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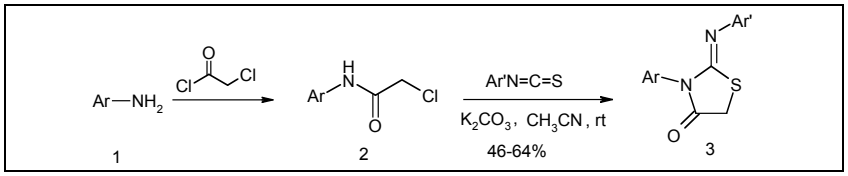

An efficient and simple route is presented to the synthesis of some iminothiazolidinone derivatives. α–Chloro amide derivatives undergo coupling reaction with isothiocyanate in the presence of a mild base, followed by nucleophilic substitution of chlorine by the sulfur atom of isothiocyanate.

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INTRODUCTION

There has been considerable interest in the chemistry of the 4–thiazolidinone ring system, with regard to their wide array of uses as pharmacologically active heterocyclic compounds. They are known to possess a wide range of diverse biological activities such as anti cancer activities [1-5].

Some imino derivatives of thiazolidinone have also shown to be strong anti-inflammatory [6], antiviral [7], antimicrobial [8], and anti hepatic [9] agents but they have not been investigated in medicinal chemistry extensively, which may be due to the lack of efficient synthetic methods for these compounds. Some medicinally relevant iminothiazolidinones have been presented in Figure 1. On the other hand, the development of simple synthetic routes for widely used organic compounds from readily available reagents is one of the major tasks in organic synthesis [10].

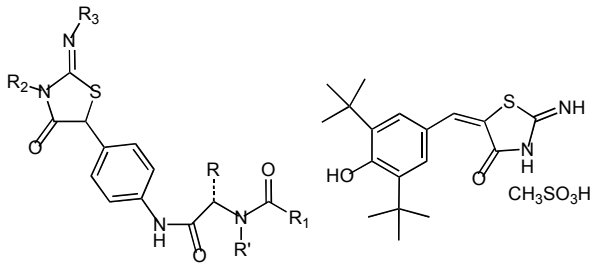


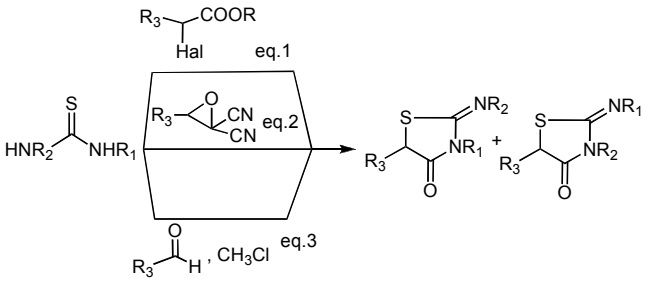
Figure 1. Two examples of medicinal iminothiazolidinones (inhibitor of HCV replication) Darbufelon (anti inflammatory).

In the present work we wish to report a simple and regioselective synthesis of 2-imino-4-thiazolidinone derivatives.

RESULTS AND DISCUSSION

The common strategy to construct iminothiazolidinone derivatives is the condensation of thiourea derivatives with α–halo esters or acids in the presence of an inorganic base (*i.e.* NaOAc) and in a polar solvent such as ethanol or acetic acid (Scheme 1, Eq. 1) [11].

Scheme 1. The reported routes to the synthesis of Iminothiazolidinone derivatives



Also, there are some other routes to prepare these compounds. The reactions of thiourea with gem-dicyano epoxide (Scheme 1, Eq. 2) or an aldehyde in the presence of choloform (Scheme 1, Eq. 3) are among other typical procedures [12].

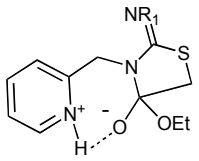
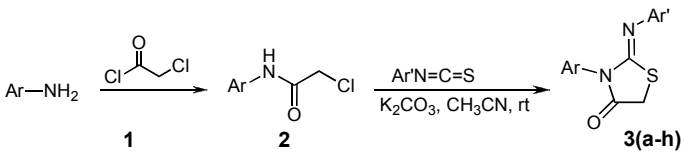


Figure 2. Enhanced regioselectivity by using the Heteroaryl ring

For unsymmetrical thiourea (R_1, R_2), both of the two possible regioisomeric iminothiazolidinone products are formed. The regioselectivity is influenced by electronic factor that predispose electron withdrawing substituent to maintain conjugative stabilization with the imine's nitrogen [11f].

Scheme 2



3	Ar	Ar'
a	Ph	4-NO_2Ph
b	2,4-dimethoxy Ph	4-NO_2Ph
c	3-acetoxy Ph	4-NO_2Ph
d	4-Cl Ph	4-NO_2Ph
e	2-Tolyl	4-NO_2Ph
f	3-methoxy Ph	4-NO_2Ph
g	1- naphtyl	4-NO_2Ph
h	1- naphtyl	4-Tolyl

In the absence of electronic properties between R_1 and R_2 groups, the reaction of thiourea with α–halo acids or esters proceeds with minimal regioselectivity.

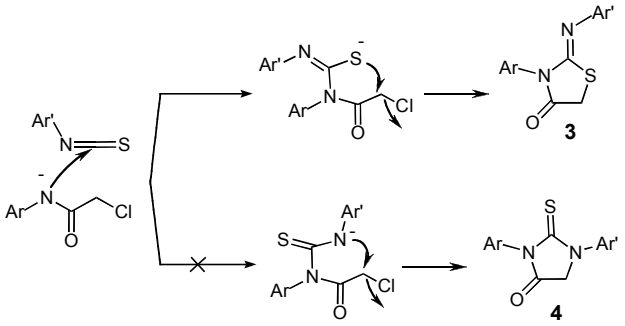
Recently, some iminothiazoldinone derivatives have been synthesized with high regioselectivity using a hetero aryl methyl thiourea instead of aryl methyl thiourea in the absence of NaOAc. It has been suggested that potential hydrogen bond between the protonated heterocycle and the reacting carbonyl ester drives the proximal thiourea nitrogen to cyclize (Figure 2) [11f].

Here in we report an efficient and new method for the regioisomer preparation of iminothizolidinone derivatives. The reaction of aromatic amines 1 with choloro acetyl choloride afforded the corresponding amide derivatives 2. Then the compound 2 reacted smoothly with isothiocyanates in the presence of a weak base such as K_2CO_3 in CH_3CN to produce iminothiazolidinones 3 (Scheme 2).

In a typical procedure amide 2 (1 mmol) was reacted with isothiocyanate (1 mmol) at room temperature in the presence of K_2CO_3 in acetonitrile, which took about 15 hours. After conventional work up, the product was purified by simple crystallization from suitable solvent in good yield. To demonstrate the generality of this methodology different aromatic amides 2 were used (Table 1).

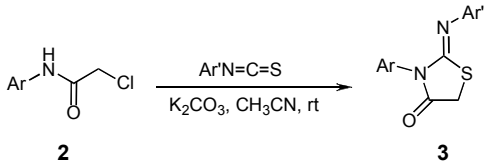
We have not established the mechanism of the reaction, however a possible mechanism is proposed in scheme 3. The first step involves the addition of amide derivatives 2 to isothiocyanate in the presence of base; subsequent cyclization takes place by nucleophilic substitution of chlorine by the sulphure atom of isothiocyanate.

Scheme 3. Proposed Mechanism



Considering the fact that isothiocyanate is an ambident nucleophile, two different final structures of the heterocycles could be considered, thiohydantion **4** or

Table 1
Physical and Analytical Data of Compound **3(a-h)**.



Entry	Product	Time (h)	M.P (°C)	Yield[a] (%)	Elemental analysis found (%)	calc (%)
1	**3a**	14	178-180	53	C, 57.4; H, 3.7; N, 13.5	C, 57.50; H, 3.54; N, 13.41
2	**3b**	18	164-166	58	C, 54.7; H, 4.2; N, 11.1	C, 54.68; H, 4.05; N, 11.25
3	**3c**	17	177-179	42	C, 57.4; H, 3.9; N, 11.6	C, 57.46; H, 3.69; N, 11.82
4	**3d**	17	207-209	49	C, 51.9; H, 3.0; N, 12.0	C, 51.80; H, 2.90; N, 12.08
5	**3e**	15	209-211	53	C, 58.7; H, 4.1; N, 12.8	C, 58.70; H, 4.00; N, 12.84
6	**3f**	18	181-183	40	C, 56.1; H, 4.0; N, 12.1	C, 55.97; H, 3.82; N, 12.24
7	**3g**	14	197-200	64	C, 62.3; H, 3.8; N, 11.3	C, 62.81; H, 3.61; N, 11.56
8	**3h**	24	186-188	46	C, 72.0; H, 4.8; N, 7.9	C, 72.26; H, 4.85; N, 8.43

[a] Isolated yield.

iminothiazolidinone **3**. Spectroscopic data reveals that chlorine atom has been substituted by the nucleophile and cyclization has taken place. Two structures, thiohydantion **4** or iminothiazolidinone **3** are both consistent with these features.

It is not evident from the classical spectroscopic data (elemental analysis, ^{1}HNMR, ^{13}CNMR, and IR) which compound is exactly produced. Therefore, more attempts have been made to assure the structural assignment. Using X-Ray single crystal analysis of **3d** reveals that compound **3** is formed and the imino geometry for **3** is also established (Figure 3) [13].

In conclusion, the presented method is a complementary procedure along with the previously reported methods. Most of these methods have been based on using thiourea as a starting material but they have been limited by unsymmetrical thiourea, due to the formation of two regioisomers. However, in the current study only one of the two possible isomers is obtained.

EXPERIMENTAL

X-ray structure was recorded with a Brucker SMART 1000 CCD area detector by XRSC, Moscow, Russia. Elemental analysis were preformed by analytical laboratory of Research Institute of Petroleum Industry (RIPI), Tehran, Iran. IR spectra were recorded as KBr pellets on a Nicolet spectrometer (Magna 550). Melting points were measured on a Büchi B540 apparatus. ^{1}H and ^{13}C NMR are recorded ($CDCl_3$ solution) with a Brucker DRX-500 ADVANCE spectrometer. The α–chloro amides (**2**) were prepared according to the known method [14].

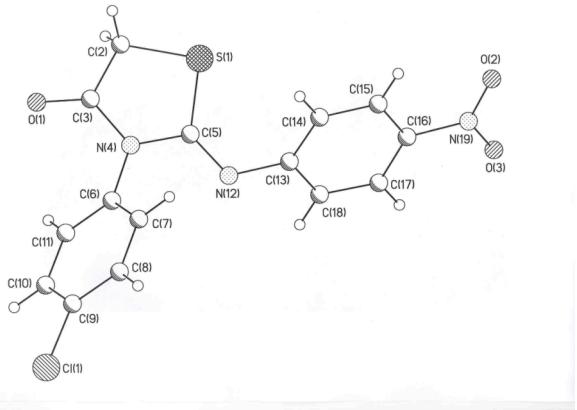


Figure 3. Crystal structure of compound **3d**.

General Procedure for Preparation of Compounds (3a-h). To a stirred solution of amide derivatives (**2a-h**) (1 mmol) and potassium carbonate (1.5 mmol) in acetonitrile (5 ml) was added isothiocyanate (1 mmol) during about 5 minutes. The reaction mixture was further stirred at room temperature for the required time. The solvent was removed under reduced pressure and the residue was purified by column chromatography using petroleum ether/ethyl acetate (2-4:1), and the product was recrystallized from chloroform.

2-[(4-Nitrophenyl)imino]-3-phenyl-1,3-thiazolan-4-one (3a). Yellow crystal (chloroform), mp 178-180°; ir (KBr) (ν_{max}/cm^{-1}): 861, 1154, 1336, 1508, 1585, 1638, 1738 ^{1}H nmr: δ 4.07 (2H, s, CH_2), 7.05 (2H, d, J=8.6Hz, CH), 7.39 (2H, d, J=7.6Hz, CH), 7.50 (1H, t, J=7.4Hz, CH), 7.57 (2H, t, J=7.6Hz, CH), 8.26 (2H, d, J=8.6Hz, CH), ^{13}C nmr: δ 33.53 (CH_2), 122.10 (2CH), 125.60 (2CH), 128.39 (2CH), 129.81 (CH), 129.97 (2CH), 134.73 (C), 144.99 (C), 154.51 (C),156.97(C), 171.45 (C). *Anal.* Calcd. for $C_{15}H_{11}N_3O_3S$: C, 57.50; H, 3.54; N, 13.41. Found: 57.4; H, 3.7; N, 13.5.

3-(2,4-Dimethoxyphenyl)-2-[(4-nitrophenyl)imino]-1,3-thiazolan-4-one (3b). Pale yellow crystal (chloroform), mp 164-166°; ir (KBr) (ν_{max}/cm^{-1}): 869, 1038, 1115, 1181, 1346, 1515, 1585, 1646, 1738 ^{1}H nmr: δ 3.88 (3H, s, OCH_3), 3.91(3H, s, OCH_3), 4.03 (2H, AB quarted, J= 17.0 Hz, CH_2), 6.61(1H, s, CH), 6.62 (1H, d, J=8.5Hz, CH), 7.03 (2H, d, J=8.5Hz, CH), 7.18(1H, d, J=8.5Hz, CH), 8.24(2H, d, J=8.5Hz, CH) ^{13}C nmr: δ 33.39 (CH_2), 56.02 (OCH_3), 56.34 (OCH_3), 100.35 (CH), 105.54 (CH), 116.13 (C),122.19 (2CH), 125.51 (2CH), 130.58 (CH), 144.84 (C), 155.00 (C), 156.16(C), 156.81(C), 162.31 (C), 171.48 (C). *Anal.* Calcd. for $C_{17}H_{15}N_3O_5S$: C, 54.68; H, 4.05; N, 11.25. Found: C, 54.7; H, 4.2; N, 11.1.

3-(3-Acethylphenyl)-2-[(4-nitrophenyl)imino]-1,3-thiazolan-4-one (3c). Yellow crystal (chloroform), mp 177-179°; ir (KBr) (ν_{max}/cm^{-1}): 861, 1154, 1338, 1508, 1585, 1638, 1738 ^{1}H nmr: δ 2.69 (3H, s, CH_3), 4.13 (2H, s, CH_2), 7.08 (2H, d, J=8.5Hz, CH), 7.64 (1H, d, J=7.8Hz, CH), 7.71 (1H, t, J=7.8Hz, CH), 8.04 (1H, s, CH), 8.09 (1H, d, J=7.8Hz, CH), 8.25 (2H, d, J=8.5Hz, CH), ^{13}C nmr: δ 26.95(CH_3), 33.46 (CH_2), 121.99 (2CH), 125.54 (2CH), 128.33 (CH), 129.44 (CH), 130.11 (CH), 132.88 (CH), 135.32 (C), 138.90 (C), 145.16 (C), 154.06 (C),156.53(C), 171.03 (C), 196.87 (C). *Anal.* Calcd. for $C_{17}H_{13}N_3O_4S$: C, 57.46; H, 3.69; N, 11.82. Found: C, 57.4; H, 3.9; N, 11.6.

3-(4-Chlorophenyl)-2-[(4-nitrophenyl)imino]-1,3-thiazolan-4-one (3d). Yellow crystal (chloroform), mp 207-209°; ir (KBr) (ν_{max}/cm^{-1}): 896, 1156, 1195, 1335, 1505, 1579, 1622, 1728, ^{1}H nmr: δ 4.10 (2H, s, CH_2), 7.07 (2H, d, J=8.8Hz, CH), 7.37 (2H, d, J=8.6Hz, CH), 7.55 (2H, d, J=8.6Hz, CH), 8.25 (2H, d, J=8.8Hz, CH) ^{13}C nmr: δ 38.22 (CH_2), 126.76 (2CH), 130.41 (2CH), 134.45 (2CH), 134.98 (2CH), 137.77 (C), 140.54 (C), 149.91 (C), 158.86 (C), 161.34 (C), 175.86 (C). *Anal.* Calcd. for $C_{15}H_{10}N_3O_3ClS$: C, 51.80; H, 2.90; N, 12.08. Found: C, 51.9; H, 3.0; N, 12.0.

3-(2-Methylphenyl)-2-[(4-nitrophenyl)imino]-1,3-thiazolan-4-one (3e). Pale yellow crystal (chloroform), mp 209-211°; ir (KBr) (ν_{max}/cm^{-1}): 789, 862, 1112, 1290, 1344, 1511, 1586, 1645, 1734, ^{1}H nmr: δ 2.33 (3H, s, CH_3), 4.13 (2H, s, CH_2), 7.06 (2H, d, J=8.8Hz, CH), 7.28 (1H, d, J=7.4Hz, CH), 7.40-7.47 (3H, m, CH), 8.24 (2H, d, J=8.8Hz, CH) ^{13}C nmr: δ22.89 (CH_3), 38.31 (CH_2), 126.83 (CH), 130.33 (CH), 132.58 (CH), 133.64 (CH), 135.28 (CH), 136.61 (CH), 138.64 (C), 141.11 (C), 149.81 (C), 175.84 (C). *Anal.* Calcd. for $C_{16}H_{13}N_3O_3S$: C, 58.70; H, 4.00; N, 12.84. Found: C, 58.7; H, 4.1; N, 12.8.

3-(3-Methoxyphenyl)-2-[(4-nitrophenyl)imino]-1,3-thiazolan-4-one (3f). Yellow crystal (chloroform), mp 181-183°; ir (KBr) (ν_{max}/cm^{-1}): 856, 1109, 1290, 1312, 1337, 1507, 1577, 1618, 1736 ^{1}H nmr: δ 3.88 (3H, s, OCH_3), 4.09 (2H, s, CH_2), 6.94 (1H, s, CH), 6.99 (1H, d, J=7.9Hz, CH), 7.05(1H, d, J=8.4Hz, CH), 7.07(2H, d, J=8.9Hz, CH), 7.49(1H, dd, J=7.9Hz, J=8.4Hz CH),

8.24(2H, d, J=8.9Hz, CH) ^{13}C nmr: δ 33.52 (CH_2), 56.63 (OCH_3), 114.45 (CH), 115.39 (CH), 120.51 (CH), 122.10 (2CH), 125.59 (2CH), 130.68 (CH), 135.66 (C), 144.99 (C), 154.49 (C), 156.85 (C), 160.77 (C), 171.35 (C). *Anal*. Calcd. for $C_{16}H_{13}N_3O_4S$: C, 55.97; H, 3.82; N, 12.24. Found: C, 56.1; H, 4.0; N, 12.1.

3-(1-Naphthyl)-2-[(4-nitrophenyl)imino]-1,3-thiazolan-4-one (3g). Yellow crystal (chloroform), mp 197-200°; ir (KBr) (ν_{max}/cm^{-1}): 777, 861, 1115, 1161, 1354, 1515, 1584, 1646, 1738 ^{1}H nmr: δ 4.25 (2H, AB quarted, J= 17.3 Hz, CH_2), 7.01 (2H, d, J=8.8Hz, CH), 7.56 (1H, d, J=7.1Hz, CH), 7.60-7.72 (4H, m, CH), 8.00 (1H, d, J=8.0Hz, CH), 8.05 (1H, d, J=8.2Hz, CH), 8.21 (2H, d, J=8.8Hz, CH) ^{13}C nmr: δ 38.49 (CH_2), 126.75 (2CH), 126.84 (CH), 130.28 (2CH), 130.81 (CH), 131.94 (CH), 132.19 (CH), 132.71 (CH), 134.15 (CH), 134.57 (C), 135.71 (CH), 136.19 (C), 139.80 (C), 149.79 (C), 159.11 (C), 161.26 (C), 176.22 (C). *Anal*. Calcd. for $C_{19}H_{13}N_3O_3S$: C, 62.81; H, 3.61; N, 11.56. Found: C, 62.3; H, 3.8; N, 11.3.

2-[(4-Methylphenyl)imino]-3-(1-naphthyl)-1,3-thiazolan-4-one (3h). Pale yellow crystal (chloroform), mp 186-188°; ir (KBr) (ν_{max}/cm^{-1}): 777,1161, 1361, 1508, 1631, 1731 ^{1}H nmr: δ 2.36 (3H, s, CH_3), 4.14 (2H, AB quarted, J= 17.0 Hz, CH_2), 6.75 (2H, d, J=7.9Hz, CH), 7.1 (2H, d, J=7.9Hz, CH), 7.52-8.0 (7H, m, CH), ^{13}C nmr: δ 26.22(CH_3), 38.32 (CH_2), 125.92 (2CH), 127.32 (CH), 130.88 (CH), 131.78 (CH), 132.27 (CH), 132.49 (CH), 134.03 (CH), 134.83 (C), 134.94 (2CH), 135.37 (CH), 136.90 (C), 139.40 (C), 139.86 (C), 150.73 (C), 159.63 (C), 176.85 (C). *Anal*. Calcd. for $C_{20}H_{16}N_2OS$: C, 72.26; H, 4.85; N, 8.43. Found: C, 72.0; H, 4.8; N, 7.9.

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