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

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Abstract – A convenient and rapid method for the preparation of 2H-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, and some of them are well known to use as herbicides. In particular, some fused heterocycles, such as 2H-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. Therefore, exploring fused heterocycles as herbicides has become a subject of intensive research. Generally speaking, these fused heterocycles contain two part; (i) aromatic/heterocyclic moiety (ii) 2H-1,2,4-thiadiazole-[2,3-a]pyrimidines moiety. The aromatic/heterocyclic moiety is either phenyl or pyridinyl with substituted group in different position. Although some fused heterocycles have been described, 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 and their application in herbicidal processes. As an extension of our previous study, we herein synthesize five 2H-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 2H-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

\[ \text{Scheme 1. Syntheses of 3a-3e} \]

\[ \text{N-(5,7-disubstituted-2H-[1,2,4]thiadiazolo[2,3-a]pyrimidin-2-yliden)-2-(2,4-dichlorophenoxy) propanamides 3a-3e were prepared by a facile one-pot reaction. As shown in Scheme 1, 3a-3c and 3e were obtained by the coupling reactions of 1 with 4,6-disubstituted-2-amino-pyrimidine via the acylated reaction and isothiocyanation, followed by the cyclization using Br}_2 \text{as an oxidant reagent in 81%, 76%, 83% and 71% isolated yields, respectively. For comparison, the corresponding thioureas 2a-2e were also synthesized using a similar strategy. Structures of 3a-3c and 3e were characterized using IR, }^{1}\text{H NMR, GC/MS and elemental analyses. All results were in full agreement with the proposed structures. Being comparing 2a-2e with 3a-3e, the characteristic absorptions of IR spectra around 3374 cm}^{-1} \text{ (}\nu_{\text{N-H}}\text{) and 1110 cm}^{-1} \text{ (}\nu_{\text{S=O}}\text{) in 2a-2e disappears completely in 3a-3e, suggesting that there are in the absence the N-H and the S=O groups in 3a-3e. In addition, the strong absorptions around 1695 cm}^{-1} \text{ (}\nu_{\text{C=O}}\text{) in 2a-2e shift to normal ranges around 1740 cm}^{-1} \text{ in 3a-3e, indicating that there are not the intramolecular hydrogen-bonding interactions in 3a-3e. Due to absence of active protons in 3a-3e, no signal above 8.5 ppm in }^{1}\text{H NMR spectra is observed, while 2a-2e present two singlet signals around 12.2 and 12.4 ppm in low fields belong to NH protons that are ascribe to the deshielding effect of the highly exchangeable NH protons because of the electron-withdrawing effect. All these observations confirmed the formation of 2H-1,2,4-thiadiazolo[2,3-a]pyrimidine species. Although the cyclization reactions should present two geometrical isomers when the pyrimidine ring possesses different substituents at 4- and 6-positons, such as 2d, a single reaction product 3d was obtained as sole product (Figure 1).} \]

\[ \text{Figure 1. Two possible geometrical isomers on cyclization of 2d} \]
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) 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 $f(E) = 2\sum(C_i HOMO)$ in which $f(E)$ are generally utilized to estimate susceptibility to electrophilic reaction, and $C_i$ 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](image)

**Structural Determination**

X-Ray crystallographic structure determination of 3d (Figure 3) further confirmed our result. 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. 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 thia diazolo[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°]. In comparison with the reported compound 3d, 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 SOCl₂ (5 mL) was refluxed for 1 h. After removing SOCl₂, 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, 3.21 mmol) 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 Et₂O (50 mL). The combined organic layer was washed with water and brine, and then dried over Na₂SO₄. 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 (CDCl₃, 400MHz) δ: 7.46~7.45 (d, J₁ = 2.4 Hz, 1H, Ph-H), 7.33 (s, 1H, Ph-H), 7.06~7.05 (q, J₁ = 2.4 Hz, J₂ = 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 C₁₆H₁₄Cl₂N₄O₄S: 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-d₆, 400MHz) δ: 7.59~7.58 (d, J₁ = 2.4 Hz, 1H, Ph-H), 7.32 (s, 1H, Ph-H), 7.29~7.27 (q, J₁ = 2.4 Hz, J₂ = 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 C₁₅H₁₁Cl₃N₄O₃S: C, 41.54; H, 2.56; N, 12.92. Found: C, 41.63; H, 2.76; N, 12.92.

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 (CDCl₃, 400MHz) δ: 7.36~7.35 (d, J₁ = 2.4 Hz, 1H, Ph-H), 7.27 (s, 1H, Ph-H), 7.06~7.03 (q, J₁ = 2.4 Hz, J₂ = 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, OCH₂Me), 4.38~4.32 (q, 2H, J = 6.8 Hz, OCH₂Me), 1.80~1.79 (d, J = 6.4 Hz, 3H, CHMe), 1.58~1.54 (t, J = 6.8 Hz, 3H, OCH₂Me), 1.45~1.41 (t, J = 6.8 Hz, 3H, OCH₂Me); 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 C₁₈H₁₈Cl₂N₄O₄S: 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 (CDCl₃, 400MHz) δ: 7.37~7.36 (d, J₁ = 2.4 Hz, 1H, Ph-H), 7.27 (s, 1H, Ph-H), 7.07~7.04 (q, J₁ = 2.4 Hz, J₂ = 8.8 Hz, 1H, Ph-H), 6.45 (s, 1H, Py-H), 4.65~4.59 (q, 2H, J = 6.8 Hz, OCH₂Me), 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, OCH₂Me); 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 C₁₇H₁₆Cl₂N₄O₃S: C, 47.78; H, 3.77; N, 13.11. Found: C, 47.83; H, 3.91; N, 13.09.
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