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EFFICIENT SYNTHESIS OF 4-THIAZOLIDINONE DERIVATIVES IN ETHANOL

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ABSTRACT
A series of thiazolidinone derivatives have been synthesized via one-pot multicomponent reaction involving aromatic aldehyde, amine and thioglycolic acid in the presence of Eton's reagent in ethanol under reflux condition. The significant features of this method include short reaction time, operational simplicity, high yields and easy isolation of products.

Keywords: *Thiazolidinone, thioglycolic acid, Eton's reagent, multicomponent reaction.*

INTRODUCTION

Compounds containing thiazolidinone plays an important role as a widely used pharmacophore and belongs to diverse scaffolds in medicinal chemistry [1]. They have found their uses as antiviral, antimicrobial, anti-inflammatory, anticonvulsant, antimalarial, anti-fungal [2], anti-tubercular [3,4], anti-HIV agents, anti-diabetic agents [5] and protein tyrosine phosphate inhibitors [6]. Among various thiazolidinone derivative, 4-thiazolidinone are one of the most studied thiazolidinone moiety in drug discovery and its design and majority of the biologically active thiazolidinone derivatives reported are 4- thiazolidinones [7-9]. Multicomponent reactions are key choice for organic synthesis due to operational simplicity, reduced steps and minimal waste generation [10].

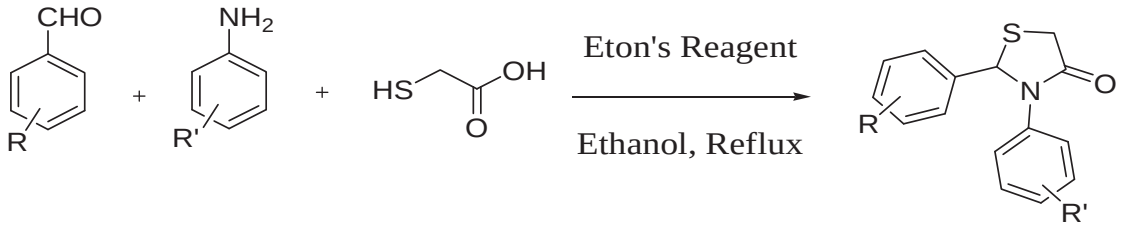
In spite of their importance, various methods have been developed for the synthesis of 4- thiazolidinones by three-component tandem reaction between aldehyde, amine and thioglycolic acid in presence of various catalysts[11-17]. The reported method has its own merits and demerits, but some of these methods have certain demerits, such as use of organic solvents, long reaction times, utilize of specific conditions and tedious workup procedure. In this protocol we have developed a convergent synthesis of 4-thiazolidinone derivatives via one pot multicomponent reaction of aromatic aldehyde, aniline and thioglycolic acid using Eton's reagent in ethanol under reflux condition.

EXPERIMENTAL

All starting chemicals were purchased from Sigma Aldrich and used without further purification. Reaction progress was monitored by TLC on aluminium plates precoated with silica gel using Petroleum ether: ethyl acetate (7 : 3) as an eluent and visualized under UV light. Melting points were determined in open capillaries using Electrothermal Mk3 apparatus and are uncorrected. Infrared (IR) spectra in KBr discs were recorded using a Perkin-Elmer FT-IR spectrometer wave-numbers in the IR spectra are given in cm^{-1}. ^1H NMR spectra were measured on Bruker Avance II 400 MHz NMR spectrometer in DMSO-d_6 as a solvent and chemical shifts had been expressed on the δ (ppm) scale downfield from TMS as an internal well-known reference.

General procedure for the synthesis of thioazolidinone

A mixture of aromatic aldehyde (1, 1mmol), aniline (2, 1mmol) and thioglycolic acid was stirred in 5 mL of ethanol and Eton's reagent was added in a round bottom flask equipped with a magnetic bar and condenser. Reaction mixture stirred for 5-10 min at room temperature and followed by reflux for 1-2 h. Progress of the reaction was monitored by TLC on aluminium plates precoated with silica gel using Petroleum ether: ethyl acetate (8 : 2) as an eluent. After completion of reaction, the reaction mixture was poured into ice water to give a precipitate. The precipitate was filtered, washed with water, dried in air and recrystallized from ethanol to give respective products.



Scheme 1

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RESULT AND DISCUSSION

Firstly a model reaction was conducted using aromatic aldehyde, aniline and thioglycolic acid without any catalyst and solvent at room temperature (Scheme-1). It was observed that the reaction did not proceed well even until 12 h (Table 1, entries 1). Later, the reaction was performed in the presence of catalytic amounts of Eton's reagent (20 mol %) at room temperature but reaction did not proceed well, again this reaction carried out in reflux condition in the presence of different solvent at room temperature, the yield were again not inspiring (Table 1, entry 4-5). Further, the reaction was carried out in ethanol at reflux condition came out as the elevated conditions for the reaction in terms of yield and time (Table 2).

Table-1: Optimization of reaction condition

Entry	Condition	Time (h)	Yield (%)
1	Catalyst and solvent free at Room Temperature	12	-----
2	Eton's reagent, solvent free at Room Temperature	12	10
3	Eton's reagent, solvent free at Reflux	5	40
4	Eton's reagent Water at Reflux	4	45
5	Eton's reagent CH_3CN at Reflux	3	70
6	Eton's reagent Ethanol at Reflux	2	91

In a subsequent investigation for the substrate scope using the optimized reaction conditions, we found that various aromatic aldehydes and their corresponding products were obtained in high yields (Table 2).

SPECTRAL DATA OF SOME REPRESENTATIVE COMPOUNDS

1) **2-(4-nitrophenyl)-3-phenylthiazolidin-4-one** (4): M. P.139-140ºC, IR (KBr) cm^{-1}: 1672 (C=O), 1585, 1520, 1511, 1480, 1375, 1332; ^{1}H NMR (400 MHz, DMSO-d_6): 7.67-7.85 (m, 4H, Ar-H), 7.28-7.52 (m, 5H, Ar-H), 5.86 (s, 1H, C-H) 3.92-4.1 (dd, 2H, CH_2)
2) **2-(4-chlorophenyl)-3-phenylthiazolidin-4-one** (5) :): M. P.130-132ºC, IR (KBr) cm^{-1}: 1675 (C=O), 1595, 1520, 1453, 1370, 730; ^{1}H NMR (400 MHz, DMSO-d_6): 7.73-7.87 (m, 4H, Ar-H), 7.15-7.45 (m, 5H, Ar-H), 5.9 (s, 1H, C-H) 3.95-4.2 (dd, 2H, CH_2)

Table-2: Synthesis of 1,3-thiazolidin-4-ones using Eton's Reagent under reflux condition

Entry	R	R'	Time (h)	Yield (%)	M.P.(°C)
1	H	H	2	91	132-134
2	p-CH_3	H	2.5	88	122-124
3	m-NO_2	H	2	92	177-179
4	p-NO_2	H	1.5	95	139-140
5	p-Cl	H	1.5	91	130-132
6	m-Cl	H	2	90	136-138
7	p-CH_3	p-Cl	2	89	178-180
8	m-NO_2	p-Cl	1.5	92	184-186
9	p-NO_2	p-Cl	1.5	94	163-165
10	p-Cl	p-Cl	2	90	209-211
11	m-Cl	p-Cl	2.5	92	195-197

CONCLUSION

We have developed a protocol for the convergent synthesis of 4-thiazolidinone derivatives via one pot multicomponent reaction of aromatic aldehyde, aniline and thioglycolic acid using Eton's reagent in ethanol under reflux condition. The present protocol has several advantage over reported protocol, such as mild reaction condition, good functional group tolerance, excellent yield and easy workup procedure.

REFERENCES

1. Kidwai M, Bala R., Kumar K., (1995). Synthesis of new 4-thiazolidinones and 2-azitidiones with their vitro biological activities,Indian J PharmaSci, 57(6) 252-259.
2. Joshi D. G., Oza H. B., Parekh H. H., (2001), Synthesis of some novel 1,3,4-oxadiazoles and 5-oxo-imidazolines as potent biologically active agents, Indian J HeterocycleChem, 11, 145-148.
3. Kachhadia V. V., Patel M. R. Joshi H. S., (2005), Heterocyclic systems containing S/N regioselectivenucleophiliccompetition: facile synthesis, antitubercular and antimicrobial activity of thiohydantoins and iminothiazolidinones containingthe benzo[b]thiophene moiety, J Serb Chem Soc., 70(2), 153-161.

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4. Maccari, R., Vitale, R. M., Ottana, R., Rocchiccioli, M., Marrazzo, A., Cardile, V., Graziano, A.C., Amodeo, P., Mura, U., and Del Corso, A., (2014), Structure-activity relationships and molecular modelling of new 5-arylidene-4-thiazolidinone derivatives as aldose reductase inhibitors and potential anti-inflammatory agents, Eur. J. Med. Chem., 81, 1-14.
5. Kaminskyy D., Khyluk D., Vasylenko O., Lesyk R., (2012), An efficient method for the transformation of 5-ylidenerhodanines into 2,3,5-trisubstituted-4-thiazolidinones, Tetrahedron Lett. 53(5), 557-559.
6. Jain A. K., Vaidya A., Ravichandran V., Kashaw S. K., Agrawal R.K.,(2012), Recent developments and biological activities of thiazolidinone derivatives: a review,Bioorganic Med. Chem. 20, 3378-3395..
7. Li Y., Giulianotti M., Houghten R.A., (2009), Solid-phase synthesis of 2-alkylidene-6-alkyl-imidazo [2,1-b]thiazole-3,5[2H,6H]-dione derivatives, Tetrahedron Lett., 50 (42), 5857-5889.
8. Singh S.P., ParmarS.S., Raman K., Stenberg V.I., (1981), Chemistry and biological activity of thiazolidinones, Chem. Rev. 81(2), 175-203.
9. Brown F.C., (1961), 4-Thiazolidinones, Chem. Rev. 61(5), 463-521,
10. Li X. T., Liu Y. H., Liu X., Zhang Z. H., (2015), Meglumine catalyzed one-pot, three-component combinatorial synthesis of pyrazoles bearing a coumarin unit,RSC Adv., 5, 25625-25633.
11. Srivastava S. K., Srivastava S. L., Srivastava S. D., (2002), Synthesis of new 1, 2, 4-triazolo-thiadiazoles and its 2-oxoazetidines as anti-microbial, anticonvulsant and anti-inflammatory agents. J. Ind. Chem. Soc., 77(2), 2357-2363.
12. Sharma R. C., Kumar D., (2002), Synthesis of some new thiazolidin-4-ones as possible antimicrobial agents, J. Ind. Chem. Soc.,77, 492-493.
13. Rawal R. K., Srivastava T., Haq W., Katti S. B., (2004), An expeditious synthesis of thiazolidinones and tetathiazanones, J. Chem. Res., 5, 368-369.
14. Srivastava T., Haq W., Katti S. B., (2002), carbodiimide Mediated Synthesis of 4-thiazolidinones by One-pot Three-component Condensation, Tetrahedron, 58, 7614-7619.
15. Yadav A. K., Kumar M., Yadav T., Jain R.,(2009), An ionic liquid mediated one-pot synthesis of substituted thiazolidinones and benzimidazoles, Tetrahedron Lett.,50, 5031-5034.
16. Zhang X. Y., Li X. Y., Li D. F., Qu G. R., Wang J. J., Loiseau P. M., Fan X. S., (2009), Ionic liquid mediated and promoted eco-friendly preparation of thiazolidinone and pyrimidine nucleoside–thiazolidinone hybrids and their antiparasitic activities, Bioorg. Med. Chem. Lett., 19, 6280-6283.
17. Kanagarajana V., Thanusua J., Gopalakrishnana M., (2009), three component one-pot synthesis of novel pyrimidino thiazolidin-4-ones catalyzed by activated fly ash, Green Chem.Lett. Rev., 2(3), 161-167.