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One-pot synthesis of 1,3-thiazolidin-4-one using $Bi(SCH_2COOH)_3$ as catalyst

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ABSTRACT

A catalytic multi-component reaction involving aromatic amine, aromatic aldehydes, mercapto acid as substrates and $Bi(SCH_2COOH)_3$ as catalyst under solvent free conditions, afforded thiazolidin-4-one in good yields. The efficiency of the catalyst was proved with a variety of substrates, ranging from electron-deficient to electron-rich aldehydes.

1. Introduction

Multi-component reactions (MCRs) and improvement of the methods for multi-component reactions have been of considerable interest in current day research. As a one-pot reaction, MCRs permit rapid access to combinatorial libraries of complex molecules, especially in drug discovery [1]. The thiazolidin-4-one ring system is a core structure found in various synthetic pharmaceutical compounds, displaying a broad spectrum of biological activities [2–7]. Consequently, several synthetic methods have been developed for the synthesis of 4-thiazolidinones. The main synthetic routes to thiazolidin-4-ones involve cyclo-condensation of azomethines (Schiff's base) with mercaptoacetic acid [8]. There are also reports using chemical agents, such as *N*-methylpyridinium tosylate [9] as desiccant, to assist the formation of thiazolidinone derivatives. The use of [BmIm]OH [10], Hunig's base [11], and Baker's yeast [12] has also been reported to expedite the cyclo-condensation of the azomethines and thioglycolic acid. However, these methodologies suffer from one or more disadvantages, such as costly dehydrating agents, require prolonged heating and tedious work-up. Therefore, it was thought worthwhile to develop a new method for the cyclo-condensation. As a result, we showed that aromatic amine, aromatic aldehydes, and 2-mercaptoacetic acid, under solvent free conditions gave thiazolidin-4-one.

2. Experimental

The purity of compounds was checked by thin layer chromatography (TLC) using *n*-hexane/ethyl acetate (1/1, v/v) as an eluent. IR spectra were acquired on a galaxy series FT-IR 5000 spectrophotometer as KBr discs. NMR spectra were recorded on Bruker spectrophotometer (300 MHz) in DMSO-d_6 using TMS as an internal standard. Elemental analyses for C, H, N and S were performed on a Vario EL III elemental analyzer.

2.1. General procedure for the synthesis of thiazolidine-4-one **4a–k**

Aromatic aldehydes **1a–f** (1 mmol), aromatic amine **2a–d** (1 mmol), thioglycolic acid **3** (1.2 mmol), and catalyst (10 mol%) were mixed. The reaction mixture was then heated (70 °C) for 2 h. The progress of the reaction was monitored by TLC using *n*-hexane/ethyl acetate (1/1). After the completion of the reaction, the reaction mixture extracted with ethylacetate (3 × 5 mL) and the organic layer washed with 5% sodium bicarbonate. The organic layer was then dried over anhydrous Na_2SO_4, concentrated, and recrystallized from *n*-hexane/ethyl acetate to afford the purified product.

2.2. Representative spectral data

2.2.1. 2-(2-Nitrophenyl)-3-p-tolylthiazolidin-4-one (**4i**)

IR (KBr, cm^{-1}): ν 3034 (aromatic CH stretch.), 2928 (aliphatic CH stretch.), 1725 (C=O), 1550 (C=C), 1530, 1350 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 7.99 (d, 1H, J = 8.1 Hz, $H_{arom.}$), 7.69–7.73 (m, 2H, $H_{arom.}$), 7.49–7.54 (m, 1H, $H_{arom.}$), 7.33 (d, 2H, J = 8.3 Hz,

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Table 1
Thiazolidin-4-one **4a-k**.

Entry	R^2	R^1	Yields (%)	Mp (found)	Mp (reported) [13]
4a	4-Me	4-Me	90	120–122	119–120
4b	H	H	75	130–132	131–132
4c	4-Me	H	75	110–112	106–107
4d	H	4-Cl	88	123–124	110–111
4e	4-Cl	H	90	129	129–130
4f	H	4-Me	70	118–119	115–117
4g	4-NO_2	Ph	70	162–164	133–134
4h	H	4-NO_2	86	105–106	102–103
4i	4-Me	2-NO_2	85	134–136	–
4j	4-Me	3-NO_2	79	151–152	–
4k	H	3-NO_2	76	176–178	–

$H_{arom.}$), 7.10 (d, 2H, $H_{arom.}$, J = 8.2 Hz), 6.75 (s, 1H, S–CH–N), 4.00 (d, 1H, J = 15.7 Hz, CH_2), 3.80 (d, 1H, J = 15.8 Hz, CH_2), 2.20 (s, 3H, CH_3); Calcd. for: $C_{16}H_{14}N_2O_3S$: C 61.13, H 4.49, N 8.91, S 10.20; Found: C 60.92, H 4.42, N 8.80, S 10.27.

*2.2.2. 2-(3-Nitrophenyl)-3-p-tolylthiazolidin-4-one (**4j**)*

IR (KBr, cm^{-1}): ν 3051 (aromatic CH stretch.), 2956 (aliphatic CH stretch.), 1731 (C=O), 1521, 1346 (NO_2); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.23 (s, 1H, $H_{arom.}$), 8.07 (d, 1H, J = 7.8 Hz, $H_{arom.}$), 7.90 (d, 1H, J = 7.4 Hz, $H_{arom.}$), 7.59 (t, 1H, J = 7.9 Hz, $H_{arom.}$), 7.20 (d, 2H, J = 8.0 Hz, $H_{arom.}$), 7.09 (d, 2H, J = 8.0 Hz, $H_{arom.}$), 6.68 (s, 1H, S–CH–N), 4.00 (d, 1H, J = 15.7 Hz, CH_2), 3.90 (d, 1H, J = 15.6 Hz, CH_2), 2.19 (s, 3H, CH_3); Calcd. for: $C_{16}H_{14}N_2O_3S$: C 61.13, H 4.49, N 8.91, S 10.20; Found: C 60.95, H 4.44, N 8.79, S 10.08.

*2.2.3. 2-(3-Nitrophenyl)-3-phenylthiazolidin-4-one (**4k**)*

IR (KBr, cm^{-1}): ν 3044 (aromatic CH stretch.), 2936 (aliphatic CH stretch.), 1730 (C=O), 1540, 1347 (NO_2); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.24 (s, 1H, $H_{arom.}$), 8.07 (d, 1H, J = 8.1 Hz, $H_{arom.}$), 7.90 (d, 1H, J = 7.7 Hz, $H_{arom.}$), 7.59 (t, 1H, J = 7.8 Hz, $H_{arom.}$), 7.28–7.36 (m, 4H, $H_{arom.}$), 7.13–7.17 (m, 1H, $H_{arom.}$), 6.72 (s, 1H, S–CH–N), 4.10 (d, 1H, J = 15.7 Hz, CH_2), 3.93 (d, 1H, J = 15.7 Hz, CH_2); $C_{15}H_{12}N_2O_3S$: C 59.99, H 4.03, N 9.33, S 10.68; Found: C 59.71, H 3.93, N 9.11, S 10.48.

3. Results and discussion

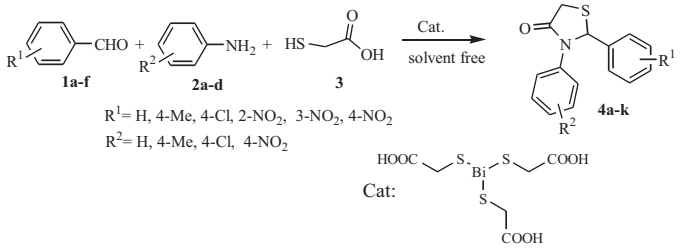
Herein, we report a novel and facile synthesis of 1,3-thiazolidin-4-one in good yields. In a one-pot procedure, compounds **4a–k** (Table 1) were obtained in the course of a three component reaction with aromatic aldehyde **1a–f**, aromatic amine **2a–d** and mercaptoacetic acid **3** using 2,2′,2″-bismuthinetriyltris(sulfanediyl)triacetic acid [$Bi(SCH_2COOH)_3$] at an ambient temperature under solvent free conditions within 2 h.

Initially, we condensed *p*-toluidine (1.0 mmol), 4-methylbenzaldehyde (1 mmol), thioglycolic acid (1.2 mmol) under solvent free conditions. They were stirred at room temperature for 24 h in the absence of the catalyst but led to very poor yields (entry 1, Table 2).

To enhance the yield of the desired product the temperature of the reaction was increased to 70 °C, with no appreciable increment

Table 2
Optimization of the reaction condition for product **4a**.

Entry	Catalyst	Time (h)	T (°C)	Yields (%)
1	–	24	rt	7
2	–	2	70	7
3	Cat. (5 mol%)	2	70	30
4	Cat. (10 mol%)	2	70	81
5	Cat. (15 mol%)	2	70	80
6	Cat. (10 mol%)	3	80	80



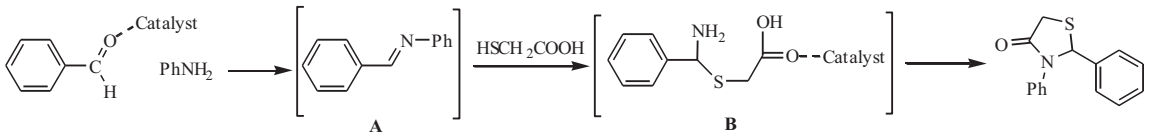
Scheme 1. Synthesis of thiazolidinon-4-one **4a–k**.

in the product yield observed (entry 2, Table 2). Then we repeated the reaction in the presence of catalyst and also evaluated the amount of catalyst required for this transformation using 5 mol% and we obtained 30% yields. Maximum yield (81%) was obtained when the reaction was carried out with 10 mol% of the catalyst. Any further increase of catalyst loading does not affect the yield (entry 5, Table 2). The reaction temperature was also examined and 70 °C was found to be the optimum temperature. Reducing the temperature from 70 °C led to a significant decrease in the yield of the desired product **4a**.

We further examined a wide variety of aromatic aldehydes with various substituents to establish the utility of this reaction. *Ortho*-, *meta*- and *para*-substituted aromatic aldehydes undergo this one-pot multi-component synthesis with aromatic amine and thioglycolic acid to afford 1,3-thiazolidin-4-ones **4a–k** in good yields (Scheme 1 and Table 1). Aryl aldehydes bearing electron withdrawing and donating functionalities smoothly undergo cyclo-condensation to the respective thiazolidin-4-ones with good yields. Reaction profile is very clean and no side products are formed.

^{1}H NMR spectra of all synthesized compounds reveal a singlet signal at region δ 6.67–7.75 attributed to the resonance of the methine proton (S–CH–N). The appearance of the IR absorption signals due to the carbonyl group of the synthesized compounds **4a–k**, clearly confirmed the formation of thiazolidin-4-ones.

A proposed mechanism for the reaction is outlined in Scheme 2. Based on this mechanism, it is highly probable that the carbonyl groups of aldehydes and acid have to be activated, which occurs when the carbonyl oxygen is coordinated by catalyst. Therefore, it may be proposed that the catalyst facilitates the formation of imine intermediate [A] by increasing the electrophilicity of the carbonyl group of the aldehyde.



Scheme 2. Postulated mechanism for thiazolidin-4-one synthesis.

4. Conclusion

For the first time, a novel, facile, one-pot three component method for the synthesis of substituted thiazolidin-4-one catalyzed by 10 mol% of catalyst has been developed in good yield. Compared to the previously reported methods, mild reaction conditions, easy work-up, clean reaction profile, shorter reaction times, and wide range of applicable substrates are key advantages of this methodology.

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