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SYNTHESIS AND CHARACTERIZATION OF A NEW SERIES OF 3-(4-ANTIPYRINYL)-2-THIOHYDANTOIN DERIVATIVES

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Abstract – This paper reports the reaction of 4-antipyrinyl isothiocyanate with DL-amino acids affording a new heterocyclic series of 3-(4-antipyrinyl)-2-thiohydantoin derivatives in mild conditions. The reaction proves to be simple and the experiment is easy to operate with high yields (86-96%).

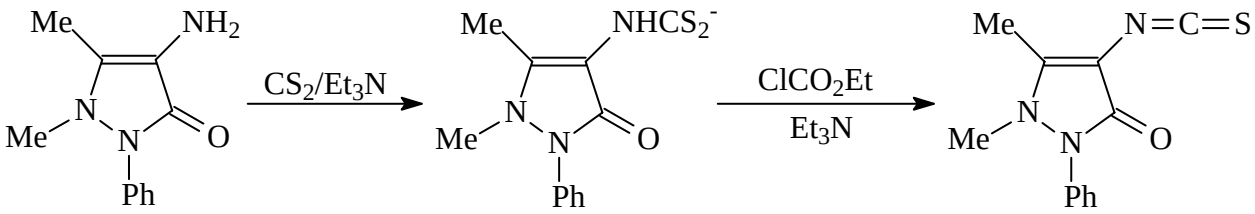
INTRODUCTION

It's well known that thiohydantoin derivatives display a wide range of biological properties, including anticonvulsant,[1] antiviral,[2] antitumor,[3] as well as herbicidal and fungicidal agents.[4] Recent studies have shown that some thiohydantoin derivatives have anti-proliferation effect on human vascular endothelial cells,[5] and some can be used to synthesize novel optically active poly(amide-imide)s using microwave irradiation.[6] Therefore, particularly intense interest has been directed towards the synthesis of them.[7] However, there are not such heterocyclic thiohydantoin compounds as antipyrinyl derivatives.

The 4-aminoantipyrine is a versatile reagent which has been extensively utilized in heterocyclic synthesis. It has been found that 4-aminoantipyrine and its derivatives possess antibacterial[8] and anti-inflammatory[9] properties. Meanwhile, the Schiff bases of 4-aminoantipyrine and its complexes have a variety of applications including in the biological, clinical, analytical and pharmacological areas,[10] too. Here, we reported a synthesis of 4-antipyrinyl isothiocyanate, which prompted us to investigate the synthesis of new heterocyclic compounds.

In view of this, and as part of our earlier investigations on 3-aryl-2-thiohydantoins, we studied the reaction between this isothiocyanate and free amino acid, and synthesized a new heterocyclic series of 3-(4-antipyrinyl)-2-thiohydantoin derivatives recently. The reaction proves to be extremily simple and highly efficient.

RESULTS AND DISCUSSION

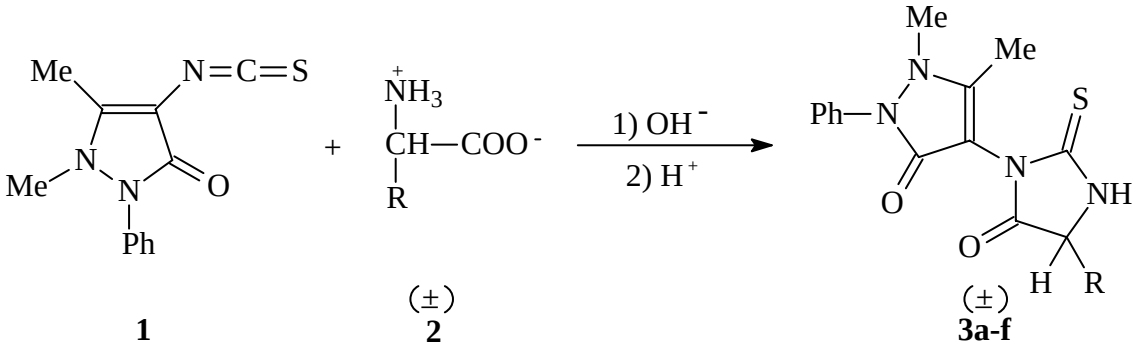


1

Scheme 1

4-Antipyrinyl isothiocyanate (**1**) was prepared from the reaction of 4-aminoantipyrine with carbon disulfide and ethyl chlorocarbonate in presence of triethylamine (**Scheme 1**). The structure of the compound (**1**) was confirmed by MS spectra [245 (M^+)], elemental analysis, IR (N=C=S, 2038 cm^{-1}) and ^{1}HNMR spectra (the signals of no NH protons).

All of the products (**3a-f**) were synthesized by the reaction of free DL-amino acid (alanine, valine, leucine, phenylalanine, methionine, tyrosine) with 4-antipyrinyl isothiocyanate in the presence of sodium hydroxide followed acidified by hydrochloric acid (**Scheme 2**). Since the amino acid is zwitterions, the amine group exists in the form of NH_3^+, which can reduce the nucleophilic activity of amino group. Due to the low nucleophilic activity, amino acid reacted slowly with 4-antipyrinyl isothiocyanate. So, the amine group of free amino acids must be activated by a suitable reagent before derivatizing to 4-antipyrinyl isothiocyanate which is necessary to form finally 3-(4-antipyrinyl)-2-thiohydantoins, and we here select sodium hydroxide as base catalyst. In briefly, the 3-(4-antipyrinyl)-2-thiohydantoins are formed via a condensation reaction in which the amino acids underwent nucleophilic addition followed by ring closure.



1 **2** **3a-f**

3a R=Me **3b R=Pr-*i*** **3c R=Bu-*i***
3d R=CH_2Ph **3e R=CH_2CH_2SMe** **3f R=$CH_2C_6H_4$-OH(*p*)**

Scheme 2

All the reaction were performed smoothly in acetone-water and completed with high yields (86-96%). The products reported were characterized on the basis of IR, MS, ^{1}H NMR, ^{13}C NMR spectrum and elemental analysis.

In conclusion, we report a simple and efficient method for the synthesis of a new series of 3-(4-antipyrinyl)-2-thiohydantoin. This method has the merits of needing only simple apparatus, and the experiment is easy to operate. It was also worthy of note that the asymmetric center of amino acid was not involved in the reaction and the configuration had not been changed in this condition, and we measured the optical activity of products **3**, which showed there was no optical activity.

EXPERIMENTAL

Melting points were determined with a Kofler micro melting point apparatus and were uncorrected. IR were recorded on a FTS-40 spectrophotometer using KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker DPX-400 sepectrometer at 400 and 100 MHz, respectively, using TMS as internal standard and $CDCl_3$ or DMSO-d_6 as solvent. COSY, NOESY, HSQC and HMQC experiments were performed on a 400 MHz multinuclear Bruker spectrometer. Chemical shifts (δ) were expressed in ppm downfield from internal standard TMS and coupling constants *J* were given in Hz. MS spectra were recorded on a HP-5 6890/5973 GC-MS spectrometer. Elemental analyses were performed on PE-2400 CHN elemental analyzer.

Preparation for 4-antipyrinyl isothiocyanate (**1**). The 2.03 g (0.01 mol) of 4-aminoantipyrine was dissolved in the minimun amount of benzene and treated with 0.66 mL (0.01 mol) of the carbon disulfide and 1.4 mL (0.01 mol) of triethylamine, and the solution was stirred and heated to 70-80°C for 3 h. After complete precipitation of the triethylammonium dithiocarbamate salt, the solution was filtered; the solid was washed with anhydrous ether and airdried for about 10 min. The salt was then dissolced in about 30 mL of chloroform, treated with 1.4 mL (0.01 mol) of triethylamine. To this solution was added 1.02 mL (0.01 mol) of ethyl chlorocarbonate dropwise slowly. The resulting solution was stirred for 1 h at rt. Then the chloroform solution was washed with 3 mol/L HCl and twice with water and was dried over sodium sulfate. The chloroform was evaporated to get the crude product, then purified by silica gel column chromatography ($CHCl_3$:CH_3OH=19:1).

A general procedure is described for 3-(4-antipyrinyl)-2-thiohydantoins (**3a-f**). A mixture of amino acid (1 mmol), 4-antipyrinyl isothiocyanate (0.245 g, 1 mmol), sodium hydroxide (0.04 g, 1 mmol), water (5 mL), and acetone (5 mL) was placed in a round bottom flask and stirred for 2 h at refluxing temperature. Then, the mixture was acidified with 3 mol/L hydrochloric acid and stirring is continued for 10 mins. The progress of the reaction is monitored by TLC. After completion of the reaction, the resulting precipitate is filtrated, dried and recrystallized from ethanol.

4-Antipyrinyl isothiocyanate (1): Pale yellow crystals; Yield: 51% mp: 146-147°C; IR(KBr): 3056, 2924, 2853, 2038 (vs, N=C=S), 1674 (C=O), 1617 (C=C), 1595, 1497, 753, 697 cm^{-1}; ^{1}H NMR (400

MHz, $CDCl_3$): δ 2.29 (s, 3H, C=C-CH_3), 3.11 (s, 3H, N-CH_3), 7.32-7.49 (m, 5H, *J*=8.0 Hz, ArH); MS: *m/z* =245 (M^+,B), 77, 56. Anal. Calcd for $C_{12}H_{11}N_3OS$: C,58.76; H,4.52; N,17.13. Found C,58.87; H,4.54; N,17.01.

5-Methyl-3-(4-antipyrinyl)-2-thiohydantoin (3a): White tabular; Yield: 89% mp: 254-256℃; IR(KBr): 3121 (N-H), 2992, 2938, 1764 (C=O), 1655 (C=C-C=O), 1630 (C=C), 1595, 1529, 1490, 1291(C=S), 764, 699 cm^{-1}; ^1H NMR(400 MHz, DMSO-d_6) δ: 1.40 (d, 3H, *J*=7.2 Hz, CH_3); 2.14 (s, 3H, CH_3); 3.21 (s, 3H, CH_3); 4.52 (q, 1H, *J*=7.2 Hz, N-CH); 7.35-7.56 (m, 5H, *J*=8.0 Hz, ArH); 10.51 (s, 1H, N-H); ^{13}C NMR(100 MHz, DMSO-d_6) δ: 10.57, 17.54, 36.33, 55.93 (N-CH), 102.90, 125.38, 127.88, 130.20, 135.82, 155.60, 161.86 (C=C-C=O), 175.87 (C=O), 182.83 (C=S); MS: *m/z* =316(M^+,B), 230, 186, 77, 56. Anal. Calcd for $C_{15}H_{16}N_4O_2S$：C, 56.94; H, 5.10; N, 17.71. Found: C, 57.05; H, 5.05; N, 17.76.

5-Isopropyl-3-(4-antipyrinyl)-2-thiohydantoin (3b): White tabular; Yield: 91% mp: 226-228℃; IR(KBr): 3139 (N-H), 3074, 2962, 2879, 1762 (C=O), 1656 (C=C-C=O), 1623 (C=C), 1593, 1520, 1274 (C=S), 756, 700 cm^{-1}; ^1H NMR(400 MHz, DMSO-d_6) δ: 0.93 (d, 3H, *J*=6.8 Hz, CH_3), 1.05 (d, 3H, *J*=6.8 Hz, CH_3), 2.11 (s, 3H, CH_3), 2.20 (m, 1H, CH), 3.21 (s, 3H, CH_3), 4.43 (d, 1H, *J*=3.2 Hz, N-CH), 7.36-7.56 (m, 5H, *J*=8.0 Hz, ArH), 10.56 (s, 1H, N-H); ^{13}C NMR(100 MHz, DMSO-d_6) δ: 11.61, 17.17, 19.06, 31.44, 36.33, 65.22 (N-CH), 102.92, 125.40, 127.91, 130.20, 135.81, 155.33, 161.84(C=C-C=O), 174.43 (C=O), 183.70 (C=S); MS: *m/z*=344 (M^+,B), 302, 245, 230, 186, 77, 56. Anal. Calcd for $C_{17}H_{20}N_4O_2S$：C, 59.28; H, 5.85; N, 16.27. Found: C, 59.36; H, 5.90; N, 16.19.

5-Isobutyl-3-(4-antipyrinyl)-2-thiohydantoin (3c): White tabular, Yield: 96% mp: 250-252℃; IR(KBr): 3141 (N-H), 3066, 2952, 2897, 1765 (C=O), 1668 (C=C-C=O), 1620 (C=C), 1595, 1524, 1496, 1299 (C=S), 759, 697 cm^{-1}; ^1H NMR(400 MHz, DMSO-d_6) δ: 0.93 (d, 3H, *J*=6.4 Hz, CH_3), 0.95 (d, 3H, *J*=6.4 Hz, CH_3), 1.65 (m, 2H, *J*=6.8 Hz), 1.89 (m, 1H, CH), 2.13 (s, 3H, CH_3), 3.21 (s, 3H, CH_3), 4.53 (t, 1H, *J*=6.4 Hz, N-CH), 7.36-7.56 (m, 5H, *J*=8.0 Hz, ArH), 10.62 (s, 1H, N-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 183.11 (C=S), 174.49 (C=O), 161.86 (C=C-C=O), 155.49, 135.83, 130.20, 130.16, 127.87, 125.38, 125.21, 102.95, 58.91 (N-CH), 41.31, 36.34, 25.02, 24.03, 22.69, 11.58. MS: *m/z*=358 (M^+,B), 315, 302, 245, 230, 186, 77, 56, 43. Anal. Calcd for $C_{18}H_{22}N_4O_2S$：C, 60.31; H, 6.19; N, 15.63. Found: C, 60.35; H, 6.23; N, 15.51.

5-Benzyl-3-(4-antipyrinyl)-2-thiohydantoin (3d): White tabular, Yield: 95% mp: 273-275℃; IR(KBr): 3184 (N-H), 3060, 2927, 2851, 1764 (C=O), 1653 (C=C-C=O), 1614 (C=C), 1593, 1507, 1489, 1294 (C=S), 759, 740, 700 cm^{-1}; ^1H NMR(400 MHz, DMSO-d_6) δ: 1.36 (s, 3H, CH_3), 3.09 (s, 3H, CH_3), 3.13 (d, 2H, *J*=4.0 Hz, CH_2), 4.88 (t, 1H, *J*=4.0 Hz, N-CH), 7.21-7.53 (m, 10H, *J*=8.0 Hz, ArH), 10.62 (s, 1H, N-H); ^{13}C NMR(100 MHz, DMSO-d_6) δ: 10.56, 36.14, 36.69, 60.97 (N-CH), 102.49, 125.38, 127.86,

128.04, 129.28, 130.16, 131.00, 135.40, 135.74, 155.36, 161.74 (C=C-C=O), 174.05 (C=O), 183.06 (C=S); Anal. Calcd for $C_{21}H_{20}N_4O_2S$: C, 64.26; H, 5.14; N, 14.28. Found: C, 64.19; H, 5.16; N, 14.23.

5-(2-Methylthioethyl)-3-(4-antipyrinyl)-2-thiohydantoin (3e): Yellow tabular, Yield: 86% mp: 218-219.5℃; IR(KBr): 3122 (N-H), 3062, 2997, 2915, 1763 (C=O), 1662 (C=C-C=O), 1625 (C=C), 1593, 1525, 1491, 1283(C=S), 766, 700 cm^{-1}; ^1H NMR(400 MHz, DMSO-d_6) δ : 2.07 (m, 2H, CH_2), 2.10 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.63 (t, 2H, *J*=8.0 Hz, CH_2), 3.21 (s, 3H, CH_3), 4.59 (q, 1H, *J*=6.0 Hz, N-CH), 7.36-7.55 (m, 5H, *J*=8.0 Hz, ArH), 10.57 (s, 1H, N-H); ^{13}C NMR(100 MHz, DMSO-d_6) δ : 11.69, 15.49, 29.49, 31.19, 36.31, 59.13 (N-CH), 102.84, 125.41, 127.90, 130.20, 135.81, 155.59, 161.82 (C=C-C=O), 174.83 (C=O), 183.31 (C=S). Anal. Calcd for $C_{17}H_{20}N_4O_2S_2$: C, 54.23; H, 5.36; N, 14.88. Found: C, 54.29; H, 5.29; N, 14.82.

5-(4-Hydroxybenzyl)-3-(4-antipyrinyl)-2-thiohydantoin (3f): Yellow tabular, Yield: 91% mp: 300-302℃; IR(KBr): 3256 (O-H), 3176 (N-H), 3073, 2920, 2852, 1768 (C=O), 1634 (C=O), 1615 (C=C), 1589, 1518, 1295 (C=S), 813, 754, 697 cm^{-1}; ^1H NMR(400 MHz, DMSO-d_6) δ : 1.42 (s, 3H, CH_3), 2.99 (t, 2H, *J*=4.0 Hz, CH_2), 3.10 (s, 3H, CH_3), 4.78 (dd, 1H, *J*=4.0 Hz, N-CH), 6.67 (d, 2H, *J*=8.0 Hz, ArH), 6.98 (d, 2H, *J*=8.0 Hz, ArH), 7.52-7.29 (m, 5H, *J*=8.0 Hz, ArH), 9.27 (s, 1H, O-H), 10.59 (s, 1H, N-H); ^{13}C NMR(100 MHz, DMSO-d_6) δ : 10.57, 35.91, 36.16, 61.26 (N-CH), 102.49, 116.04, 125.20, 125.32, 127.84, 130.18, 131.94, 135.70, 155.42, 157.61, 161.75 (C=O), 174.23 (C=O), 183.04 (C=S). Anal. Calcd for $C_{21}H_{20}N_4O_3S$: C, 61.75; H, 4.93; N, 13.72. Found: C, 61.70; H, 4.85; N, 13.79.

REFERENCES

1. P. Dang and A. K. Madan, *J. Chem. Information and Computer Sci.*, 1994, **34**, 1162.
2. A. A. El-barbary, A. I. Khodair, E. B. Pedersen, and C. Nielsen, *J. Med. Chem.*, 1994, **37**, 73.
3. A. M. Al-obaid, H. I. El-Subbagh, A. I. Khodair, and M. M. A. Elmazar, *Anticancer Drugs*, 1996, **7**, 873; A. I. Khodair, *Nucleosides Nucleotides Nucleic Acids*, 2001, **20**, 1735.
4. J. Marton, J. Enisz, S. Hosztafi, and T. Timar, *J. Agric. Food Chem.*, 1993, **41**, 148.
5. C. R. Shih, J. Wu, Y. Liu, Y. C. Liang, S. Y. Lin, M. T. Sheu, and W. S. Lee, *Bio. Pharmacology*, 2004, **67**, 67.
6. K. Faghihi, K. Zamani, and S. Mallakpour, *Iranian Polymer J.*, 2002, **11**, 339; F. Khalil, Z. Khosrow, M. Azizollah and R. S. Mohammad, *European Polymer J.*, 2003, **39**, 247.
7. M. J. Lin and C. M. Sun, *Tetrahedron Lett.*, 2003, **44**, 8739; C. Gasch, B. A. B. Salameh, M. A. Pradera, and J. Fuentes, *Tetrahedron Lett.*, 2001, **42**, 8615; A. H. Mandour and E. M. Kassem, *Afinidad*, 2000, **57**, 344; L. Somsak and V. Nagy, *Tetrahedron:Asymmetry*, 2000, **11**, 1719; H. Takechi, H. Takahashi, and M. Machida, *Heterocycles*, 1999, **50**, 159; E. Ware, *Chem. Rev.*, 1950, **46**,

403; R. D. Coghill and T. B. Johnson, *J. Am. Chem. Soc.*, 1925, **47**, 184.

8. M. Alaudeen, A. Abraham, and P. K. Radhakrishnan, *Proc. Indian Acad. Sci. Chem. Sci.*, 1995, **107**, 123.
9. L. Singh, G. Mohan, R. K. Parashar, S. P. Tripathi, and R. C. Sharma, *Curr. Sci.*, 1986, **55**, 846.
10. A. M. Donia and F. A. El-Saied, *Polyhedron*, 1988, **7**, 2149; N. Raman, A. Kulandaisamy, and K. Jeyasubramanian, *Syn. and React. in Inorg. and Metal-Org. Chem.*, 2002, **32,** 1583; M. M. Habeeb, *J. Chem. Res.(S)*, 2002, **6**, 255; J. W. Schoonen and M. G. F. Sales, *Anal. and Bioanal. Chem.*, 2002, **372**, 822.