), 159.3 (C-4, C_6H_4O), 175.0 (C=O), 182.6 (C=S). Mass spectrum, *m/z*, (I_{rel}%): 223 $[M+H]^+$ (100). Anal. Cald. for $C_{10}H_{10}N_2O_2S$ in %: C 54.04, H 4.53, N 12.60. Found: C 53.86, H 4.82, N 12.35. To CH_2Cl_2-extract C_6H_{14} (10 ml) was added, the precipitated viscous white oil was isolated, dried under vacuum 3 Torr, after storing at 4°C crystallized additionally yielding (123 mg, 38.8%) thiohydantoin **1g**.

RESULTS AND DISCUSSION

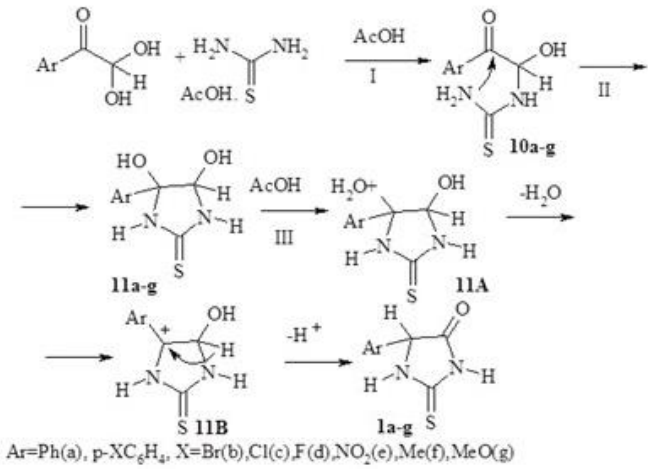
We have found that arylglyoxals hydrates reacted with thiourea in acetic acid solution at room temperatures range 17 – 23°C selectively yielding 5-aryl-2-thioxoimidazolidin-4-ones (**1a–1g**), respectively (Scheme 5). The reaction readily occurs under mild conditions in the absence of heating, microwave irradiation or presence of strong acids.



Scheme 5.

Evidently, this reaction occurs in three stage (Scheme 6) by analogy arylglyoxals reaction with N-hydroxyurea and N-alkoxyureas.[7,8] Acetic acid as prevents alternative thiazolidines formation[2] as promotes the third stage of this reaction (Scheme 6). It was regarded[2] that the lone pair electron on the sulfur atom of the thiourea would combine with the acidic proton of acetic acid and the nucleophilic affinity of the sulfur atom would be reduced with acetic acid as the solvent[2]. Thus at first stage thiourea reacts with arylglyoxal by the nitrogen atom yielding substituted thiourea **10,** which cyclizes in 5-aryl-4,5-dihydroxyimidazolidin-2-thione (**11)** at the second stage. Then intermediate **11** is protonated by acetic acid on the

oxygen atom of 5-HO group at the third stage. Further, the water molecule elimination yields "benzylic" cation **11B**, which by 1,2-hydride shift and the proton elimination transforms in thiohydantoin **1**.



Scheme 6.

It was found that the yields of 5-aryl-2-thioxoimidazolidin-4-ones (**1a–1g)** became sufficient after 1–4 days maintaining of the reaction mixture at room temperature. The structure of obtained **1a–1g** was proved by the data of ^{1}H and ^{13}CNMR and mass spectra. In ^{1}H NMR spectra in 5-aryl-2-thiohydantoins (**1a-1g)** "benzylic" C-H chemical shift lies within the range 5.32 – 5.66 ppm, N^{1}H shift lies over the range 10.43 – 10.51 ppm, N^{3}HC(O) shift lies within the range 11.80 – 12.03 ppm. In their ^{13}CNMR spectra hydantoin "benzylic" C(H) carbon shift lies within the range 63.2 – 63.8 ppm, C=O carbon shift lies over the range 174.3– 175.0 ppm, C=S carbon shift lies within the range 182.6 – 182.9 ppm.

Conclusion

A new improved synthesis of 5-aryl-2-thioxoimidazolidin-4-ones (5-aryl-2-thiohydantoins) by interaction of arylglyoxals hydrates with thiourea in media of acetic acid at room temperature has been developed.

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