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Reaction of 1-(Methylpyridin-2-yl)-3-phenyl-thioureas with Dimethyl Acetylenedicarboxylate: Formation of Isomeric Substituted 2-imino-thiazolidin-4-one Derivatives

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ABSTRACT The reaction of 1-(methylpyridin-2-yl)-3-phenyl-thioureas (**1**-**4**) with dimethyl acetylenedicarboxylate (DMAD) led to the formation of a mixture of two isomeric 2-imino-thiazolidin-4-one derivatives. The compounds **1**-**4** can be synthesized from easily available starting materials such as phenyl isothiocyanate and 2-amino-3-methylpyridine. A plausible mechanistic explanation for the reaction has also been discussed.

KEYWORDS 2-Iminothiazolidin-4-one, Dimethylacetylenedicarboxylate, Intramolecular hydrogen bonding, Synthesis, Thiazolidinone.

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INTRODUCTION

Thiazolidinone derivatives belong to an essential group of five-membered heterocyclic compounds with sulfur and nitrogen atoms. In recent years, many studies have been done on 4-thiazolidinone derivatives with a carbonyl group in position 4. The chemical properties and the usage of these compounds have been reported in numerous pieces of literature.[1,2] Many researchers have studied the synthesis of 4-thiazolidinone derivatives in recent years.[3-5] For instance, the reaction of dimethyl acetylenedicarboxylate (DMAD) with derivatives of thiosemicarbazide and thioamides is known as a unique method for the synthesis of 2-amino-5-methoxycarbonyl-thiazolidin-4-ones.[3,6-9] For preparing 4-thiazolidinone derivatives, a standard strategy based on the reaction of DMAD with thiourea derivatives is presented herein. In addition, the effect of the intramolecular hydrogen bond between hydrogen atom of the NH group and nitrogen of pyridine on the structure of two major and minor isomers has been studied.

RESULTS AND DISCUSSION

We carried out the synthesis of four substituted 2-imino-thiazolidin-4-one derivatives by the reaction of equimolar amounts of DMAD with 1-phenyl-3- pyridin-2-yl-thiourea derivatives (**1**–**4**). The sulfur atom and the nitrogen atom of 1-phenyl-3-pyridin-2-yl-thiourea derivatives both can react with DMAD in this reaction, but the spectral data showed that compounds **1**-**4** react mainly from the side of the sulfur atom with DMAD. The reaction of compound **1** with DMAD has been investigated to understand the reaction mechanism. At first, both two NH groups connected to the C=S group can make the sulfur atom more nucleophile by resonance **[Figure 1]**. The difference between these two NH groups is due to the effect of the N atom of pyridine on the hydrogen of NH (a) by making an intramolecular hydrogen bonding **[Figure 1a**]. It is concluded that the effect of intramolecular hydrogen bonding between the nitrogen of pyridine and hydrogen of N(a) helps N(a) to make sulfur atom more nucleophilic in comparison with the effect of N(b) on nucleophilicity of the sulfur atom.[10]

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[3-(4-Methyl-pyridin-2-yl)-4-oxo-2-phenylimino-thiazolidin-5-ylidene]-acetic acid methyl ester (19 Major), [2-(4-methyl-pyridin-2-ylimino)-4-oxo-2-phenyl-thiazolidin-5-ylidene]-acetic acid methyl (20 Minor)

Yield: 3.01 g, 82%; m.p. 229–232°C; IR (KBr) vmax: 3416, 3061, 2993, 1699, 1585, 1544 cm^{-1}; Major isomer (**19**) (83%): δH (DMSO-d6 500 MHz): 2.26 (3H, s, CH_3), 4.27 (3H, s, OCH_3), 6.75 (1H, s, C5-H), 6.87-8.38 (8H, m, arom); δC (DMSO-d6 125 MHz): 20.13 (CH_3), 61.29 (OCH_3), 116.15 (CH), 121.85 (CH^{para}), 122.05 (CH), 128.48 (C_5), 128.74 ($2CH^{ortho}$), 128.89 ($2CH^{meta}$), 134.96 (CH), 143.88 (C_1), 146.70 (C), 149.87 (C_3), 153.69 (C_2), 156.67 (C_4), 163.90 (C=O amide), 165.24 (C=O ester).

Minor isomer (**20**) (17%): δ_H (DMSO-d_6 500 MHz): 2.19 (3H, s, CH_3), 3.87 (3H, s, OCH_3), 6.54 (1H, s, C_5-H), 6.90-8.44 (8H, m, arom); δ_C (DMSO-d_6 125 MHz): 19.67 (CH_3), 59.12 (OCH_3), 117.37 (CH), 123.63 (CH^{para}), 129.03 ($2CH^{ortho}$), 130.21 ($2CH^{meta}$), 1339.69 (CH), 144.28 (C_1), 148.61 (C_3), 154.12 (C_2), 164.98 (C=O amide), 166.79 (C=O ester).

[3-(5-Methyl-pyridin-2-yl)-4-oxo-2-phenylimino-thiazolidin-5-ylidene] acetic acid methyl ester (21 Major), [2-5-methyl-pyridin-2-ylimino)-4-oxo-2-phenyl-thiazolidin-5-ylidene]-acetic acid methyl (22 Minor)

Yield: 3.13 g, 89%; m.p. 231–236°C; IR (KBr) ν_{max}: 3399, 3060, 2987, 2945, 1708, 1587, 1551 cm^{-1}.

Major isomer (**21**) (79%): δ_H (DMSO-d_6 500 MHz): 2.52 (3H, s, CH_3), 3.81 (3H, s, OCH_3), 6.77 (1H, s, C_5-H), 6.82-8.36 (8H, m, arom); δ_C (DMSO-d_6 125 MHz): 17.40 (CH_3), 52.39 (OCH_3)*, 115.87 (CH), 118.10 (CH^{para})*, 120.76 (C_5), 128.47 ($2CH^{ortho}$)*, 128.89 ($2CH^{meta}$), 130.46 (C)*, 134.95 (CH)*, 139.00 (CH), 144.20 (C_1), 147.00 (C_3)*, 154.48 (C_2), 155.97 (C_4), 162.53 (C=O amide)*, 165.68 (C=O ester).

Minor isomer (**22**) (21%): δ_H (DMSO-d_6 500 MHz): 2.28 (3H, s, CH_3), 3.81[(a)] (3H, s, OCH_3), 6.81 (1H, s, C_5-H), 6.82–8.36 (8H, m, arom); δ_C (DMSO-d_6 125 MHz): 23.32 (CH_3), 115.75 (CH), 120.27 (C_5), 128.74 ($2CH^{meta}$), 139.26 (CH), 143.98 (C_1), 153.75 (C_2), 155.91 (C_4), 163.90 (C=O ester).

(**a**) Only one peak at 3.81 was formed for both major and minor isomers with the integration of six protons.

[3-(6-Methyl-pyridin-2-yl)-4-oxo-2-phenylimino-thiazolidin-5-ylidene] acetic acid methyl ester (23 Major), [2-(6-methyl-pyridin-2-ylimino)-4-oxo-2-phenyl-thiazolidin-5-ylidene]-acetic acid methyl (24 Minor)

Yield: 3.13 g, 89%; m.p. 240–245°C; IR (KBr) ν_{max}: 3450, 3061, 2988, 2946, 1708, 1570, 1553 cm^{-1}.

Major isomer (**23**) (86%): δ_H (DMSO-d_6 500 MHz): 2.53 (3H, s, CH_3), 3.81 (3H, s, OCH_3), 6.79 (1H, s, C_5-H), 6.82–8.37 (8H, m, arom); δ_C (DMSO-d_6 125 MHz): 17.41 (CH_3), 52.41 (OCH_3), 115.87 (CH), 118.12 (CH^{para})*, 120.29 (C_5), 128.49 ($2CH^{ortho}$), 130.48 ($2CH^{meta}$), 134.96 (CH)*, 139.04 (CH), 144.03 (C), 147.01 (C_1)*, 152.90 (C_3), 154.49 (C_2)*, 155.92 (C_4), 163.85 (C=O amide), 165.70 (C=O ester).

Minor isomer (**24**) (14%): δ_H (DMSO-d_6 500 MHz): 2.29 (3H, s, CH_3), 3.80 (3H, s, OCH_3), 6.78 (1H, s, C_5-H), 6.82-8.36 (8H, m, arom); δ_C (DMSO-d_6 125 MHz): 23.33 (CH_3), 52.42 (OCH_3), 115.74 (CH), 120.79 (C_5), 128.76 ($2CH^{ortho}$), 128.91 ($2CH^{meta}$), 139.29 (CH), 144.23 (C), 153.80 (C_3), 155.98 (C_4), 163.93 (C=O amide), 165.74 (C=O ester).

CONCLUSION

The reaction of 1-phenyl-3-pyridin-2-yl-thiourea derivatives with DMAD leads to two different products. This phenomenon shows that intramolecular hydrogen bonding in molecules can play a significant role in characterizing the reaction path and, consequently, the percentage of products. On the other hand, this reaction illustrates that the sulfur atom is more nucleophilic than the nitrogen atom.

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