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Chemistry

IONIC LIQUID PROMOTED KNOEVENAGEL CONDENSATION FOR THE SYNTHESIS OF NOVEL 5-((3-ARYL-1-PHENYL-1H-PYRAZOL-4-YL)METHYLENE)THIAZOLIDINE-2,4-DIONE AND THEIR BIOLOGICAL SCREENING

Namrata Shankarrao Kadu	Research Student, Department of Chemistry, Maulana Azad College of Arts, Science and Commerce, Chhatrapati Sambhajinagar, Maharashtra
Sabreena Yameen Pathan	Research Student, Department of Chemistry, Maulana Azad College of Arts, Science and Commerce, Chhatrapati Sambhajinagar, Maharashtra
Atul Vishvanathrao Ingle	Professor, Department of Chemistry, Yeshwantrao Chavan College of Arts, Commerce and Science, Sillod, Dist. Chhatrapati Sambhajinagar, Maharashtra
Nilesh Shankarrao Kadu	Associate Professor, Department of Chemistry, Bharatiya Mahavidyalaya, Amravati, Maharashtra
Prashant Deorao Netankar*	Professor, Department of Chemistry, Maulana Azad College of Arts, Science and Commerce, Chhatrapati Sambhajinagar, Maharashtra *Corresponding Author

ABSTRACT Pyrazolo-Thiazolidine-2,4-dione derivatives demonstrate different biological activities against a wide range of targets of interest to medicinal chemists. Thiazolidine-2,4-dione derivatives are synthesized by reacting thiazolidine-2,4-dione with aromatic aldehyde by the Knoevenagel reaction using conventional and modern methods. In the present studies choline hydroxide ionic liquid has been used as a convenient and effective solvent and catalyst for the synthesis of 5-((3-aryl-1-phenyl-1H-pyrazol-4-yl)methylene)thiazolidine-2,4-dione derivatives by using thiazolidine-2,4-dione and 3-(aryl)-1-phenyl-1H-pyrazole-4-carbaldehydes. Easy workup procedure, high yields and purity of the products, high catalytic activity, easy recovery and reusability of the catalyst are the features of the present method. The synthesized compounds exhibit strong antimicrobial activities against Trichophyton rubrum.

KEYWORDS : Knoevenagel Condensation, Ionic Liquid, Thiazolidine-2,4-dione, Antimicrobial Activity, etc.

INTRODUCTION

Nitrogen and sulphur containing heterocycles are widely studied in medicinal chemistry due to their immense biological properties. The presence of both nitrogen and sulphur atoms in a ring allows such compounds to engage in diverse interactions and modulate properties like lipophilicity, polarity and metabolic stability, making them valuable scaffolds for drug design[1]. Among these compounds, pyrazoles are privileged in drug discovery, appearing in many pharmaceuticals and exhibiting a diverse range of activities[2]. Pyrazole rings are versatile and allow many modifications. By placing different chemical groups at various positions on the ring, many compounds with specific biological effects are observed. Pyrazole derivatives exhibit significant pharmacological properties such as antimicrobial[3], anti-depressant[4], anti-inflammatory[5], antitumor[6] and antiviral[7].

Another privileged scaffold is thiazolidine-2,4-dione which is a key component in medicinal chemistry, contributing to a wide range of pharmacological activities. Thiazolidine-2,4-dione derivatives are well known for their broad biological potential as they serve as antidiabetic[8], anticancer[9], antidiarrheal[10], 15-hydroxyprostaglandin dehydrogenase inhibitors[11] and other therapeutic uses[12].

Combining pyrazole and thiazolidine-2,4-dione into a single molecular entity potentially enhances their biological activities. One approach to achieve this is through the Knoevenagel condensation reaction, which forms a carbon-carbon double bond between a carbonyl carbon of an aldehyde and an active methylene carbon. The Knoevenagel condensation reaction under basic conditions serves as an effective strategy for the synthesis of 2,4-thiazolidinedione derivatives. It has been reported that such condensations can be effectively accelerated using sodium hydroxide[13], ammonium hydroxide[14], pyridine[15], sodium acetate in the presence of acetic acid or its anhydride[16], Potassium carbonate in DMSO[17], morpholine in acetic acid[18], etc. Although many Knoevenagel condensation methods are effective, some suffer from drawbacks such as long reaction times, high temperature, the use of organic solvents, toxic catalysts and difficulty in purifying products and recovering catalysts, which causes damage to the environment and health.

To address these issues, ionic liquids (IL) have emerged as alternative solvents and catalysts as they offer many advantages such as they act both as solvents and catalysts, have negligible vapor pressure, they often enable milder reaction conditions, faster reaction rates and excellent yields of the products. In the context of Knoevenagel condensation, ILs have been used to accelerate reactions between carbonyl compounds and active methylene components, often under mild temperature, sometimes even solvent-free or in aqueous/green media.

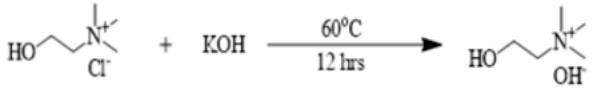
Continuing our interest in the synthesis of biologically important Nitrogen and Sulphur heterocycles[19-22], we report herein, the synthesis of 5-((3-aryl-1-phenyl-1H-pyrazol-4-yl)methylene) thiazolidine-2,4-dione derivatives by using choline hydroxide ionic liquid as a green and reusable solvent and catalyst.

MATERIALS AND METHODS

All the chemicals and solvent were AR grade and used without further purification. Melting points were determined in open capillary tubes and are uncorrected. ^{1}HNMR was recorded using a Bruker spectrometer (500MHz) using tetramethylsilane as an internal standard and D_6-DMSO as solvent. For this study, ionic liquid was synthesized according to the procedures reported in the literature.

Synthesis of Choline HydroxideIonic Liquid:

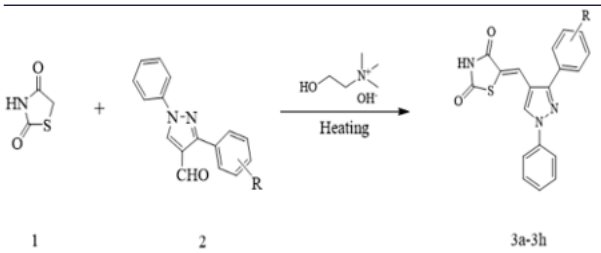
Choline chloride (10 mmol), KOH (10 mmol) and methyl alcohol (15 mL) was heated at 60°C for 12 hours with continuous stirring. The reaction mixture was cooled at room temperature and filtered to remove the KCl and the filtrate was concentrated to remove the methanol. The residue obtained was utilized without additional purification. (Scheme 1)



Scheme-1

General Procedure for the Synthesis of 5-((3-aryl-1-phenyl-1H-pyrazol-4-yl) methylene)thiazolidine-2,4-diones:

Mixture of thiazolidine-2,4-dione (1) (0.01mol) and pyrazole aldehyde (2) (0.01mol) in choline hydroxide (5ml) was heated in an oil bath at 80°C for 3 hours. After the completion of the reaction as monitored by TLC, the mixture was poured in ice-cold water, the obtained solid was washed with water and recrystallized from the mixture of EtOH: DMF (20:1) to afford the pure 5-((3-aryl-1-phenyl-1H-pyrazol-4-yl)methylene)thiazolidine-2,4-dione derivatives (3a-3h).



Scheme-2

Recyclability of the Choline Hydroxide IL:

After completion of the reaction, the reaction mixture was poured in ice cold water. The resultant solid was filtered. Filtrate was concentrated under reduced pressure using a rotary evaporator. The choline hydroxide ionic liquid thus obtained was washed with ether and reused.

RESULT AND DISCUSSION

Ionic liquids have attracted considerable interest in organic chemistry as green solvents, catalysts and reagents due to their properties such as negligible vapor pressure, minimized volatile organic compound (VOC) emissions, high thermal and chemical stability and allows reactions under mild conditions.

In this study, Choline hydroxide IL catalysed Knoevenagel condensation between (3-(aryl)-1-phenyl-1H-pyrazole-4-carbaldehydes and thiazolidine-2,4-dione was carried out under heating at 80°C to obtain the corresponding 5-((3-aryl-1-phenyl-1H-pyrazol-4-yl)methylene)thiazolidine-2,4-dione derivatives (Scheme-2).

To optimize the reaction conditions, the condensation of 3-(3-chlrophenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde and thiazolidine-2,4-dione was selected as the model reaction.

Initially, the reaction between 3-(3-chlrophenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde and thiazolidine-2,4-dione in the presence of Ethanol as a solvent was carried out, and the product was obtained in trace amount (Table 1, entry 1). The same reaction was again performed using KOH, Na_2CO_3 in ethanol, but the products was obtained in low yield. (Table 1, entries 2 and 3).

The same reaction was carried out in the presence of choline hydroxide at 80°C which gives the products in excellent yield in less reaction time (Table 2, entry 4).

Mechanistically, the choline hydroxide IL may act as a base and deprotonate the thiazolidine-2,4-dione to generate an enolate. Simultaneously, the ionic liquid could help polarize the carbonyl carbon of the pyrazole-aldehyde, thereby facilitating the nucleophilic attack by the thiazolidine enolate. This could lead to the formation of a β-hydroxy intermediate, which may then undergo elimination of water to yield the α,β-unsaturated (alkylidene) product.

Excellent yields of 5-((3-aryl-1-phenyl-1H-pyrazol-4-yl)methylene)thiazolidine-2,4-dione derivatives were obtained using various 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes (Table 2).

Table 1: Effect of Solvent and Catalyst on the Synthesis of 5-((3-(3-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)-thiazolidine-2,4-dione, (3a)

Entry	Solvent	Catalyst	Reaction Time (hrs)	Yield (%)
1	Ethanol	-	8	Trace
2	Ethanol	KOH	6	60
3	Ethanol	Na_2CO_3	5	55
4	Choline hydroxide IL	-	3	89

Table 2: Physical Data of Synthesized 5-((3-aryl-1-phenyl-1H-pyrazol-4-yl)methylene)thiazolidine-2,4-dione derivatives, (3a-3h):

Entry	R	Reaction time (hrs)	Yield (%)	M.P (oC)
3a	3-Cl	3.5	88	238
3b	4-Br	3.3	89	245
3c	3-NO_2	3.5	86	230
3d	3-Br	3.2	88	232
3e	4-F	3.4	85	265
3f	4-Me	3	89	260
3g	4-OH	3.1	88	251
3h	3-CH_3-4-OH	3.2	89	253

Table 3: Reusability of the Choline Hydroxide-IL:

Run	Yield (%)
1	90
2	88
3	85

Table 4: Antimicrobial Activity of 5-((3-aryl-1-phenyl-1H-pyrazol-4-yl)methylene) thiazolidine-2,4-dione derivatives (Zone of Inhibition in mm)

Sr. No.	Test Compound Code	Antimicrobial Sensitivity Test Against Bacteria and Fungus (After 24 Hours at 37 °C Temperature and Fungus at Room Temperature) (Zone of Inhibition in mm)					
		Gram -ve Bacteria		Gram +ve Bacteria		Fungus	
		Pseudomonas fluorescens	Escherichia coli	Staphylococcus aureus	Bacillus acne	Trichophyton rubrum	Candida albicans
1.	3a	-	-	18 mm	-	16 mm	12 mm
2.	3b	12 mm	-	18 mm	-	-	12 mm
3.	3c	-	-	11 mm	-	-	-
4.	3d	12 mm	-	14 mm	12 mm	14 mm	12 mm
5.	3e	11 mm	12 mm	18 mm	-	12 mm	12 mm
6.	3f	-	-	18 mm	12 mm	12 mm	14 mm
7.	3g	14 mm	-	18 mm	-	15 mm	14 mm
8.	3h	14 mm	-	16 mm	12 mm	14 mm	14 mm
9.	Standard ofloxacin (2mcg) for bacteria and Fluconazole (10mcg) for fungus	24 mm	24 mm	22 mm	18 mm	12 mm	18 mm

We also demonstrated that the ionic liquid can be reused for up to three cycles. After each run, the ionic liquid was recovered, purified, and reused with minimal loss in performance (Table 3). Antimicrobial activity of 5-((3-aryl-1-phenyl-1H-pyrazol-4-yl)methylene) thiazolidine-2,4-dione derivatives was also evaluated against two Gram-negative bacteria (Pseudomonas fluorescens and Escherichia coli), two Gram-positive bacteria (Staphylococcus aureus and Bacillus acne) and fungi (Trichophyton rubrum and Candida albicans). Ofloxacin (2mcg) for bacteria and Fluconazole (10mcg) for fungus was selected as the standard drug. The newly synthesized thiazolidine-2,4-dione shows good activity against bacteria and fungi. Good to moderate activity against Pseudomonas fluorescens was shown by 3g and 3h, with a maximum 14mm zone of inhibition. Escherichia coli shows moderate zone of inhibition against 3e. Compounds 3a, 3b, 3e, 3f and 3g show good activity against Staphylococcus aureus. Some compounds show moderate activity against Bacillus acne. All the synthesized compounds show excellent activity against Trichophyton rubrum, with zone of inhibition more than the standard drug. Candida albicans shows moderate to good activity for 3f, 3gand 3h. (Table 4)

All synthesized compounds were characterized by ^{1}H NMR and mass spectroscopy.

CONCLUSION

We have reported the use of Choline hydroxide IL as a promoter for the Knoevenagel condensation between pyrazole aldehydes and thiazolidine-2,4-dione as a green, efficient and recyclable solvent as well as catalyst. The reaction proceeds under mild conditions giving excellent yields of the products, avoiding corrosive reagents and high temperatures. The ionic liquid was recovered and reused multiple times with minimum loss of catalytic activity, enhancing the sustainability and cost-effectiveness of the process. This protocol offers an excellent alternative to conventional Knoevenagel condensation methods.

Spectral Analysis of the Synthesized 5-((3-aryl-1-phenyl-1H-pyrazol-4-yl)methylene)thiazolidine-2,4-dione Derivatives:

5-((3-(3-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene) thiazolidine-2,4-dione, (3a)

^{1}H NMR (500 MHz, DMSO, δ ppm): 7.9 (s, 1H), 8.6 (s, 1H), 10.7 (s, 1H), 6.9-8.1 (m, 9H); Mass: $[ES]^+$: Calculated- 381.03, Found-382.0119.

5-((3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene) thiazolidine-2,4-dione, (3b)

^{1}H NMR (500 MHz, DMSO, δ ppm): 7.1 (s, 1H), 8.5 (s, 1H), 10.2 (s, 1H), 7.4-7.9 (m, 9H); Mass: $[ES]^+$: Calculated- 424.98, Found-428.0437.

5-((3-(3-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene) thiazolidine-2,4-dione, (3c)

^{1}H NMR (500 MHz, DMSO, δ ppm): 8.2 (s, 1H), 8.7 (s, 1H), 10.6 (s, 1H), 7.3-8.6 (m, 9H); Mass: $[ES]^+$: Calculated- 392.06, Found-393.0954.

5-((3-(3-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene) thiazolidine-2,4-dione, (3d)

^{1}H NMR (500 MHz, DMSO, δ ppm): 7.3 (s, 1H), 8.6 (s, 1H), 10.2 (s, 1H), 7.4-8.1 (m, 9H); Mass: $[ES]^+$: Calculated- 424.98, Found-425.0149.

5-((3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene) thiazolidine-2,4-dione, (3e)

^{1}H NMR (500 MHz, DMSO, δ ppm): 7.3 (s, 1H), 8.4 (s, 1H), 10.0 (s, 1H), 7.4-8.1 (m, 9H); Mass: $[ES]^+$: Calculated- 365.06, Found-366.1115.

5-((1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)methylene)thiazolidine-2,4-dione, (3f)

^{1}H NMR (500 MHz, DMSO, δ ppm): 7.5 (s, 1H), 8.4 (s, 1H), 10.2 (s, 1H), 2.4 (s, 3H), 7.3-7.9 (m, 9H); Mass: $[ES]^+$: Calculated- 361.09, Found-362.1389.

5-((3-(4-hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl)methylene) thiazolidine-2,4-dione (3g)

^{1}H NMR (500 MHz, DMSO, δ ppm): 7.3 (s, 1H), 8.4 (s, 1H), 10.4 (s, 1H), 5.3 (s, 1H), 7.4-7.8 (m, 9H); Mass: $[ES]^+$: Calculated- 363, Found-364.0812.

5-((3-(4-hydroxy-3-methylphenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)thiazolidine-2,4-dione, (3h)

^{1}H NMR (500 MHz, DMSO, δ ppm): 6.9 (s, 1H), 8.6 (s, 1H), 10.6 (s, 1H), 5.1 (s, 1H), 2.2 (s, 3H), 7.2-8.0 (m, 9H); Mass: $[ES]^+$: Calculated-377.08, Found-378.1003.

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REFERENCES

1) Srinivasan, M., Sunitha, P. G., and Deattu, N. (2024), International Journal of Pharmacy and Pharmaceutical Research, 30(1), 70–81.
2) Kotnala, M., Singh, G., Singh, K., Nath, R., Panda, K. C., Kumar, A., and Dutta, S. (2024), Naturalista Campano, 28(1), 3238–3248.
3) Pimenova, E. V., and Voronina, E. V. (2001), Pharmaceutical Chemistry Journal, 35(11), 602–604.
4) Bailey, D. M., Hansen, P. E., Hlavac, A. G., Baizman, E. R., Pearl, J., DeFelice, A. F. and Feigenson, M. E. (1985), Journal of Medicinal Chemistry, 28(2), 256-260.
5) Nugent, R. A., Murphy, M., Schlachter, S. T., Dunn, C.J., Smith, R. J., Staite, N. D., Galinet, L. A., Shields, S. K., Aspar, D. G., Richard, K. A., and Rohloff, N. A. (1993), Journal of Medicinal Chemistry, 36(1), 134-139.
6) Park, H. J., Lee, K., Park, S. J., Ahn, B., Lee, J. C., Cho, H., and Lee, K. I. (2005). Bioorganic & Medicinal Chemistry Letters, 15(13), 3307–3312.
7) Janus, S. L., Magdif, A. Z., Erik, B. P., and Claus, N. (1999). Monatshefte für Chemie, 130, 1167–1174.
8) Carroll, R. T., Dluzen, D. E., Stinnett, H., Awale, P. S., Funk, M. O., and Geldenhuys, W. J. (2011), Bioorganic & Medicinal Chemistry Letters, 21(16), 4798–4803.
9) Havrylyuk, D., Zimenkovsky, B., and Lesyk, R. (2009), Phosphorus, Sulfur, and Silicon and the Related Elements, 184(3), 638–650.
10) Diurno, M. V., Mazzoni, O., Correale, G., Monterrey, I. G., Calignano, A., La Rana, G., and Bolognese, A. (1999), Il Farmaco, 54, 579–583.
11) Wu, Y., Karna, S., Choi, C. H., Tong, M., Tai, H. H., Na, D. H., Jang, C. H., and Cho, H. (2011), Journal of Medicinal Chemistry, 54(14), 5260–5264.
12) Chilamakuru, N. B., Neelima, S., Supriya, G., Sarvesha, E., Rama Devi, S., Maheswari, M. U., Mukesh, S., and Triveni, S. (2025), Oriental Journal of Chemistry, 41(1), 30–43.
13) Zipser, A. (1903), Chemisches Zentralblatt, 1, 283.
14) Brown, F. C., Bradsher, C. K., and Chilton, S. W. (1956), Journal of Organic Chemistry, 21(11), 1269–1271.
15) Bhargava, P. N., and Goswami, G. (1955), Journal of the Indian Chemical Society, 32, 763.
16) Tunçbilek, M., Bozdağ Dündar, O., Ayhan Kılcigil, G., Ceylan, M., Waheed, A., Verspohl, E. J., and Ertan, R. (2003), Il Farmaco, 58(1), 79–83.
17) Ohishi, Y., Mukai, T., Nagahara, M., Yajima, M., and Kajikawa, N. (1992), Chemical & Pharmaceutical Bulletin, 40(4), 907–911.
18) Popov-Pergal, K., Chekovich, Zh., & Pergal, M. (1994), Russian Journal of General Chemistry, 61, 2112.
19) Mahalle, S. R., Netankar, P. D., Bondge, S. P., and Mane, R. A. (2008), Green Chemistry Letters and Reviews, 1(2), 103–106.
20) Mali, J. R., Pratap, U. R., Netankar, P. D., and Mane, R. A. (2009), Tetrahedron Letters, 50(35), 5025–5027.
21) Kolsepatil, S. R., Pahade, N. V., Deshmukh, S. U., Netankar, P. D., and Lingampalle, D. L. (2018), Heterocyclic Letters, 8(1), 105–110.
22) Shaikh, A. A., Mohamad, A., Netankar, P., & Sayyad, S. K. (2019), Asian Journal of Pharmacy and Pharmacology, 5(3), 513–517.