HETEROCYCLES, Vol. 75, No. 3, 2008, pp. 655 - 660. © The Japan Institute of Heterocyclic Chemistry
Received, 7th October, 2007, Accepted, 14th November, 2007, Published online, 16th November, 2007. COM-07-11237

FACILE ONE-POT REACTION FOR THE REGIOSELECTIVE SYNTHESES OF *2H*-[1,2,4]THIADIAZOLO[2,3-*a*]PYRIMIDINE DERIVATIVES

Guohua Liu,* Mei Yao, Yunning Xue, Haibin Fang, and Xiaowei Cao*

Department of Chemistry, College of Life and Environmental Science, Shanghai Normal University, Shanghai 200234, P. R. China
E-mail: ghliu@shnu.edu.cn

Abstract – A convenient and rapid method for the preparation of 2*H*-1,2,4-thiadiazole[2,3-*a*]pyrimidine derivatives **3a-3e** was developed. The investigations of their regioselective syntheses through a comparison of the different substituted groups on the pyrimidine ring using a semi-empirical MO calculation and an X-ray crystallographic analysis was also discussed.

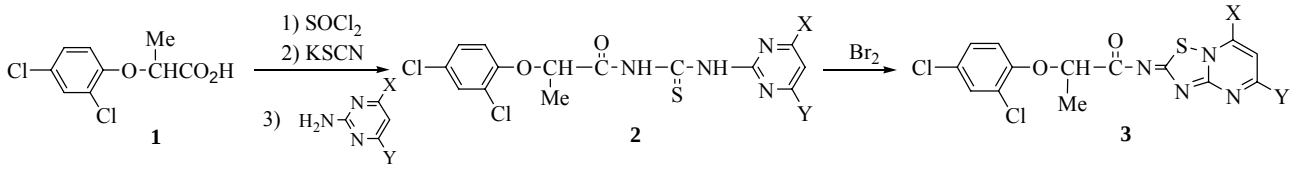
INTRODUCTION

Pyrimidine derivatives possess a wide variety of biological properties,[1] and some of them are well known to use as herbicides.[2] In particular, some fused heterocycles,[3] such as 2*H*-1,2,4-thiadiazole-[2,3-*a*]pyrimidine derivatives, have been used as inhibitors of acetolactate synthase (ALS) to catalyze first common step in branched chain amino acid biosynthesis in herbicidal process.[4] Therefore, exploring fused heterocycles as herbicides has become a subject of intensive research.[3] Generally speaking, these fused heterocycles contain two part; (i) aromatic/heterocyclic moiety (ii) 2*H*-1,2,4-thiadiazole-[2,3-*a*]pyrimidines moiety. The aromatic/heterocyclic moiety is either phenyl[3d] or pyridinyl[3c] with substituted group in different position. Although some fused heterocycles have been described,[3] the preparations require commonly a tediously synthetic process. Moreover, detailed discussions of their structures, especially investigation of their regioselective syntheses, are unavailable.

Recently, we reported a series of pyrimidinyl-substituted amides and thioureas derivatives[3c-3d, 5] and their application in herbicidal processes. As an extension of our previous study, we herein synthesize five 2*H*-1,2,4-thiadiazole[2,3-*a*]pyrimidine derivatives **3a-3e** via a one-pot reaction and report a crystal structure of **3d**. Our attention is focused on the development of a convenient and rapid method for the preparation of 2*H*-1,2,4-thiadiazole[2,3-*a*]pyrimidine derivatives and the investigation of their regioselectivity through a comparison of the different substituted groups on pyrimidine ring.

RESULTS AND DISCUSSION

Syntheses and spectral and structural analyses



a: X,Y = OMe; **b:** X = Cl, Y = OMe; **c:** X,Y = OEt; **d:** X = Cl, Y = OEt; **e:** X = Me, Y = OEt .

Scheme 1. Syntheses of **3a-3e**

N-(5,7-disubsituted-*2H*-[1,2,4]thiadiazolo[2,3-*a*]pyrimidin-2-yliden)-2-(2,4-dichlorophenoxy) propanamides **3a-3e** were prepared by a facile one-pot reaction. As shown in Scheme 1, **3a-3c** and **3e** were obtained by the coupling reactions of **1** with 4,6-disubstituted-2-amino-pyrimidine via the acylated reaction and isothiocyanation, followed by the cyclization using Br_2 as an oxidant reagent in 81%, 76%, 83% and 71% isolated yields, respectively. For comparison, the corresponding thioureas **2a-2e** were also synthesized using a similar strategy. Structures of **3a-3c** and **3e** were characterized using IR, ^{1}H NMR, GC/MS and elemental analyses. All results were in full agreement with the proposed structures. Being comparing **2a-2e** with **3a-3e**, the characteristic absorptions of IR spectra around 3374 cm^{-1} (ν_{N-H}) and 1110 cm^{-1}($\nu_{S=O}$) in **2a-2e** disappears completely in **3a-3e**, suggesting that there are in the absence the N-H and the S=O groups in **3a-3e**. In addition, the strong absorptions around 1695 cm^{-1} ($\nu_{C=O}$) in **2a-2e** shift to normal ranges around 1740 cm^{-1} in **3a-3e**, indicating that there are not the intramolecular hydrogen-bonding interactions[5a] in **3a-3e**. Due to absence of active protons in **3a-3e**, no signal above 8.5 ppm in ^{1}H NMR spectra is observed, while **2a-2e** present two singlet signals around 12.2 and 12.4 ppm in low fields belong to NH protons that are ascribe to the deshielding effect of the highly exchangeable NH protons because of the electron-withdrawing effect. All these observations confirmed the formation of *2H*-1,2,4-thiadiazolo[2,3-*a*]pyrimidine species. Although the cyclization reactions should present two geometrical isomers when the pyrimidine ring possesses different substituents at 4- and 6-positons, such as **2d**, a single reaction product **3d** was obtained as sole product (Figure 1).

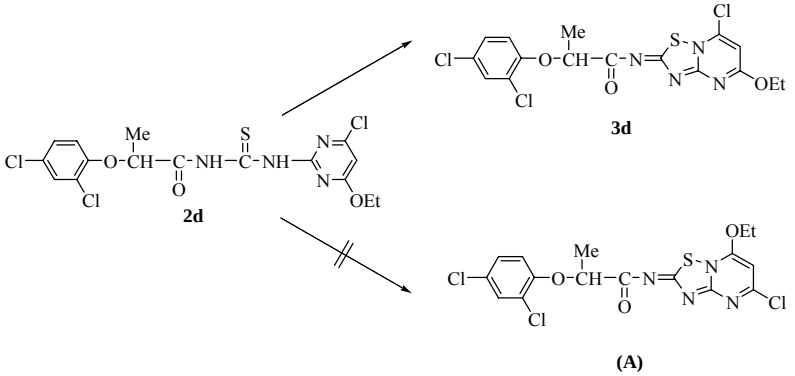


Figure 1. Two possible geometrical isomers on cyclization of **2d**

In order to explain the reason, a semi-empirical MO calculation of **2b** and **2d** was performed by using MNDO (Modified Neglect of Differential Overlap)[6] loaded on a Pentium(R) D 2.80GHz personal computer. The reaction indices of **2b** and **2d** were calculated to estimate the reactive sites using a formula $f_{(E)} = 2\Sigma(Ci,_{HOMO})$,[2] in which $f_{(E)}$ are generally utilized to estimate susceptibility to eletrophilic reaction, and *Ci* is the coefficient for atomic orbital *i* in the HOMO. Based on the calculation, the reaction indices $f_{(E)}$ of the 1- and 3-position on pyrimidine ring in **2b** and **2d** were 0.897, 0.002 and 0.878, 0.002. These results strongly suggested that **3b** and **3d** were formed through the nucleophilic attack of the sulfur atom occurring mostly at 1-postion nitrogen atom on the pyrimidine ring due to lower electron density of 1-postion nitrogen atom because of electron-withdrawing effect of the chlorine atom.

Based on the above investigation, the following possible formation processes of **3d** could be taken into consideration as shown in Figure 2. At First, the compound **2d** forms one regioisomer by the imine-enamine tautomerization. Then the resulting **B** reacts with Br_2 to form intermediate **C**, in which the nucleophilic attack of the sulfur atom would occur at 1-postion nitrogen atom on the pyrimidine ring to afford the final product **3d**.

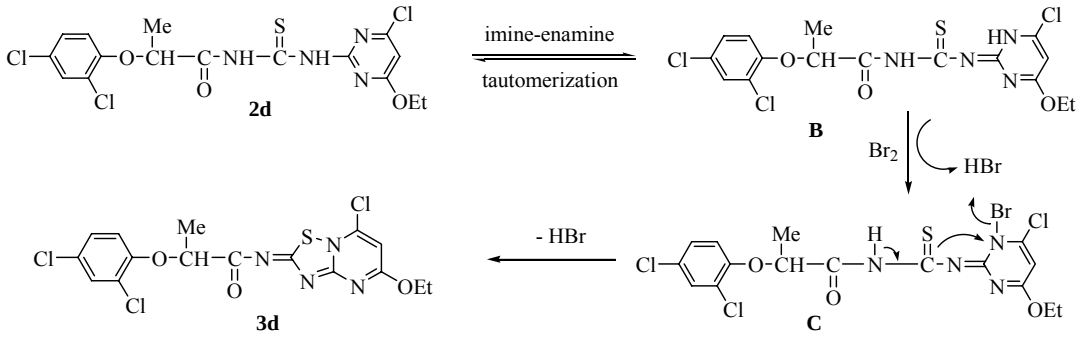


Figure 2. Proposed formation process of **3d**

Structural Determination

X-Ray crystallographic structure determination of **3d** (Figure 3) further confirmed our result.[7] It is obvious that the oxidative S-N bond-formation occurs at 1-postion nitrogen atom N(2) on the pyrimidine ring, which consolidates the nucleophilic attack of the sulfur atom of the thiourea on the 1-nitrogen atom of the pyrimidine ring. For comparison, an X-ray crystallographic structure determination of **3a** (Figure 4) was also obtained.[8,9] However, the molecular structure of **3a** is obviously different, in which **3a** contains two asymmetric independent molecules in its crystals, in which each phenoxypropionyl moieties and each thiadiazolo[2,3-*a*]pyrimidine moieties is mutually perpendicular around the amide groups with the dihedral angle of the plane defined by C(11)-N(2)-S(1)-C(10)-N(3) atoms with the plane of phenyl ring in 92.9°. Two independent molecules were linked each other by the weak intramolecular hydrogen bond of C-H---N [3.240(7) Å, 129°].[10] In comparison with the reported compound **3d**,[7] the C=O and C-N distance of the CONH bond [O(2)-C(9) of 1.240(6) Å and N(1)-C(9) of 1.334(6)Å] are in the expected range

although slightly different. Moreover, there are the intermolecular π-π interactions in the crystals of **3a**, in which each phenyl groups of **3a** is offset-stacked with the phenyl groups of adjacent molecules with the centroid separation of 3.590 Å that is quite reasonable in view of the other π-π interactions.[11]

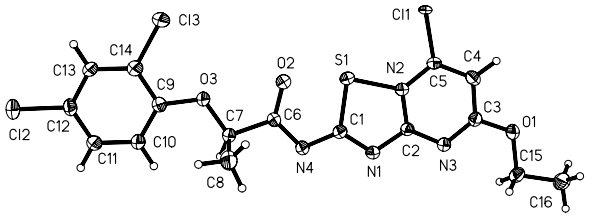


Figure 3. ORTEP drawings with atom-numbering scheme for **3d**. Ellipsoids for non-hydrogen atoms are drawn at the 50% probability level

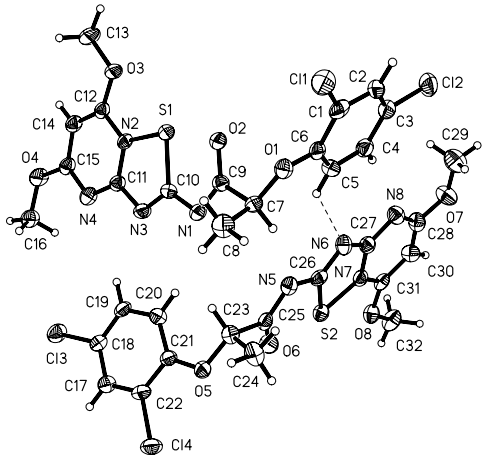


Figure 4. ORTEP drawings with atom-numbering scheme for **3a**. Ellipsoids for non-hydrogen atoms are drawn at the 50% probability level. Broken lines represent possible hydrogen-bonding interactions (CCDC 616409 for **3a**)

GENERAL SYNTHETIC PROCEDURES

Under nitrogen atmosphere, a stirred solution of **1** (0.50 g, 2.14 mmol) in $SOCl_2$ (5 mL) was refluxed for 1 h. After removing $SOCl_2$, to the residue was added a solution of KSCN (0.62 g, 6.41 mmol) in dry MeCN (10 mL) and reflux for another 2 h. After KCl was removed by filtration, to the stirred filtrate was slowly added a solution of 4,6-dimethoxy-2-aminopyrimidine (0.33 g, 2.14 mmol) in dry MeCN (5 mL) over 30 min at rt and refluxed for another 2 h. After cooling down to rt, to this stirred solution was slowly added dropwise 0.47 mL solution of bromine (1.44 g, 3.21mmol) over 20 min. The mixture was then stirred at rt overnight. After evaporating most of the solvent, water (5 mL) was added to quench the

reaction. The residue was then repeatedly extracted with Et_2O (50 mL). The combined organic layer was washed with water and brine, and then dried over Na_2SO_4. When the solvent was evaporated, the resulting residue was purified by column chromatography on silica gel (petroleum ether: EtOAc = 5:1, v/v) to give **3a** (0.74 g, 1.73 mmol) as yellow solids. Yield: 81%; mp 140-142 ˚C; IR (KBr): 2921, 2859, 1741, 1621, 1548, 1458, 1335, 1229, 800, 739 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ: 7.46~7.45 (d, J_1 = 2.4 Hz, 1H, Ph-H), 7.33 (s, 1H, Ph-H), 7.06~7.05 (q, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H, Ph-H), 6.64~6.63 (d, J = 8.8 Hz, 1H, Ph-H), 6.45 (s, 1H, Py-H), 5.22~5.17 (q, J = 6.4 Hz, 1H, CHMe), 4.13 (s, 6H, OMe), 1.57~1.58 (d, J = 6.4 Hz, 3H, CHMe); MS (EI) (70 eV) m/z (%): 430 (1.25) $[M+2]^+$, 428 (1.94) $[M]^+$, 239 (20.5), 231 (11.76), 161 (30.56), 125 (30.84), 94(100), 66 (43.54); Anal. Calcd for $C_{16}H_{14}Cl_2N_4O_4S$: C, 44.77; H, 3.29; N, 13.05. Found: C, 44.65; H, 3.41; N, 13.18.

Compound **3b***:* white solids. Yield: 76%; mp 150-153 ˚C; IR (KBr): 2921, 2847, 1748, 1605, 1515, 1478, 1364, 1323, 1254, 1184, 804, 743 cm^{-1}; ^1H NMR (DMSO-d_6, 400MHz) δ: 7.59~7.58 (d, J_1 = 2.4 Hz, 1H, Ph-H), 7.32 (s, 1H, Ph-H), 7.29~7.27 (q, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H, Ph-H), 6.99~6.97 (d, J = 8.8 Hz, 1H, Ph-H), 6.78 (s, 1H, Py-H), 5.45~5.42 (q, J = 6.4 Hz, 1H, CHMe), 4.05 (s, 3H, OMe), 1.60~1.58 (d, J = 6.4 Hz, 3H, CHMe); MS (EI) (70 eV) m/z (%): 434 (4.26) $[M+2]^+$, 432 (4.31) $[M]^+$, 243 (42.82), 215 (21.34), 161 (36.39), 94(100), 66 (56.73); Anal. Calcd for $C_{15}H_{11}Cl_3N_4O_3S$: C, 41.54; H, 2.56; N, 12.92. Found: C, 41.63; H, 2.76; N, 12.78.

Compound **3c**: white solids. Yield: 83%; mp 145-147 ˚C; IR (KBr): 2990, 2945, 1735, 1609, 1527, 1478, 1446, 1339, 1286, 1213, 1098, 800, 746 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ: 7.36~7.35 (d, J_1 = 2.4 Hz, 1H, Ph-H), 7.27 (s, 1H, Ph-H), 7.06~7.03 (q, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H, Ph-H), 6.81~6.83 (d, J = 8.8 Hz, 1H, Ph-H), 5.84 (s, 1H, Py-H), 5.23~5.20 (q, J = 6.4 Hz, 1H, CHMe), 4.63~4.57 (q, 2H, J = 6.8 Hz, OCH_2Me), 4.38~4.32 (q, 2H, J = 6.8 Hz, OCH_2Me), 1.80~1.79 (d, J = 6.4 Hz, 3H, CHMe), 1.58~1.54 (t, J = 6.8 Hz, 3H, OCH_2Me), 1.45~1.41 (t, J = 6.8 Hz, 3H, OCH_2Me); MS (EI) (70 eV) m/z (%):458 (8.65) $[M+2]^+$, 456 (8.74) $[M]^+$, 267 (19.45), 239 (25.41), 209 (65.32), 94(100), 66 (68.58); Anal. Calcd for $C_{18}H_{18}Cl_2N_4O_4S$: C, 47.27; H, 3.97; N, 12.25. Found: C, 46.98; H, 3.87; N, 12.42.

Compound **3e**: white solids. Yield: 71%; mp 214-216 ˚C; IR (KBr): 3076, 2982, 2929, 1621, 1540, 1478, 1433, 1339, 1409, 1343, 1286, 1266, 1188, 1102, 1061, 805, 780 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ: 7.37~7.36 (d, J_1 = 2.4 Hz, 1H, Ph-H), 7.27 (s, 1H, Ph-H), 7.07~7.04 (q, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H, Ph-H), 6.85~6.83 (d, J = 8.8 Hz, 1H, Ph-H), 6.42 (s, 1H, Py-H), 5.23~5.20 (q, J = 6.4 Hz, 1H, CHMe), 4.65~4.59 (q, 2H, J = 6.8 Hz, OCH_2Me), 2.65 (s, 3H, Py-Me), 1.81~1.79 (d, J = 6.4 Hz, 3H, CHMe), 1.46~1.43 (t, J = 6.8 Hz, 3H, OCH_2Me); MS (EI) (70 eV) m/z (%):428 (4.76) $[M+2]^+$, 426 (10.33) $[M]^+$, 264 (22.36), 241 (24.65), 207 (47.39), 162 (42.10), 94(100), 66 (56.64); Anal. Calcd for $C_{17}H_{16}Cl_2N_4O_3S$: C, 47.78; H, 3.77; N, 13.11. Found: C, 47.83; H, 3.91; N, 13.09.

ACKNOWLEDGEMENTS

We thank National Natural Science Foundation (No. 20673072), Shanghai Municipal Education Commission (No. 05D215) and Shanghai Leading Academic Discipline Project (projects No.T0402) for financial supports.

REFERENCES

1. a) V. Bellofatto, *Trends Parasitol.,* 2007, **23**, 187. b) N. Zhang, S. Ayral-Kaloustian, T. Nguyen, R. Hernandez, and C. Beyer, *Bioorg. Med. Chem. Lett.,* 2007, **17**, 3003. c) B. S. Holla, M. Mahalinga, M. S. Karthikeyan, P. M. Akberali, and N. S. Shetty, *Bioorg. Med. Chem.,* 2006, **14**, 2040.
2. a) M. K. Koeppe, C. M. Hirata, H. M. Brown, W. H. Kenyon, D. P. O'Keefe, S. C. Lau, W. T. Zimmerman, and J. M. Green, *Pestic. Biochem, Phys.,* 2000, **66**, 170. b) S. J. Xue, L. P. Duan, S. Y. Ke, and J. M. Zhu, *Chin. J. Struct. Chem.,* 2004, **23**, 441.
3. a) N. Okajima, I. Aoki, T. Kuragano, and Y. Okada, *Pestic. Sci.,* 1991, **32**, 91. b) Y. Liang, S. Fan, W. Y. Mo, and H. W. He, *J. Fluorine Chem.,* doi: 10.1016 (in press). c) S. J. Xue, S. Y. Ke, L. P. Duan, X. H. Wang, and Y. L. Guo, *J. Indian Chem. Soc.,* 2005, **82**, 79. d) S. J. Xue, L. P. Duan, J. S. Zou, Q. Guan, and S. Y. Ke, *Chin. J. Org. Chem.,* 2004, **24**, 1244.
4. a) J. A. McCourt, S. S. Pang, L. W. Guddat, and R. G. Duggleby, *Biochemistry*, 2005, **44**, 2330. b) K. H. Ott, J. G. Kwagh, G. W. Stockton, V. Sidorov, and G. Kakefuda, *J. Mol. Biol.,* 1996, **263**, 359. c) S. S. Pang, R. G. Duggleby, and L. W. Guddat, *J. Mol. Biol.,* 2002, **317**, 249.
5. a) G. H. Liu, Y. N. Xue, and S. J. Xue, *Acta. Cryst.,* 2006, **E62**, o133. b) G. H. Liu, Y. N. Xue, L. Z. Yang, M. Yao, and S. J. Xue, *Acta Cryst.*, 2006, **E62**, o1028.
6. a) HyperChem^{TM} Software package for Windows Molecular Modeling System version 7.5, HyperCube, Inc., Gainesville, FL, USA. b) K. Fukui, Theory of Orientation and Selection, in K. Hafner, et al. (Eds.), Reactivity and Structure Concepts in Organic Chemistry, Vol. 2, Springer-Verlag, Berlin, 1975.
7. G. H. Liu, Y. N. Xue, M. Yao, H. B. Fang, and H. Yu, *Chin. J. Strut. Chem.,* 2007, **26**, 450.
8. G. M. Sheldrick, *SHELXS97* and *SHELXL97*, University of Göttingen, Germany **1997**.
9. Bruker. *SMART, SAINT, SHELXTL* and *SADABS*. Bruker AXS Inc., Madison, Wisconsin, USA **1998**.
10. a) G. R. Desiraju and T. Steiner, The Weak Hydrogen Bond; Oxford University Press: Oxford, New York, 1991. b) Jeffrey, G. A. An Introduction of Hydrogen Bonding, Oxford University Press, New York, 1997.
11. a) M. O. Sinnokrot and D. C. Sherrill, *J. Am. Chem. Soc*., 2004, **126**, 7690. b) C. A. Hunter and K. M. Sanders, *J. Am. Chem. Soc.,* 1990, **112**, 5525.