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CONDENSATION OF AROMATIC ALDEHYDES, SUBSTITUTED AMINES AND THIOGLYCOLIC ACID UNDER CATALYST FREE CONDITIONS

Manoj P. Thakare*, Rahimullah Shaikh

Department of Chemistry, Government Vidarbha Institute of Science and Humanities, Sant Gadge Baba Amravati University, Amravati, 444604, Maharashtra, India
E-mail:manojorg@rediffmail.com

Abstract: A convenient and catalyst free protocol for 4-thiazolidinones synthesis with aromatic aldehydes, substituted amines and acid as substrates has been developed. Without using any catalyst 4-thiazolidinones were obtained in good to excellent yields in short time.

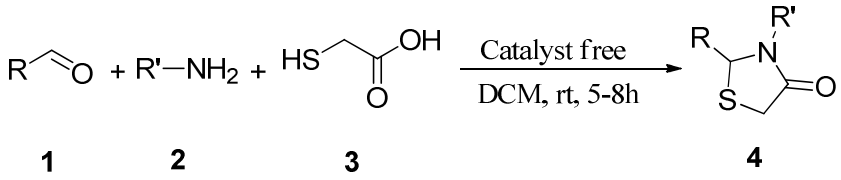
Keywords: Catalyst free, aldehydes, amines, thioglycolic acid, 4-thiazolidinones

Introduction

Substituted 4-thiazolidinones are of great importance because of their wide range of biological activities like anti HIV,[1] antioxidant,[2] anticancer,[3] antibacterial[4] and anti-tubercular.[5] 4-thiazolidinones synthesis one pot multi-component condensation of aldehyde, amine and thioglycolic acid or two step synthesis. As there is a loss of water molecule in the final step of multi-component condensation, different reagents or catalysts used for dehydration. For dehydration mostly sodium sulfate,[6] molecular sieves[7] and $ZnCl_2$[8] are use for dehydration. Other reagents such as DCC,[9] HBTU[10] and silica chloride[11] are also use for dehydration. These types of reagents or catalysts have some limitations such as high heating, longer reaction time, expensive, hazardous conditions and the formation of by-products.

By considering these limitations, we have developed new catalyst free condition for the synthesis of 4-thiazolidinones using aromatic aldehydes, substituted amines and thioglycolic acid in organic solvent. This study describes our work towards the development of new method for the preparation of substituted 4-thiazolidinones. This method avoids expensive reagents or catalysts, hazardous reaction conditions as well as high heating. This new method also avoids the formation of by-products. This method offer many advantages over the reported methods such as cleaner reaction profile, shorter reaction time, easy isolation and excellent yield of the products. At initial stage, model reaction was performed using benzaldehyde, benzyl amine and thioglycolic acid in dichloromethane at room temperature. To a stirred solution of benzaldehyde (1.0 mmol) in DCM (10 mL) was added benzylamine (1.0 mmol) at room temperature and stirred for 10 min. Thioglycolic acid (1.0 mmol) was then added to the above reaction at 0°C. The reaction was then warmed to room temperature and continued to stir for 6 h. The progress of reaction was monitored by TLC. After

completion, the reaction was concentrated under reduced pressure and purified by column chromatography (scheme 1).



Scheme 1. Aromatic aldehyde (1.0 mmol), amine (1.0 mmol), thioglycolic acid (1.0 mmol), DCM (10 mL), rt, 5-8h.

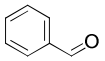
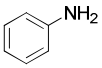
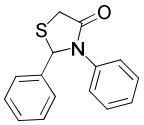
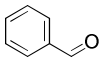
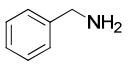
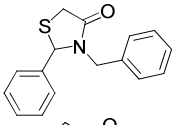
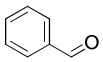
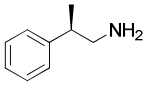
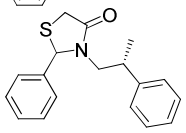
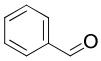
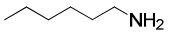
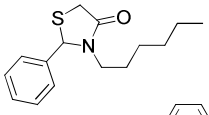
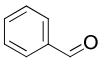
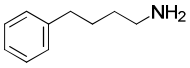
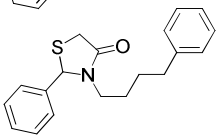
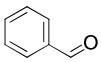
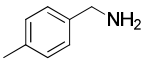
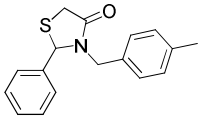
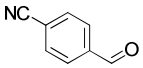
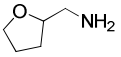
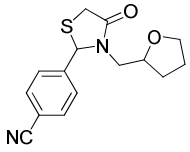
After standardization of reaction, we tried same methodology for different aromatic aldehydes and amines.

Experimental

General remarks

All reagents were purchased from commercial suppliers and used without further purification. Dichloromethane was purchased from GLR and were used as such. All reactions were run in oven-dried round bottom flask or vial containing a teflon-coated stir bar and sealed with septum. Analytical thin layer chromatography was carried out on silica pre-coated glass plates (Silica gel 60 F254, 0.25 mm thickness) and visualized with UV light at 254 nm. ^{1}H NMR spectra were recorded on Bruker 400-MHz Ultrashield Advance II 400 model (400 and 100 MHz, respectively) at ambient temperature with $CDCl_3$ or DMSO-*d6* as solvents. Data for ^{1}H are recorded as follows: δ chemical shift (ppm), multiplicity (s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet), coupling constant (Hz), integration. Spectra were referenced internally to the residual proton resonance in $CDCl_3$ (δ 7.26 ppm), DMSO-d6 (δ 2.50 ppm) or with tetramethylsilane (TMS, δ 0.00 ppm) as the internal standard. Chemical shifts (δ) were reported as part per million (ppm) in δ scale downfield from TMS. Liquid chromatography/mass spectrometry (LC/MS) data was obtained to verify molecular mass and analyze purity of products. The specifications of the LC/MS instrument are the following: Electrospray (+) ionization, mass range of 100-1000 Da, 20V cone voltage, Acquity BEH C-18 column (2.1 x 100mm, 1.7 μm), and gradient mobile phase consisting of 5 mM ammonium acetate in water and acetonitrile, and a flow rate of 0.5 mL/min.

Table 1: Synthesis of 4-thiazolidinones using aldehyde, amine and thioglycolic acid in DCM at room temperature

Entry	Aldehyde	Amines	Product (4a-j)	Time (h)	Yield (%)[a]
1				6	80[b]
2				5	89[b]
3				7	78
4				5	93
5				6	77
6				5	91
7				8	86

[a]Isolated yields obtained using 1.0 mmol of amine, 1.0 mmol of aldehyde, 1.0 mmol of thioglycolic acid in DCM at room temperature. [b]Ref 9

General procedure for the synthesis of 4-thiazolidinones (4a-g):

To a stirred solution of aromatic aldehyde (1.0 mmol) in DCM was added amine (1.0 mmol) at room temperature and stir for 10 min. Thioglycolic acid (1.0 mmol) was then added to the above reaction mixture at 0^{o}C and stirring was continued for another 5-8 h. The progress of reaction was monitored by thin layer chromatography. The reaction mixture was concentrated under reduced pressure to afford crude product. The residue was then purified by column chromatography using ethyl acetate in hexane as an eluent to afford the pure product **4a-g** (table 1).

2,3-Diphenylthiazolidin-4-one (4a): (80%) white solid; ^{1}H NMR (400 MHz, $CDCl_3$): 7.260-7.302 (7H, m), 7.141-7.178 (3H,m), 6.093 (1H, s), 4.002 (1H, d, *J=16 Hz*), 3.875 (1H, d, *J=16 Hz*).

3-Benzyl-2-phenylthiazolidin-4-one (4b): (89%) white solid; ^{1}H NMR (400 MHz, DMSO-d_6): 7.380-7.419 (3H, m), 7.293-7.353 (3H, m), 7.220-7.243 (2H, m), 7.090-7.108 (2H, m), 5.386 (1H, s), 5.164 (1H, d, *J=14.8 Hz*), 3.928 (1H, d, *J=12.0 Hz, J=10.0 Hz*), 3.769 (1H, d, *J=15.6 Hz*), 3.537 (1H, d, *J=14.8 Hz*). LCMS calcd for $C_{16}H_{15}NOS$ (M^{+}) 270.09, found 270.16.

2-Phenyl-3-((R)-2-phenylpropyl)thiazolidin-4-one (4c): (78%) brown solid; ^{1}H NMR (400 MHz, DMSO-d_6): 7.279-7.404 (6H, m), 7.121-7.260 (3H,m), 7.024-7.043 (1H, m), 5.477 (0.5H, s), 4.757 (0.5H, s), 3.845-3.993 (1H, m), 3.672-3.782 (1.5H, m), 3.481(0.5H, d, J=*15.2 Hz*), 2.586-3.178 (2H, m1.160-1.258 *(*3H,m*)*. LCMS calcd for $C_{18}H_{19}NOS$ (M^+) 298.12, found 298.26.

3-Hexyl-2-phenylthiazolidin-4-one (4d): (93%) off white solid; ^{1}H NMR (400 MHz, DMSO-d_6): 7.260-7.410 (5H, m), 5.619 (1H,s), 3.797-3.839 (1H, m), 3.630-3.718 (2H, m), 2.610-2.680 (1H, m), 1.270-1.460 (2H, m), 1.209-1.250 (6H, m), 0.844 (3H, t, *J=6.8 Hz*). LCMS calcd for $C_{15}H_{21}NOS$ (M^+) 264.13, found 264.15.

2-Phenyl-3-(4-phenylbutyl)thiazolidin-4-one (4e): (77%) brown solid; ^{1}H NMR (400 MHz, $CDCl_3$): 7.327-7.435 (3H, m), 7.235-7.319 (4H,m), 7.160-7.197 (1H, m), 7.057-7.119 (2H, m), 5.544 (1H, s), 3.667-3.338 (3H, m), 2.515-2.711 (3H, m), 1.409-1.637 (4H, m). LCMS calcd for $C_{19}H_{21}NOS$ (M^+) 312.13, found 312.32.

3-(4-Methylbenzyl)-2-phenylthiazolidin-4-one (4f): (91%) white solid; ^{1}H NMR (400 MHz, DMSO-d_6): 7.296-7.447 (5H, m), 7.126 (2H,d, J=*7.6 Hz*), 6.970 (2H, d, *J=8.0 Hz*), 5.507 (1H, s), 4.843 (1H, d, *J=15.2 Hz*), 3.953 (1H, d, *J=16.4 Hz*), 3.767 (1H, d, *J=15.6 Hz*), 3.505 (1H, d, *J=15.2 Hz*),2.275 (3H, s). LCMS calcd for $C_{17}H_{17}NOS$ (M^+) 284.10, found 284.00.

2-Phenyl-3-((tetrahydrofuran-2-yl)methyl)thiazolidin-4-one (4g): (86%) off white solid; ^{1}H NMR (400 MHz, DMSO-d_6): 7.871 (1H, d, *J=8.0 Hz*), 7.522-7.556 (2H,m), 5.988-6.047 (1H, s), 3.864-3.912 (2H, m), 3.561-3.740 (4H,m), 2.396-2.615 (1H,m), 2.476-2.877 (2H, m). LCMS calcd for $C_{15}H_{16}N_2O_2S$ (M^+) 289.09, found 289.14.

Conclusion

In summary, we developed a highly efficient and novel method under catalyst free condition to access 4-thiazolidinones. The reaction is quite versatile and cost-effective. This method eliminates high heating, longer reaction time, expensive chemicals, hazardous conditions and the formation of by-products.

Acknowledgements

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