Mannich reaction in the synthesis of N,S-containing heterocycles. 1. Synthesis of novel derivatives of imidazo[2,1-*b*][1,3,5]thiadiazine*

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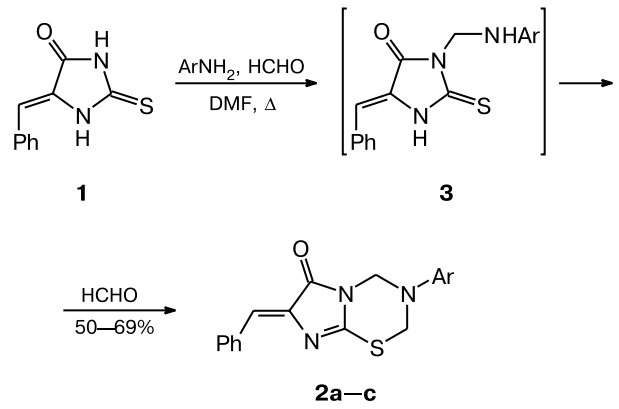
Reactions of (*Z*)-5-benzylidene-2-thiohydantoin with formaldehyde and primary aromatic amines afforded novel derivatives of imidazo[2,1-*b*][1,3,5]thiadiazine in 50—69% yields.

Key words: Mannich reaction, (*Z*)-5-benzylidene-2-thiohydantoin, formaldehyde, primary amines, imidazo[2,1-*b*][1,3,5]thiadiazines.

The Mannich reaction is known to be one of the most important synthetic methods in organic chemistry.[1] At present, the great potentialities of this reaction are far from being exhausted and are still of interest for chemists. For instance, a number of recent studies are devoted to the "nonclassical" Mannich synthesis using new substrates under modified aminomethylation conditions.[2] The intramolecular Mannich reactions[3] are of particular attention since they are very promising for design of novel carbo- and heterocyclic systems. With the present work, we open up a series of publications concerned with the study of the structures, methods for the synthesis, and chemical transformations of nitrogen- and sulfur-containing heterocyclic compounds obtained by the Mannich reaction.

1,3,5-Thiadiazine derivatives belong to a promising class of heterocyclic compounds[4] with a broad spectrum of biological activities. In particular, some functionalized thiadiazines have been found to exhibit fungicidal, herbicidal,[5,6] acaricidal, insecticidal,[7] and antibacterial properties.[8,9] Fused derivatives of 1,3,5-thiadiazine are most suitably synthesized by the "double" Mannich condensation of mercaptoazoles and mercaptoazines with formalin and primary amines.[9—14] Earlier, we have demonstrated that pyrido[2,1-*b*][1,3,5]thiadiazine derivatives can be obtained under the conditions of this reaction.[15] Proceeding further in those investigations, we studied condensation of easily accessible (*Z*)-5-benzylidene-2-thiohydantoin (**1**) with formaldehyde and primary amines and found that this reaction readily occurs in boiling DMF without any catalyst to give novel imidazo[2,1-*b*][1,3,5]thiadiazine derivatives (**2**) (Scheme 1).

Scheme 1



1 **3** **2a—c**

Ar = Ph (**a**); 4-FC_6H_4 (**b**); 2-MeC_6H_4 (**c**)

It should be noted that the aminomethylation of thiohydantoin **1** and some of its structural analogs has been repeatedly studied earlier;[1b,16] however, we were the first to obtain imidazothiadiazine derivatives in such a way. It has been shown with a number of examples that the aminomethylation of 5,5-disubstituted 2-thiohydantoins exclusively involves the N(3) atom.[1b,16] Based on this, we assumed that the reaction intermediate is aminomethylthiohydantoin **3**, whose structure permits subsequent cyclocondensation with formaldehyde along the only possible pathway leading to imidazo[2,1-*b*][1,3,5]thiadiazines **2**. It is worth noting that documented examples

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of the synthesis of compounds containing the imidazo[2,1-*b*][1,3,5]thiadiazine fragment are few.[6,14,17—20] Taking into account that some imidazothiadiazines have found to exhibit fungicidal[6] and pesticidal[21] properties, development of methods for the synthesis of such structures appears to be promising.

The structures of compounds **2a—c** were confirmed by spectroscopic and elemental analysis data. For instance, the IR spectra of the compounds obtained contain no absorption bands at 3600—3000 cm^{-1} characteristic of the N—H fragment; instead, the stretching vibrations of the conjugated amide CO group and the C=N fragment are manifested as bands at 1703—1692 and 1630—1625 cm^{-1}, respectively. The ^1H NMR spectra of compounds **2a—c** show, apart from the characteristic signals of the aromatic protons, a singlet for the methine proton at δ 7.62—7.66 and two peaks for the methylene protons of the 1,3,5-thiadiazine ring at δ 4.82—4.99 and 5.10—5.32, which are resolved as broadened pseudosinglets at an operating frequency of 200 MHz.

Thus, the aminomethylation of 5-arylidene-2-thiohydantoins offers a simple and convenient route to novel substituted imidazo[2,1-*b*][1,3,5]thiadiazines, which are promising starting material and objects for bioscreening.

Experimental

^1H NMR spectra were recorded on a Varian Gemini 200 instrument (200 MHz) in DMSO-d_6 with Me_4Si as the internal standard. IR spectra were recorded on an IKS-29 spectrophotometer (Nujol). Elemental analysis was carried out on a Perkin-Elmer C,H,N-Analyser instrument. The course of the reaction was monitored and the purity of the compounds obtained was checked by TLC on Silufol UV-254 plates in acetone—heptane (1 : 1); spots were visualized in the iodine vapor and with the use of a UV detector. Melting points were determined on a Kofler hot stage and are given uncorrected.

The starting 5-(benzylidene)-2-thiohydantoin (**1**) was prepared according to a known procedure.[22]

Imidazo[2,1-*b*][1,3,5]thiadiazines 2 (general procedure). An excess 37% formalin (3 mL) was added to a suspension of thiohydantoin derivative **1** (0.6 g, 2.9 mmol) and the corresponding amine (2.9 mmol) in DMF (5 mL). The reaction mixture was refluxed for 3 min with vigorous stirring: the resulting solution yielded a finely crystalline precipitate. The mixture was stirred at ~20 °C for 2 h. Light yellow crystals of the corresponding imidazothiadiazine **2a—c** were filtered off and washed with EtOH.

7-(*Z*)-Benzylidene-3-phenyl-2,3,6,7-tetrahydro-4*H*-imidazo[2,1-*b*][1,3,5]thiadiazin-6-one (2a) was obtained in 69% yield, m.p. 194—196 °C. Found (%): C, 66.73; H, 4.73; N, 13.21. $C_{18}H_{15}N_3OS$. Calculated (%): C, 67.27; H, 4.70; N, 13.07. IR, ν/cm^{-1}: 1703 (C=O), 1625 (C=N). ^1H NMR, δ: 4.99, 5.32 (both *pseudo*-s, 2 H each, $C(2)H_2$, $C(4)H_2$); 6.96 (m, 3 H, $NC_6\underline{H}_5$); 7.25 (m, 2 H, $NC_6\underline{H}_5$); 7.43 (m, 5 H, Ph); 7.62 (s, 1 H, PhC$\underline{H}$=).

7-(*Z*)-Benzylidene-3-(4-fluorophenyl)-2,3,6,7-tetrahydro-4*H*-imidazo[2,1-*b*][1,3,5]thiadiazin-6-one (2b) was obtained in 55% yield, m.p. 162—164 °C. Found (%): C, 63.03; H, 4.19; N, 12.45. $C_{18}H_{14}FN_3OS$. Calculated (%): C, 63.70; H, 4.16; N, 12.38. IR, ν/cm^{-1}: 1700 (C=O), 1625 (C=N). ^1H NMR, δ: 4.94, 5.28 (both *pseudo*-s, 2 H each, $C(2)H_2$, $C(4)H_2$); 7.02 (m, 4 H, 4-FC_6H_4); 7.46 (m, 5 H, Ph); 7.62 (s, 1 H, PhC$\underline{H}$=).

7-(*Z*)-Benzylidene-3-(2-methylphenyl)-2,3,6,7-tetrahydro-4*H*-imidazo[2,1-*b*][1,3,5]thiadiazin-6-one (2c) was obtained in 50% yield, m.p. 198—201 °C. Found (%): C, 67.51; H, 5.15; N, 12.62. $C_{19}H_{17}N_3OS$. Calculated (%): C, 68.04; H, 5.11; N, 12.53. IR, ν/cm^{-1}: 1692 (C=O), 1630 (C=N). ^1H NMR, δ: 2.34 (s, 3 H, Me); 4.82, 5.10 (both *pseudo*-s, 2 H each, $C(2)H_2$, $C(4)H_2$); 6.92 (d, 1 H, $H(3)_{Ar}$, ^3J = 7.6 Hz); 7.06 (m, 2 H, $H(4)_{Ar}$, $H(5)_{Ar}$); 7.22 (d, 1 H, $H(6)_{Ar}$, ^3J = 7.5 Hz); 7.54 (m, 5 H, Ph); 7.66 (s, 1 H, PhC$\underline{H}$=).

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References

1. (a) F. F. Blicke, in *Organic Reactions*, Ed. R. Adams, Wiley—Interscience, New York, 1942, p. 303; (b) M. Tramontini, *Synthesis*, 1973, 703; (c) M. Tramontini and L. Angiolini, *Tetrahedron*, 1990, **46**, 1791; (d) E. F. Kleinman, in *Comprehensive Organic Synthesis*, *Vol.* **2**, Eds B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, p. 893.
2. M. Arend, B. Westermann, and N. Risch, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 1045.
3. L. E. Overman and D. J. Ricca, in *Comprehensive Organic Synthesis*, *Vol.* **2**, Eds B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, p. 1007.
4. R. K. Smalley, in *Comprehensive Heterocyclic Chemistry II*, *Vol.* **6**, *Six-Membered Rings with Two or More Heteroatoms and Fused Carbocyclic Derivatives*, Ed. A. J. Boulton, Elsevier, Oxford, UK, 1996.
5. M. S. Chande, R. N. Dravid, and N. P. Shetgiri, *Proc. Indian Acad. Sci. Chem. Sci.*, 1988, **100**, 53; M. Ertan, A. A. Bilgin, E. Palaska, and N. Yulug, *Arzneim. Forsch.*, 1992, **42**, 160; M. Ertan, H. G. Ayyildiz, and N. Yulug, *Arzneim. Forsch.*,1991, **41**, 1182; S. Yadav Lal Dhar, A. Vaish, and S. Sharma, *J. Agric. Food Chem.*, 1994, **42**, 811.
6. S. Liu, X. Qian, J. Chen, and G. Song, *Monatsh. Chem.*, 2000, **131**, 953.
7. Jpn Pat. 0 859 643; *Chem. Abstr.*, 1996, **125**, 10860u; Jpn Pat. 03 215 478; *Chem. Abstr.*, 1992, **116**, 59409g; Jpn Pat. 03 197 474; *Chem. Abstr.*, 1992, **116**, 41489y.
8. (a) Zh. Wang, Haoxin Shi, and Haijian Shi, *Synth. Commun.*, 2001, **31**, 2841; (b) Zh. Wang, T. You, Haijian Shi, and Haoxin Shi, *Molecules*, 1996, **1**, 89. Avail. URLs: http://www.mdpi.net/molecules/list96.htm; http://www.springerlink.com; (c) Zh. Wang, T. You, Hai-Jian Shi, and Hao-Xin Shi, *Gaodeng Xuexiao Huaxue Xuebao*, 1997, **18** (4), 550; *Chem. Abstr.*, 1997, **127**, 95265t; (d) Hao-Xin Shi, Hai-Jian Shi, and Zh. Wang, *Youji Huaxue*, 2000, **20** (3), 344; *Chem. Abstr.*, 2000, **133**, 120280c.

9. C. Ochoa, E. Perez, R. Perez, M. Suarez, E. Ochoa, H. Rodriguez, A. G. Barrio, S. Muelas, J. J. Nogal, and R. A. Martinez, *Arzneim. Forsch*., 1999, **49**, 764; Q. Song, Zh. Zhang, Zh. Li, G. Mi, and Y. Ding, *Zhongguo Yaowu Huaxue Zazhi*, 1997, **7**, 93; *Chem. Abstr.*, 1999, **130**, 25042f; E. Ilhan, G. Capan, N. Ergenc, M. Uzun, M. Kiraz, and D. Kaya, *Farmaco*, 1995, **50**, 787.
10. Haijian Shi, Zh. Wang, and Haoxin Shi, *Synth. Commun*., 1999, **29**, 2027.
11. Z. A. Hozein, A. O. S. Abd El-Wareth, H. A. H. El-Sherief, and A. M. Mahmoud, *Z. Naturforsch., Teil B*, 1997, **52**, 1401.
12. Haijian Shi, Haoxin Shi, and Zh. Wang, *J. Heterocycl. Chem.*, 2001, **38**, 929.
13. Haijian Shi, Zh. Wang, and Haoxin Shi, *Chimia*, 1997, **51**.
14. Z. A. Hozein, *J. Chem. Res. (S)*, 2000, 99.
15. V. V. Dotsenko, S. G. Krivokolysko, A. N. Chernega, and V. P. Litvinov, *Dokl. Akad. Nauk*, 2003, **389**, 763 [*Dokl. Chem.*, 2003, **389**, 92 (Engl. Transl.)].
16. Y. Aly, A. El-Barbary, and A. El-Shehawy, *Phosphorus, Sulfur, Silicon, Relat. Elem*., 2004, **179**, 185.
17. D. Griffiths, R. Hull, and T. P. Seden, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1240.
18. F. Saczewski and M. Gdaniec, *J. Chem. Soc., Perkin Trans. 1*, 1992, 47.
19. D. Hesek, A. Rybar, J. Alfoldi, J. Bella, and V. Patoprsty, *Collect. Czech. Chem. Commun.,* 1996, **61**, 1642.
20. M. V. Vovk, V. I. Dorokhov, and L. I. Samarai, *Dokl. Akad. Nauk Ukr.*, 1993 (11), 140.
21. Fr. Pat. 2 512 450; *Chem. Abstrs*, 1983, **99**, 70775.
22. T. B. Johnson and B. H. Nicolet, *J. Am. Chem. Soc.*, 1911, **33**, 1973.

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