



Tungstic acid catalysed Knoevenagel condensation: Synthesis of 5-arylidene -2, 4-thiazolidinediones

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ABSTRACT

The Knoevenagel condensation between aromatic aldehyde and 2,4-thiazolidinedione catalysed by solid acid catalyst, tungstic acid is presented. Tungstic acid is heterogeneous, cheaper and reusable catalyst. The resulting products 5-arylidene-2, 4-thiazolidinediones are highly useful for precursors of hypoglycaemic agent.

Keywords: 5-Arylidene-2, 4-thiazolidinedione, heterogeneous, Tungstic acid, Knoevenagel condensation.

I. INTRODUCTION

The Knoevenagel condensation between aromatic aldehyde with active methylene compound is one of the important C-C bond forming reactions in organic synthesis. The reaction is useful in the synthesis of substituted alkenes, α , β -unsaturated nitriles, esters, acids, dyes and polymers.¹⁻⁵

5-Arylidene -2,4-thiazolidinediones are important structural elements in medicinal chemistry and are found to possess significant hypoglycaemic, anti-inflammatory, aldosereductase inhibitor, tyrosine phosphate inhibitor, antihypertensive and anticancer activities. It can act as potentially challenging aldose reductase inhibitors and 15-hydroxyprostaglandin dehydrogenase inhibitor.⁶⁻

⁸Knoevenagel condensation of 5-arylidene- 2, 4 thiazolidinedione with aldehyde is a key step in synthesis of some clinically used antidiabetic agents like rosiglitazone, englitazone and netoglitazone.⁹⁻¹⁰ 2,4-thiazolidinedione is an active methylene compound which useful in the synthesis of potent antidiabetic compounds as well as other biological active compounds.¹¹

5-Arylidene-2, 4-thiazolidinediones are usually synthesised using different catalysts like ethylenediammonium diacetate,¹² polyethylene

glycol,¹³ ammonium acetate,¹⁴ Thiourea,¹⁵ L-proline,¹⁶ baker's yeast,¹⁷ alum,¹⁸ pyridine,¹⁹ hydrochloric acid,²⁰ ionic liquid²¹ and piperidine.²²

The used of above catalysts having some drawbacks like catalyst not reusable, reaction required longer time period, low yields of the products, tedious work up, therefore there is need to develop new protocol.

Literature reveals that the Knoevenagel condensation is base catalysed reaction, especially for the synthesis of 5-arylidene-2, 4-thiazolidinediones base is needed, there is no use of acid as a catalyst. In view of this we have attempted first time acid catalysed Knoevenagel condensation for synthesis of 5-arylidene-2, 4-thiazolidinediones.

Tungstic acid used as solid catalyst in organic synthesis for different advantages like recovery and reusability, easy isolation because of insolubility of catalyst in organic solvent. Therefore recyclability of catalyst is possible.²³⁻²⁴

Tungstic acid refers to hydrated forms of tungsten trioxide, WO_3 . The simplest form, the monohydrate, is $WO_3 \cdot H_2O$, the dihydrate $WO_3 \cdot 2H_2O$ is also known. The solid state structure of $WO_3 \cdot H_2O$ consists of layers of octahedral coordinated $WO_5 (H_2O)$ units where 4

vertices are shared. The dihydrate has the same layer structure with the extra H₂O molecule intercalated between the layers. The monohydrate is a yellow solid and insoluble in water. The classical name for this acid is acid of wolfram.²⁵

Tungstic acid catalysis is not much explored as a catalyst but there are some reports available where it is used as a catalyst in reactions like oxidation of cyclohexanone, synthesis of 3,3-bis(1H-indol-3-yl)indolin-2-one²⁶, hydroxylation of olefins and epoxidation of olefins.

In view of the pharmacological importance of 5-arylidene-2,4-thiazolidinediones and the drawbacks associated with their reported methods, therefore here it was thought worthwhile to develop a safer route for the synthesis of 5-arylidene-2,4-thiazolidinediones by using tungstic acid as a catalyst.

II. RESULTS & DISCUSSION

Here, Knoevenagel condensation between aromatic aldehyde with 2,4-thiazolidinedione as active methylene compound for the formation of highly biologically active compound 5-arylidene-2,4-thiazolidinedione using tungstic acid as an efficient catalyst is described.

In order to get the best experimental conditions the reaction of benzaldehyde with 2,4-thiazolidinedione in the presence of tungstic acid (15 mol%) as a model reaction in different solvents.

Initially the model reaction was carried out in ethanol at room temperature but we found that there is no formation of the desired product. Then we changed the solvent and used solvents like methanol, acetonitrile, benzene and N,N-dimethylformamide. Then also there is no formation of the desired product even after 30 hours of stirring.

Then it was thought to do the reaction at reflux temperature in the above solvents i.e. ethanol, methanol, acetonitrile, benzene, and N,N-dimethylformamide (DMF). From the above mentioned solvents only in N,N-dimethylformamide was an excellent 89% yield of the product (**Table 1**) as compared to other solvents at 100 °C in 12 hours. Thus the N,N-dimethylformamide was chosen as a solvent for further studies.

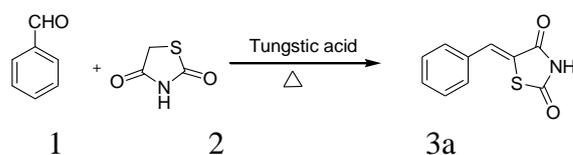
To check the effect of catalyst the model reaction was run without catalyst in DMF at 100 °C but there is no formation of the desired product even after 20 hours. From the above experiment it was confirmed that the reaction is catalysed by tungstic acid.

After getting the best solvent for this transformation it was decided to vary the catalyst amount to find out the optimum amount of catalyst. Then the model reaction was run with 5, 10, 15, 20 mol % catalyst. After analysis of the results we concluded that the model reaction with 15 mol % catalyst gives better results, therefore the model reaction in DMF and 15 mol % catalyst at 100 °C was selected for onward reactions.

Then the variety of aromatic aldehydes with substitution either electron donating or electron withdrawing group at ortho, meta and para positions of benzaldehyde were successfully condensed with 2,4-thiazolidinedione under optimum conditions for the formation of the desired products (**Table 2** entry 1-10) and also the heterocyclic aldehyde is successfully used for the condensation to obtain heteroaryl-2,4-thiazolidinedione (**Table 2** entry 11-12).

The geometry of 5-arylidene-2,4-thiazolidinedione may be E or Z. It is well known that E and Z isomers can be distinguished by the ¹H NMR spectral characterisation. Benzylidene proton appears below 7.42 δ ppm in the E isomer and above 7.90 δ ppm in the Z isomer. From the spectral data (¹H NMR), it was confirmed that the entire product obtained are Z isomers.

The catalyst used is heterogeneous and it provides a surface for the completion of condensation between aldehydes and 2,4-thiazolidinedione. Plausibly the reaction is accelerated due to tungstic acid because it protonates aldehydes to make them more electrophilic and then the conjugate base of tungstic acid abstracts a proton from the active methylene of 2,4-thiazolidinedione. Then 2,4-thiazolidinedione attacks the aldehyde to form a new C-C bond and in the last step there is dehydration leading to the final product, arylidene-2,4-thiazolidinedione.



Scheme 1.

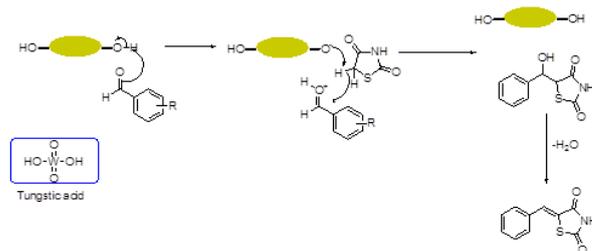


Figure 1. Plausible mechanism of Knoevenagel condensation of aryl aldehyde and 2,4-thiazolidinedione.

Table 1. Screening of solvent on synthesis of synthesis of 5-benzylidene-2, 4-thiazolidindione by using tungstic acid.^a

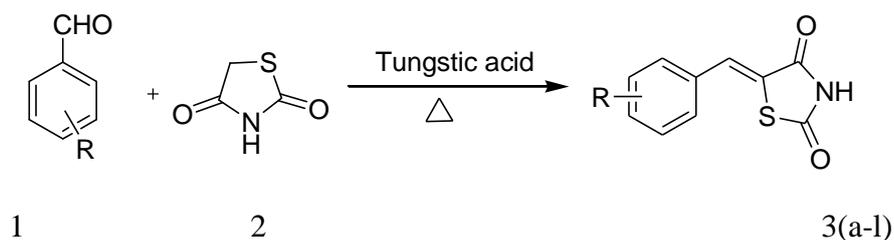
Entry	Solvent	Time (hrs)	Yield ^b (%)
1	Ethanol	20	15
2	Methanol	20	20
3	Benzene	20	Trace
4	DMF	12	89
5	Water	20	-
6	Acetonitrile	20	30

^aReaction condition : benzaldehyde 5 mmol, 2,4-thiazolidinedione 5 mmol, tungstic acid 15 mol % in 15 mL solvent under reflux . ^bIsolated yield.

Table2. Screening of catalyst for the synthesis of 5-benzylidene-2, 4-thiazolidindione ^a

Sr. No.	Catalyst (%)	Time (hrs)	Yield(%)
1	0	20	-
2	5	20	-
3	10	20	-
4	15	12	89
5	20	12	90

^aReaction condition : benzaldehyde (5 mmol), 2,4-thiazolidinedione (5 mmol), tungstic acid 15 mol % in 15 mL DMF solvent at 100 °C for 12 h. . ^bIsolated Yield.



Scheme 2.

Table 3. Synthesis of arylidene -2, 4-thiazolidinediones by using tungstic acid.^a

Entry	R	Product ^c	Yield ^b (%)	Melting point (°C)
1	H	3a	89	238-240
2	4-NO ₂	3b	70	258-260
3	4-Cl	3c	65	228-230
4	4-OMe	3d	72	218-220
5	4-N(CH ₃) ₂	3e	67	280-282
6	4-OH	3f	70	308-310
7	2-Cl	3g	66	210-212
8	3-NO ₂	3h	60	188-190
9	2-OH	3i	65	228-230
10	5-Br, 2-OH	3j	55	232-234
11	Furyl	3k	65	240-242
12	2-Chloro 3-formyl quinoline	3l	60	242-244

^aReaction condition : benzaldehyde 5 mmol, 2,4-thiazolidinedione 5 mmol, tungstic acid 15 mol % in 15 ml DMF solvent at 100 °C for 12 h. ^bIsolated Yield. ^cProducts are confirmed by the comparison of their physical constants and spectral data i.e. ¹H-NMR, ¹³C-NMR, MS with those are reported in the literature.^{17, 21}

III. EXPERIMENTAL SECTION

General: All chemicals used were obtained from commercial suppliers and used without further purification. Progress of the reaction was monitored by thin layer chromatography on MERKs silica plate. Melting point taken in open capillary method. FTIR Spectra were recorded on IR AFINITY spectrometer with KBr pallet. ¹H-NMR & ¹³C-NMR were recorded on Bruker DRX FT NMR at 300 MHz using TMS as internal standard. Mass spectral data were obtained by JEOL accuTOF DART mass spectrometer.

General experimental procedure for synthesis for 3 (a-l) compounds:

A mixture of 2, 4-thiazolidinedione (5 mmol), benzaldehyde (5 mmol), tungstic acid (0.18 g), was taken in RB flask with DMF (15 mL). Reaction mixture was heated at 100 °C with continuous stirring. Progress of reaction was monitored by thin layer chromatography in ethyl acetate: hexane (1:3) solvent system. After completion of the reaction, catalyst was removed by

filtration with washing with excess of ethanol. Filtrate was concentrated under vacuum. Precipitated solid was recrystallized with ethanol. Finally all compounds are confirmed by melting point and spectral characterisation.

5-Benzylidene-2, 4-thiazolidinedione (3a):

FTIR (KBr, cm⁻¹) 3300, 3100, 1740, 1710, 1580.

¹H-NMR (300 MHz, DMSO-d₆): δ 7.48 (m, 5H), 7.79 (s, 1H), 12.64 (s, 1H).

¹³C-NMR (100 MHz, DMSO)- δ 123.5, 129.34, 130.04, 130.44, 131.80, 133.04, 167.35, 167.91.

DART-MS (ESI+, m/z): 206 (M+).

IV. CONCLUSION

In summary, we have first time used solid acid catalyst for the Knoevenagel condensation of aryl aldehydes and 2, 4-thiazolidinediones. The developed protocol is an efficient, eco-friendly and catalyst tungstic acid is reusable.

V. ACKNOWLEDGMENT

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VI. REFERENCES

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