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Synthesis of substituted 4-methylphenyl-2-iminothiazolidinone compounds *via* one-pot method

F. T. Tuğcu*

Faculty of Arts and Sciences, Department of Chemistry, Yildiz Technical University, Istanbul, Turkey

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Iminothiazolidinone derivatives, a class of nitrogen-containing heterocycles, have garnered significant attention in chemical research due to their remarkable biological and pharmacological activities such as antimicrobial, anti-inflammatory, anticonvulsant, antioxidant, antidiabetic, antitumor, and sedative characteristics [1-3]. This study aims to contribute to the field by synthesizing new iminothiazolidinone derivatives with potential biological activity. The synthesis is conducted using a one-pot multicomponent reaction technique, allowing for efficient and cost-effective production of these compounds. The chosen methodology involves a single-step approach, wherein thiourea derivatives, hetaryl aldehydes, and chloroacetic acid are subjected to a one-pot reaction, progressing in a domino-process fashion. This method offers advantages over traditional multi-step organic reactions, ensuring ease of execution within a shorter timeframe and at reduced costs.

Keywords: Iminothiazolidinone, thiourea, one-pot reaction, multicomponent reaction, solvent free

INTRODUCTION

In the recent years, a significant portion of chemical research is dedicated to the synthesis of novel compounds with the potential for biological activity, and the subsequent measurement of their activities. Iminothiazolidinone derivatives, which are nitrogen-containing heterocycles, have recently gained substantial importance due to their elevated biological and pharmacological activities. Among heterocyclic compounds, iminothiazolidinones, particularly those exhibiting antimicrobial, anti-inflammatory, anticonvulsant, anti-hyper lipidemic, antihypertensive, neuroleptic, and sedative properties, play a crucial role, contributing to the production of macrocyclic complex drugs and holding significance in industrial applications [1-6].

Considering literature research, the primary objective of this study is to synthesize some new iminothiazolidinone derivatives with potential biological activity. The synthesis of these new iminothiazolidinone derivatives is undertaken to contribute not only to the class of heterocyclic compounds but also to benefit synthetic drug production. In this study, the new compounds are synthesized using a one-pot multicomponent reaction technique.

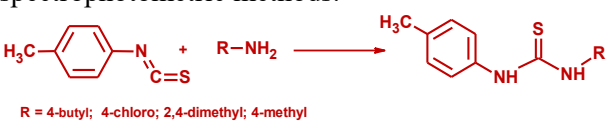
The reactions, conducted by a one-pot method, progress in a domino-process fashion, making them more straightforward to execute compared to classical multi-step organic reactions. This method enables the synthesis of new organic molecules in a shorter time and at a lower cost.

Utilizing the one-pot multicomponent reaction technique, cyclization is achieved by exploiting thiourea derivatives, hetaryl aldehydes, and chloroacetic acid, resulting in new 2-imino-4-thiazolidinone derivatives [7].

EXPERIMENTAL

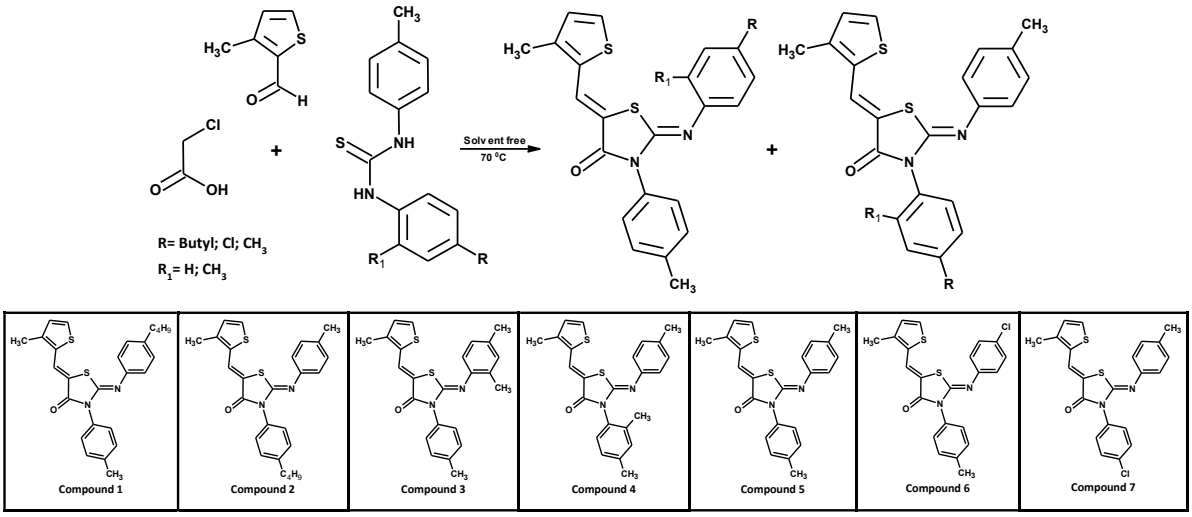
The study consists of two parts. In the first part, substituted thiourea compounds, which were planned to be used as substrates in the reactions, were obtained from substituted phenyl isothiocyanate and substituted amine compounds (Scheme 1).

In the second part, original imino-thiazolidinone compounds were synthesized by reacting the prepared substituted thiourea compounds with chloroacetic acid and thiophene aldehyde using the one-pot multicomponent method (Scheme 2). Measurements to elucidate the structures of the compounds obtained were performed using spectrophotometric methods.



Scheme 1. Synthesis of the thiourea compounds

* To whom all correspondence should be sent:
E-mail: *ftugcu@yildiz.edu.tr*



Scheme 2. Synthesis of the iminothiazolidinones

Compound 1: 3-(4-butylphenyl)-5-[(3-methylthiophen-2-yl) methylene]-2-(p-tolylimino) -thiazolidin-4-one: Mixture of 0.126 g (1.0 mmol) thiophene-3-aldehyde, 0.298 g (1.0 mmol) 1-(4-butylphenyl)-3-(4-methylphenyl) thiourea and 0.113 g (1.0 mmol) chloroacetic acid was placed in a round-bottomed balloon. TLC control was performed at regular intervals, and it was mixed first at room temperature for 24 hours and then at 40^0C for 24 hours with the help of a magnetic stirrer. After the reaction was completed, the two isomer products were purified by applying column chromatography (dichloromethane/hexane: 4/1) to the dark solid mixture that was left to cool. $C_{26}H_{26}N_2OS_2$ (446.63 g/mol). FT-IR (ATR): 3029, 2924, 2854, 1716, 1639, 1599, 1504, 1360, 1261, 1171, 1141, 879, 836 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.95 (3H, t), 1.37 (2H, m), 1.60 (2H, m), 2.41 (3H, s), 2.42 (3H, s), 2.61 (2H, t), 6.88 (2H, d, J=8.2 Hz), 6.98 (1H, d, J=5.0 Hz),7.16 (2H, d, J=8.2 Hz), 7.34 (4H, s), 7.48 (1H, d, J=5.0 Hz), 8.05 (1H, s) ppm. ^{13}C NMR ($CDCl_3$)**:** δ 14.02, 14.52, 21.35, 22.40, 33.61, 35.18, 118.65, 120.95, 122.57, 127.77, 129.15, 129.46, 129.99, 131.06, 132.35, 132.54, 138.83, 139.41, 142.43, 145.81, 150.44, 166.63 ppm.

Compound 2: 2-(4-butylphenylimino)-5-[(3-methylthiophen-2-yl)-methylene)-3-p-tolyl-thiazolidin-4-one: $C_{26}H_{26}N_2OS_2$ (446,63 g/mol). FT-IR (ATR): 3069, 2954, 2856, 1712, 1638, 1595, 1506, 1366, 1269, 1167, 1147, 839, 796 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.95 (3H, t), 1.40 (2H, m), 1.64 (2H, m), 2.35 (3H, s), 2.42 (3H, s), 2.66 (2H, t), 6.88 (2H, d, J=8.2 Hz), 6.97 (1H, d, J=5.0 Hz),7.14 (2H, d, J=8.2 Hz), 7.33 (2H, d, J=8.6 Hz), 7.36 (2H, d, J=8.6 Hz), 7.47 (1H, d, J=5.0 Hz), 8.04 (1H, s) ppm. ^{13}C NMR ($CDCl_3$)**:** δ 13.98, 14.52, 21.02, 22.50, 33.31, 35.47, 118.62, 120.99, 122.57, 127.69, 129.28, 129.44, 129.85, 131.05, 132.42, 132.53, 134.34, 142.42, 143.65, 145.80, 150.72, 166.65 ppm.

Compound 3: 2-(2,4-dimethylphenylimino)-5-[(3-methylthiophen-2-yl) methylene]-3-p-tolylthiazolidin-4-one: $C_{24}H_{22}N_2OS_2$ (418,54 g/mol). FT-IR (ATR): 3099, 3066, 3011, 2918, 2853, 1708, 1634, 1589, 1510, 1355, 1261, 1169, 1113, 867, 809 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.12 (3H, s), 2.31 (3H, s), 2.42 (6H, s), 6.78 (2H, d, J=7.9 Hz), 6.97 (1H, d, J=5.0 Hz), 7.16 (2H, d, J=8.2 Hz), 7.34 (4H, s), 7.48 (1H, d, J=5.0 Hz), 8.05 (1H, s) ppm. ^{13}C NMR ($CDCl_3$): δ 14.59, 17.95, 21.09, 21.47, 118.96, 119.83, 122.67, 127.24, 127.87, 129.54, 129.77, 130.04, 130.15, 131.15, 131.51, 132.54, 132.66, 134.42, 139.01, 142.49, 144.55, 150.29, 166.77 ppm.

Compound 4: 3-(2,4-dimethylphenyl)-5-[(3-methylthiophen-2-yl) methylene]-2-(p-tolyl-imino) thiazolidin-4-one: $C_{24}H_{22}N_2OS_2$ (418,54 g/mol). FT-IR (ATR): 3077, 3062, 3007, 2920, 2851, 1703, 1633, 1591, 1503, 1364, 1273, 1157, 828, 724 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.26 (3H, s), 2.34 (3H, s), 2.37 (3H, s), 2.42 (3H, s), 6.85 (2H, d, J=8,2 Hz), 6.97 (1H, d, J=5.0 Hz), 7.14 (2H, d, J=8.2 Hz), 7.17 (1H, s), 7.18-7.20 (2H, m), 7.47 (1H, d, J=5.0 Hz), 8.04 (1H, s). ^{13}C NMR ($CDCl_3$): δ 14.59, 17.74, 20.71, 21.16, 118.74, 120.88, 122.74, 128.08, 128.48, 129.56, 129.92, 130.02, 131.19, 131.67, 132.01, 132.55, 134.46, 135.84, 139.55, 142.53 145.94, 150.21, 166,52 ppm.

Compound 5: 5-[(3-methylthiophen-2-yl) methylene]-3-p-tolyl-2-(p-tolylimino) thiazolidin-4-one: $C_{23}H_{20}N_2OS_2$ (404,55 g/mol). FT-IR (ATR): 3029, 2924, 2854, 1716, 1639, 1599, 1504, 1360, 1261, 1171, 1141, 879, 836 cm^{-1}. ^{1}H NMR ($CDCl_3$) : δ 2.35 (3H, s), 2.41 (3H, s), 2.42 (3H, s), 6.88 (2H,

d, J=8,2 Hz), 6.97 (1H, d, J=5,0 Hz), 7.15 (2H,d, J=7.9 Hz), 7.34 (4H, s), 7.48 (1H, d, J=5,0 Hz), 8.04 (1H, s) ppm. ^{13}C NMR ($CDCl_3$): δ 14.52, 21.02, 21.35, 118.60, 120.99, 122.60, 127.77, 129.45, 129.83, 130.03, 131.05, 132.32, 132.52, 134.33, 138.88, 142.44, 145.78, 150.72, 166.64 ppm.

Compound 6: 2-[(4-chlorophenyl) imino]-3-(4-methylphenyl)-5-[(3-methylthiophen-2-yl) methylidene]-1,3-thiazolidin-4-one: $C_{22}H_{17}ClN_2OS_2$ (424.97 g/mol). FT-IR (ATR): 3069, 1691, 1633, 1587, 1491, 1356, 890, 834 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.41 (3H, s), 2.42 (3H, s), 6.99 (1H, d, J=5.0 Hz), 7.34 (4H, s), 7.41 (2H, brd, J=8.8 Hz),7.50 (1H, d, J=5.0 Hz), 7.51 (2H, brd, J=8.8 Hz), 8.05 (1H, s) ppm. ^{13} C NMR ($CDCl_3$)**:** δ 14.60, 21.30, 114.22, 118.65, 120.81, 122.34, 123.64, 129.35, 129.58, 131.62, 132.35, 133.50, 134.60, 138.74, 141.14, 143.01, 154.18, 166.38 ppm.

Compound 7: 3-(4-chlorophenyl)-2-[(4-methylphenyl) imino]-5-[(3-methylthiophen-2-yl) methylidene]-1,3-thiazolidin-4-one: $C_{22}H_{17}ClN_2OS_2$ (424.97 g/mol). FT-IR (ATR): 3069, 1680, 1621, 1568, 1497, 1345, 882, 828 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.35 (3H, s), 2.42 (3H, s), 6.87 (2H, d, J=8,2 Hz), 6.92 (2H, brd, J=8.6 Hz), 6.98 (1H, d, J=5.0 Hz), 7.14 (2H, d, J=8.2 Hz), 7.32 (2H, brd, J=8.6 Hz),7.49 (1H, d, J=5.0 Hz), 8.04 (1H, s) ppm. ^{13} C NMR ($CDCl_3$)**:** δ 14.60, 21.30, 114.62, 118.25, 120.41, 122.54, 123.69, 129.55, 129.88, 131.42, 132.45, 133.10, 134.34, 138.15, 141.01, 142.91, 153.88, 166.30.

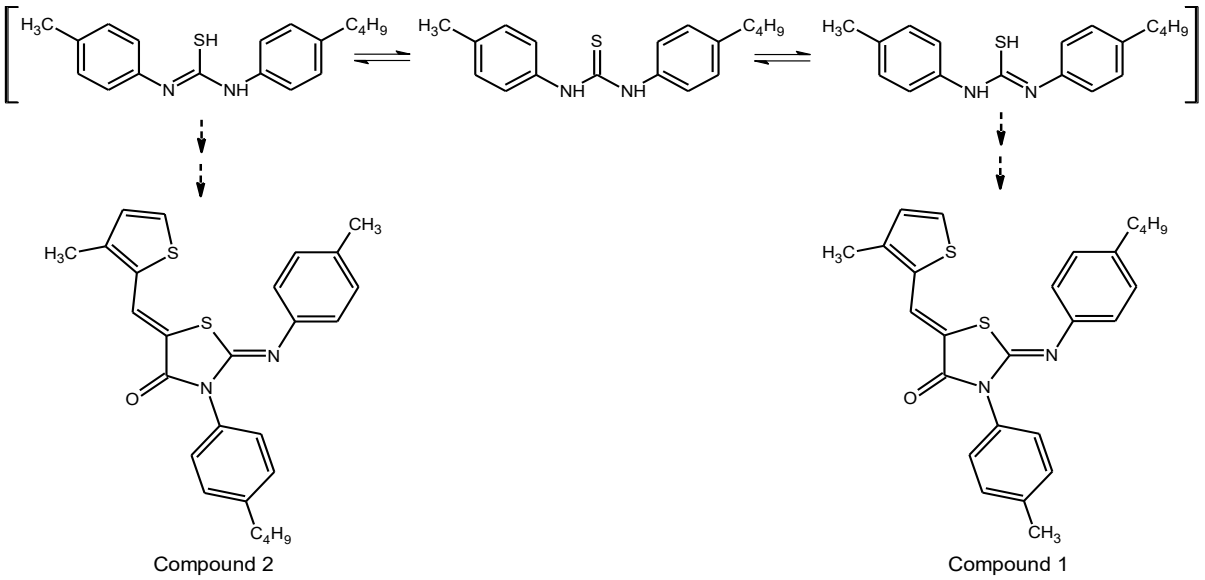
RESULTS AND DISCUSSION

To synthesize the targeted iminothiazolidinone compounds with the highest yield, studies were carried out to determine the optimum ratios of the starting materials and the ratio of 1:1:1.2 (aldehyde, thiourea and chloroacetic acid, respectively) was determined as the optimum condition.

As is known from literature studies, heterocyclic compounds are generally formed by intramolecular or intermolecular cyclization reactions of substances in a straight chain structure. In arylthioureas, when the groups attached to both nitrogen atoms are different, the two structures obtained when the thion-thiol tautomer is written can give a cyclocondensation reaction with chloroacetic acid, thus two isomer products are synthesized. The synthesis of compounds 1 and 2 is given below as an example [8].

The structures of the iminothiazolidinone compounds synthesized as a result of these one-pot three-component condensation reactions carried out in a solvent-free environment were elucidated by IR, ^{1}H and ^{13}C magnetic resonance spectroscopy methods. The results obtained are supported by the values stated in the sources [9-11].

As a result, in this study, 3 substituted thioureas and 7 original (new) 5-substituted-2-imino-4-thiazolidinone compounds were synthesized in very high yields and their structures were elucidated by FT-IR, ^{1}H NMR and ^{13}C NMR data.



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