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Research Article

One-Pot Multicomponent Synthesis of Novel 2-Imino-1,3-Thiazolidin-4-One

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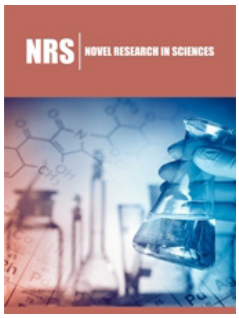
Abstract

A novel series of 2-imino-1,3-thiazolidin-4-one were synthesized via simple efficient method through one-pot three-component reaction of phenyl isothiocyanate, primary amines and dimethyl acetylene dicarboxylate. The same products were synthesized via conventional route by reaction of the corresponding thiourea derivatives with dimethyl acetylene dicarboxylate

Keywords: 1,3-thiazolidin-4-one; Dimethyl acetylene dicarboxylate (DMAD); One-pot multicomponent reaction; Thiourea derivatives; Phenyl isothiocyanate



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Introduction

Researcher's interest in the chemistry of thiazolidine families has increased recently, due to a wide spectrum of biological properties shown by them [1,2]. Their derivatives were found in large numbers of biologically active compounds, including antifungal [3], anti-inflammatory [4,5], anti-diabetic [6], antimicrobial [7,8], antioxidant [9], antimalarials [10], anticancer [11-13], anti-HIV [14], and anticonvulsant [15,16] agents. Recent studies have also exposed that thiazolidine scaffolds have inhibitory effects towards the cytosolic CA II and hCA IX [17]. Thiourea derivatives are very important starting material in organic synthesis; they are simply synthesized with great variableness at the two substituents, also they provide a bifunctional site for 1,3-bielectrophiles yielding numerous heterocyclic products. From chemical view, dimethyl acetylenedicarboxylate (DMAD) can be used as 1,3-bielectrophiles and react with thiourea derivatives to afford 1,3-thiazolidin-4-ones. Following up our previous findings on the improvement of new methods for the production of new heterocyclic compounds such as; pyridine, imidazole and anilinopyrimidine derivatives [18-21] and due to pharmaceutical applications of 1,3-thiazolidin-4-one, herein we aimed to further investigate the synthesis of novel 2-imino-1,3-thiazolidin-4-one derivatives by simple one-pot method from readily available starting materials under catalyst free condition, which involves the direct interaction between phenyl isothiocyanate, primary amines and dimethyl acetylenedicarboxylate.

Result and Discussion

In this work, we wish to report a new route for synthesis a novel series of highly functionalized 1,3-thiazolidin-4-one derivatives by facile method through one-pot three-component reaction of phenyl isothiocyanate, primary amines and dimethyl acetylenedicarboxylate. This protocol offers flexibility in tuning the molecular complexity and diversity. The reactions proceeded to completion almost in 2.0hrs. and pure products were obtained in good to excellent yields, without using any chromatographic techniques, simply by filtration and recrystallization. As an initial test, we run a model reaction by stirring an equimolecular aramounts of phenyl isothiocyanate 1 and phenethylamine 2a in ethanol at room temperature for about one hour then dimethyl acetylenedicarboxylate 3 was added and the reaction mixture was stirred for one hour, that afforded desired product methyl 4-oxo-3-(2-phenylethyl)-2-(phenylimino)-1,3-thiazolidin-5-ylidene]acetate 4a in excellent yield. After optimization of the procedure, the scope of the technique was investigated with a series of primary aliphatic and aromatic amines to yield the corresponding 1,3-thiazolidin-4-one 4b-k, (Method A, Figure 1). The same 1,3-thiazolidin-4-one 4a-k was also synthesized by an classical route via reaction of corresponding thioureas 5a-k with dimethyl acetylenedicarboxylate 3 (Method B, Figure 1). Also, we found that, phenyl hydrazine reacts with phenyl isothiocyanate 1 and dimethyl acetylene dicarboxylates 3 by the same manner to give 1,3-thiazolidin-4-one 4i. While hydrazine

hydrate and ethylenediamine react with phenyl isothiocyanate 1 and DMAD 3 to produce dimer of 1,3-thiazolidin-4-one 4j and 4k, respectively (Table 1). It is reasonable to assume that the formation of 1,3-thiazolidin-4-one 4 begins with the formation of thiourea 5 by reaction between phenyl isothiocyanate and primary amine followed by nucleophilic attack of thiourea's sulfur atom on the C≡C bond of DMAD to give intermediate I, which undergoes intramolecular cyclization through nucleophilic attack of the NH group onto the carbonyl group, followed by elimination of methanol to yield 1,3-thiazolidin-4-one 4. (Figure 2).

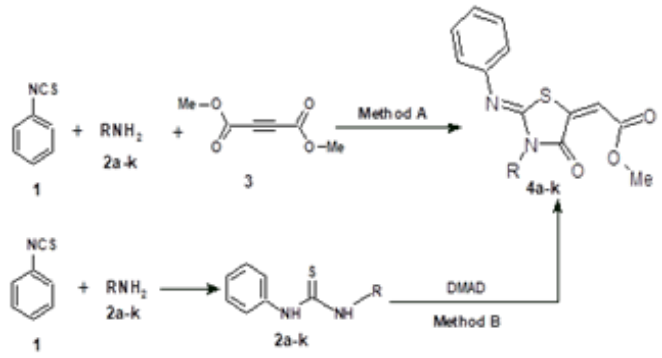


Figure 1: Synthesis of 2-imino-1,3-thiazolidin-4-one.

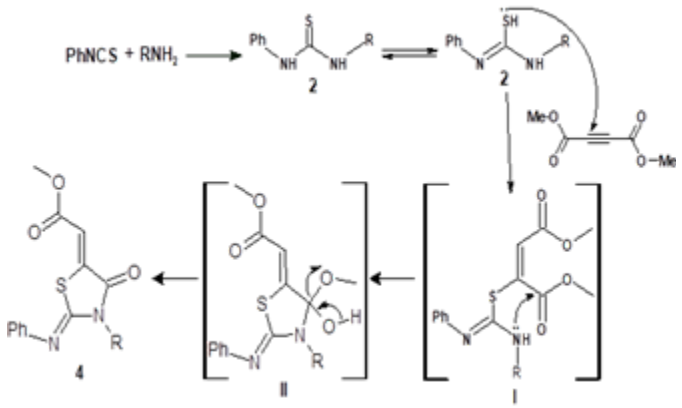
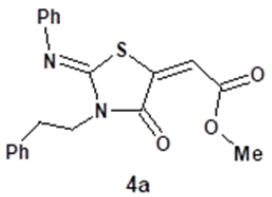
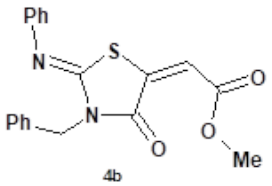
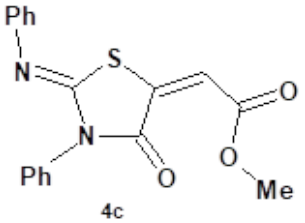
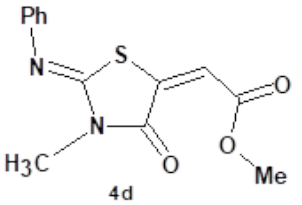
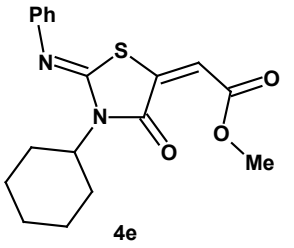
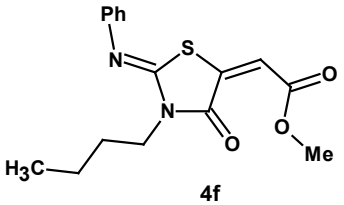
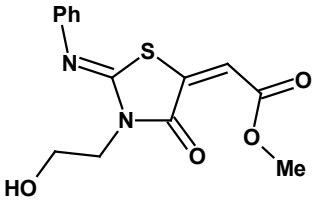
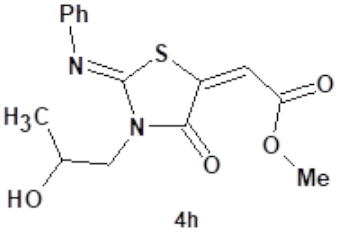
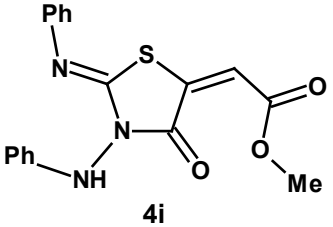
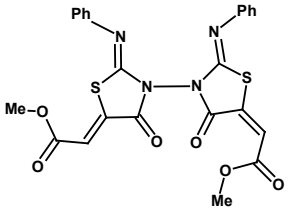
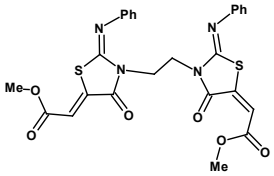


Figure 2: Reaction mechanism for the formation of 1,3-thiazolidin-4-one 4.

Table 1: Synthesis of 1,3-thiazolidin-4-one 4a-k.

Entry	R	Product 2	Yield%	
			Method A	Method B
1	$PhCH_2CH_2$	 4a	76	80
2	$PhCH_2$	 4b	82	85

3	Ph[22]	 4c	71	79
4	CH_3	 4d	86	85
5	cyclohexyl	 4e	77	78
6	$CH_3CH_2CH_2CH_2$	 4f	84	86
7	$HOCH_2CH_2$	 4g	71	75
8	$CH_3CH(OH)CH_2$	 4h	80	80
9	PhNH	 4i	69	73

10	NH_2	 4j	68	69
11	$H_2NCH_2CH_2$[23]	 4k	90	91

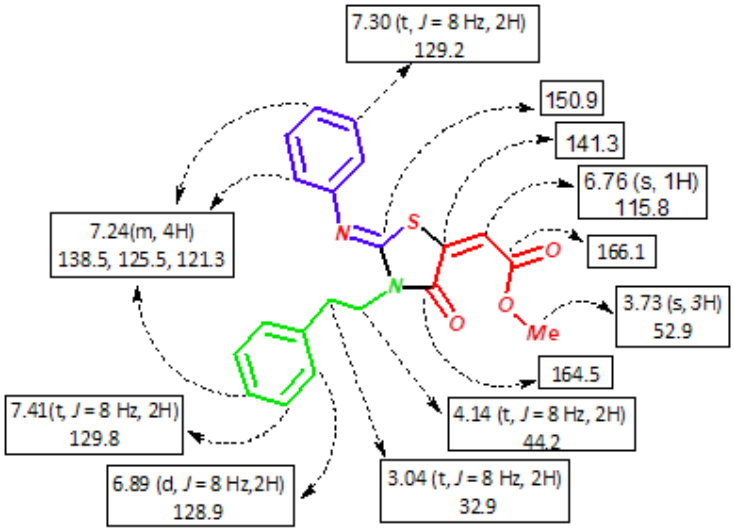


Figure 3: 1HNMR and 13CNMR chemical shift of 4a.

The chemical structures of 1,3-thiazolidin-4-one 4a-k were confirmed based on their spectral (IR, ^1H, ^{13}C NMR) and elemental analysis data. For example, the IR spectrum of 4a showed an absorption bands at 1716, 1665cm^{-1} due to the two carbonyl groups. Its ^1H NMR spectrum showed the presence of two triplet signals at δ 3.04, 4.14ppm with coupling constant J=8Hz, characteristic of two methylene protons; a singlet signal at 3.73ppm for the methoxyl protons; it also exhibited a singlet signal at δ6.76ppm due to the vinylic proton; also it showed four signals at 7.41-6.89ppm characteristic for aromatic protons. The ^{13}C NMR spectrum of 4a showed thirteen signals at 166.1, 164.5, 150.9, 147.8, 141.3, 138.5, 129.8, 129.2, 128.9, 126.9, 125.5, 121.3, 115.8 which are assigned to carbons of the carbonyl, aromatic and vinyl groups, while the H_3CO is characterized by signal at 52.9ppm, finally the two methylene groups appears at 44.2, 18.9ppm (Figure 3).

Conclusion

A new series of the 1,3-thiazolidin-4-one were prepared from available starting materials via one-pot three-component reaction of phenyl isothiocyanate, primary amines and dimethyl acetylenedicarboxylate. The same products were prepared via traditional method by reaction of the corresponding thiourea derivatives with dimethyl acetylenedicarboxylate.

Supporting information

Experimental procedures and characterization data for new compounds 4a-k associated with this manuscript can be found via the supplementary content section of this article's webpage.

Experimental

General procedure for synthesis of compounds 4a-k:

a) Method A

A mixture of phenyl isothiocyanate1(5.0mmol) and primary amine 2(5.0mmol) was stirred in ethanol (40ml) at room temperature for about 1hr. and then dimethyl acetylenedicarboxylate (5.0mmol)3 was added. The reaction mixture was stirred for about 1hr. under an air atmosphere. After completion of reaction (monitored by TLC), the precipitate was filtered and recrystallized from appropriate solvent to give 4a-k.

b) Method B

Equimolecular amounts (5.0mmol) of thiourea derivatives 5 and dimethyl acetylenedicarboxylate 3 in ethanol (40ml) were

stirred for about 1hr. at room temperature under an air atmosphere. After completion of reaction (monitored by TLC), the precipitate was filtered and recrystallized from appropriate solvent to give 4a-k.

Methyl [4-oxo-3-(2-phenylethyl)-2-(phenylimino)-1,3-thiazolidin-5-ylidene] acetate (4a)

(Method A76 %, Method B 80) as a white solid, mp: 129-130 °C; ϑ_{max}(ATR) 3076, 2971, 2911, 1716, 1665cm^{-1}. ^{1}H NMR (400Hz,DMSO-d_6) δ7.41(t, J=8Hz, 2H,CH_{arom}), 7.30 (t, J=8Hz, 2H, CH_{arom}), 7.24(m, 4H, CH_{arom}), 6.89(d, J=8Hz, 2H, CH_{arom}), 6.76(s, ^{1}H, CH_{vinyl}), 4.14 (t, J=8Hz, 2H,CH_2), 3.73 (s, 3H, OCH_3), 3.04 (t, J=8Hz, 2H,CH_2). ^{13}CNMR(100MHz, DMSO-d_6) δ166.1, 164.5, 150.9, 147.8, 141.3, 138.5, 129.8, 129.2, 128.9, 126.9, 125.5, 121.3, 115.8, 52.9, 44.2, 32.9. Anal. Calcd. for $C_{20}H_{18}N_2O_3S$ (366): C, 65.55; H, 4.95; N, 7.64. Found: C, 65.83; H, 4.79; N, 7.60 [21-23].

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