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A simple approach to the synthesis of 3-substituted rhodanines and thiazolidine-2,4-diones

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Thiazolidine-2,4-diones;
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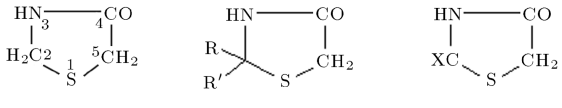
Abstract. A novel synthesis of 3-substituted rhodanine and thiazolidine-2,4-dione derivatives, starting from aliphatic primary amines, carbon disulfide, and methyl 2-bromoacetate, is described. The reaction proceeds successfully both in water and under solvent-free conditions, but 2-thioxothiazolidin-4-one (rhodanine) derivatives were obtained under solvent free-conditions, and thiazolidine-2,4-dions were formed when water was used as the solvent.

1. Introduction

Natural penicillin is a powerful antibiotic with a broad spectrum that has a thiazolidine ring in its structure [1]. The thiazolidinediones (TZDs, IIIA) or glitazones (I) are derivatives of thiazolidine with a carbonyl group in the 4-position. The main differences in the properties and structure of thiazolidines are related to the atom or group which is attached to the carbon atom in the 2-position (X in formula III or R and R′ in formula II). Such groups include alkyl or aryl (formula II), oxygen (formula IIIA, thiazolidine-2,4-dione), sulfur (formula IIIB, rhodanine), and imino (formula IIIC, pseudo-thiohydantoin). Compounds in which alkyl or aryl groups replace the hydrogen atoms in the 2-position are named derivatives of 2-imino-4-thiazolidinone (formula IIID). Variations in the substituent attached to the nitrogen atom and the methylene carbon atom are possible for the structures shown as formulas II and III:



I II III

A: X=O
B: X=S
C: X=NR
D: X=NN=CRR′

Thiazolidinediones (TZDs) are reported to show a variety of biological activity. Depending on the substituent, this heterocycle structure can demonstrate different pharmacological properties. TZDs are a class of chemotherapeutics which enhance the action of insulin in liver, muscle and fat tissue, and are used for the treatment of type 2 diabetes mellitus [2-8]. They increase the action of insulin in the liver, muscle and fat tissues.

Rhodanine derivatives are attractive compounds due to their outstanding biological and pharmacological activity, which include antimicrobial [4,9-14], antiviral [15], and anticonvulsant [16] effects. Additionally, rhodanine-based molecules have been popular as small molecule inhibitors of numerous targets such as HCV NS3 protease [17], aldose reductase [18,19], β-lactamase [20], antidiabetic agents [21], cathepsin D [22], and histidine decarboxylase [23]. Therefore,

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the syntheses of these compounds are of considerable interest.

Several synthetic approaches for the synthesis of TZDs are reported in the literature [24-30]. Most of these methods give unsatisfactory yields, even after prolonged reaction time. They also have critical isolation procedures for obtaining the pure product. In some cases, expensive metal precursors and volatile organic solvents are used. They also require harsh reaction conditions, such as high temperature and strong acidic media. Also, synthesis of rhodanine compounds usually has multi step procedures when prepared by Knoevenagel condensation [31]. For example, 4-thiazolidinones were prepared using sodium chloroacetate with ammonium salt of dithiocarbamates in the presence of HCl [32] or by the reaction of amines with thiocarbonyldiimidazole in the presence of triethylamine in dichloromethane [33].

2. Experimental

2.1. General procedure

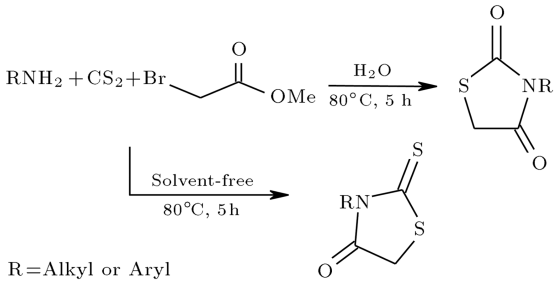
All reactions were carried out in an atmosphere of air. All chemicals and solvents except water (tap water) were purchased from Merck or Fluka and used as received. All reactions were monitored by TLC on silica gel 60 F254 (0.25 mm), visualization being effected with UV and/or by developing in iodine. ^{1}H NMR and ^{13}C NMR were recorded on a Brucker 500 MHz spectrometer. Chemical shifts are reported in (ppm) relative to TMS or $CDCl_3$ as internal.

2.2. General procedure for the preparation of 3-substituted thiazolidendiones

Carbon disulfide (3 mmol) was mixed with an amine (1.2 mmol) in H_2O (5 mL, or without any solvent) to form the dithiocarbamates (for primary aromatic amines, the dithiocarbamate's triethylamine salts of amines were used). When the dithiocarbamate was completely formed (monitored by TLC), the dithiocarbamates (or dithiocarbamate's triethylamine salts) were then treated with methyl 2-bromoacetate (1 mmol) to form the S-carboxymethyl dithiocarbamate. The latter was heated at 80°C for 5h and then the reaction mixture was cooled to room temperature and diluted with ethyl acetate. The organic phase was washed with water, dried over Na_2SO_4, filtered and evaporated in *vacuo* to give the crude product. In most cases, pure products were obtained. Further purification was carried out by column chromatography on silica gel if needed, using a 1:3 ratio of ethyl acetate and petroleum ether as eluent.

3. Results and discussion

We recently reported a green, one-pot and simple method for the synthesis of dithiocarbamates from amines, CS_2 and different nucleophile acceptors, such as alkyl halides, activated olefins and epoxides under solvent-free and aqueous conditions [34]. Also, Alizadeh reported a simple and effective approach for the synthesis of rhodanine derivatives via three-component reactions in water [35].



Scheme 1. The reaction under solvent-free and in water.

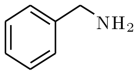
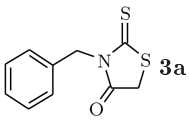
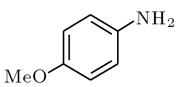
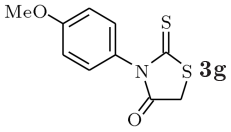
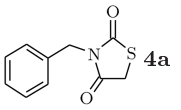
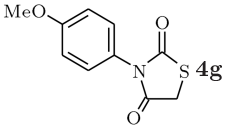
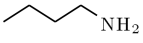
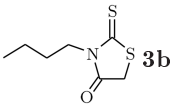
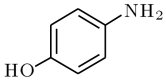
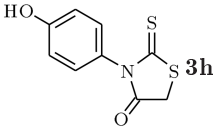
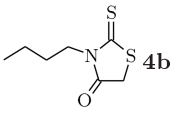
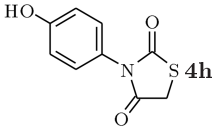
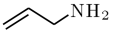
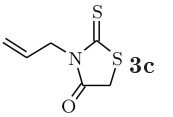
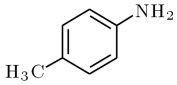
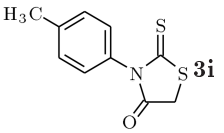
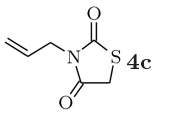
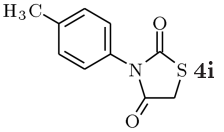
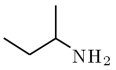
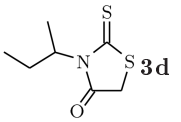
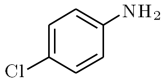
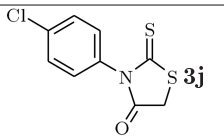
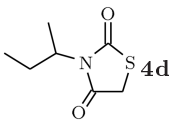
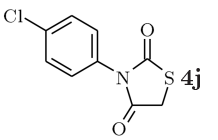
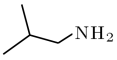
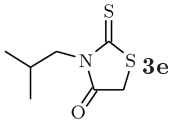
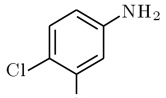
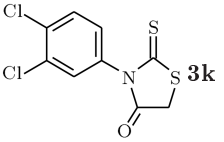
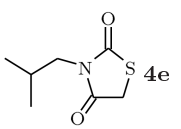
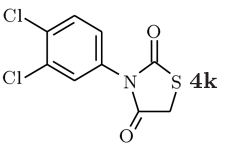
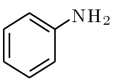
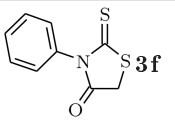
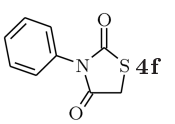
On this basis, and in continuation of our ongoing interest in the discovery of green and efficient methods for the synthesis of novel dithiocarbamates, and the use of these intermediates in organic transformations, including synthesis of hetrocyclic compounds [36], we designed a novel method for the preparation of thiazolidine-2,4-dion and 2-thioxothia-zolidin -4-one (rhodanine) derivatives from amines, carbon disulfide, and methyl 2-bromoacetate, respectively, in water and under solvent-free conditions (Scheme 1).

Initially, we carried out the reaction of benzylamine **1a** (1.2 mmol), carbon disulfide (3 mmol), and methyl 2-bromoacetate **2** (1 mmol) at 80°C without using any solvent. Under these conditions, we obtained product **3a** at 90% yield (Table 1, entry 1). The reaction was also carried out in different organic solvents such as CH_2Cl_2, CH_3CN and H_2O. In CH_2Cl_2 and CH_3CN, the yields were similar to those of solvent-free, while, using water as a solvent, product **4a** was obtained.

In the next step, the scope and limitations of this simple process were explored using a wide range of aliphatic and aromatic primary amines. In general, aliphatic primary amines such as benzylamine, n-butylamine and allylamine work well to give corresponding heterocyclic compounds. Relatively hindered primary amines such as 1-phenylethylenamine and cyclohexylamine undergo efficient addition with methyl 2-bromoacetate to give the dithiocarbamate acyclic intermediate in good yields, but only trace amounts of the pertinent heterocycle products are obtained.

The experimental procedures for aliphatic amines are different from those of aromatic amines. In the case of aliphatic primary amines, the heterocyclic products were prepared by a one-pot three-component reaction. But, for aromatic amines, the dithiocarbamate salts were prepared with triethylamine in diethyl ether.

Table 1. 3-Substituted thiazolidine-2,4-dione and 2-thioxothiazolidin-4-one (rhodanine) derivative.

Entry	Amine	Product	Yiled %	Entry	Amine	Product	Yiled %
1		 **3a**	90	13		 **3g**	90
2		 **4a**	84	14		 **4g**	83
3		 **3b**	95	15		 **3h**	82
4		 **4b**	91	16		 **4h**	75
5		 **3c**	75	17		 **3i**	62
6		 **4c**	72	18		 **4i**	54
7		 **3d**	76	19		 **3j**	68
8		 **4d**	68	20		 **4j**	65
9		 **3e**	82	21		 **3k**	70
10		 **4e**	76	22		 **4k**	65
11		 **3f**	81				
12		 **4f**	75				

Then, after removing the solvent and excess triethylamine, the residual dithiocarbamate salts were used in the next step.

As shown in Table 1, good to excellent yields of 2-thioxothiazolidin-4-one and thiazolidine-2,4-dion derivatives were obtained by the one-pot reaction of dithiocarbamate salts, with methyl 2-bromoacetate. This method needs no acid or base, and ring closure occurs just by heating the S-carboxymethyl dithiocarbamate. The structures of all products were established by spectroscopic methods.

4. Conclusion

In summary, we have developed an economical and practical method for the synthesis of a wide range of thiazolidinediones using inexpensive and readily available reagents under neutral conditions. This process introduces a highly efficient method with moderate conditions and a simple work up procedure. The reaction proceeds smoothly in water or under solvent-free conditions, which is an important feature for the development of green chemistry.

5. Selected spectroscopic data

5.1. 3-Benzylthiazolidine-2,4-dione (4a)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (m, 2H), 7.17 (m, 3H), 4.60 (s, 2H), 3.82 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.7, 171.3, 135, 129.2, 128.5, 128, 45.4, 34.0.

5.2. 3-Butyl-2-thioxothiazolidin-4-one (3b)

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.91 (s, 2H), 3.62 (t, J = 7.4 Hz, 2H,), 1.47 (m, 2H), 1.26 (m, 2H), 0.85 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.0, 174.0, 42.0, 35.7, 29.9, 20.2, 14.0.

5.3. 3-Butylthiazolidine-2,4-dione (4b)

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.89 (s, 2H), 3.52 (t, J = 7.4 Hz, 2H), 1.5 (m, 2H), 1.25 (m, 2H), 0.87 (t, J = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.1, 171.8, 42.0, 33.9, 29.1, 20.2, 14.0

5.4. 3-Phenylthiazolidine-2,4-dione (4f)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (m, 2H), 7.43 (m, 1H), 7.3 (m, 2H), 4.1 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 170.5, 133.0, 129.0, 128.0, 127.0, 125, 34.0.

5.5. 3-(4-Methoxyphenyl)-2-thioxothiazolidin-4-one (3g)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13 (d, J = 9.0 Hz, 2H), 7.1 (d, J = 9.0 Hz, 2H), 4.16 (s, 2H), 3.83 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.4, 173.7, 160.6, 129.8, 127.6, 115.2, 55.7, 36.4.

5.6. 3-(4-Methoxyphenyl)thiazolidine-2,4-dione (4g)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 (d, J = 9.0 Hz, 2H), 6.97 (d, J = 9.0 Hz, 2H), 4.07 (s, 2H), 3.82 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.1, 170.9, 160.3, 128.7, 125.6, 115.1, 55.7, 33.9. MS: m/z (%): M+ = 223 (60.8), 149 (100), 134 (58.1), 120 (38.8), 106 (37.0).

5.7. 3-(4-Hydroxyphenyl)-2-thioxothiazolidin-4-one (3h)

^{1}H NMR (500 MHz, $CDCl_3$/DMSO-d_6): δ 9.18 (s, 1H), 6.8-6.7 (m, 4H), 3.99 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$/ DMSO-d_6): δ 202.4, 173.9, 158.7, 128, 126, 116, 36.4.

5.8. 2-Thioxo-3-p-tolylthiazolidin-4-one (3i)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (d, J = 8.2 Hz, 2H), 7.12-7.11 (d, j = 8.40 Hz, 2H), 4.2 (s, 2H), 2.46 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.8, 173.95, 140.0, 132.0, 130.0, 120.0, 36.7, 21.6.

5.9. 3-(4-Chlorophenyl)-2-thioxothiazolidin-4-one (3j)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 8.6 Hz, 2H), 4.23 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.1, 173.5, 136.3, 133.6, 130.3, 130.1, 127, 36.7.

5.10. 3-(3,4-Dichlorophenyl)-2-thioxothiazolidin-4-one (3k)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, J = 8.5 Hz, 1H), 7.46 (d, J = 2.4 Hz, 1H), 7.13 (dd, J = 2.4, 8.5 Hz, 1H), 4.23 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.6, 173.2, 134.8, 134.2, 134.1, 131.7, 131, 128.3, 36.7.

5.11. 3-(4-Methoxyphenyl)thiazolidine-2,4-dione (4g)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 (d, J = 9.0 Hz, 2H), 6.97 (d, J = 9.0 Hz, 2H), 4.07 (s, 2H), 3.82 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.1, 170.9, 160.3, 128.7, 125.6, 115.1, 55.7, 33.9. MS: m/z (%): M^+ = 223 (60.8), 149 (100), 134 (58.1), 120 (38.8), 106 (37.0).

5.12. 3-(3,4-Dichlorophenyl)thiazolidine-2,4-dione (4k)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (d, J = 8.9 Hz, 1H), 7.46 (d, J = 2.4 Hz, 1H), 7.19 (dd, J = 2.4, 8.6 Hz, 1H), 4.16 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 170.4, 134.2, 133.8, 132.0, 131.4, 129.6, 126.9, 34.2.

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