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Silica Supported Dodecatungstophosphoric Acid (DTP/ SiO_2) Mediated Synthesisof 4-Thiazolidinone Derivatives

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1 **Research Paper - Chemistry**

ABSTRACT

The DTP/SiO_2catalyzed one pot multicomponent synthesis of 4-thiazolidinone reported by the reaction of aromatic aldehydes, anilines, and mercaptoacetic acid. The recovered catalyst was reused for four to five cycles. Moreover, this method includes high yields, easy workup, recyclability, functional group flexibility and less reaction time

Keywords: DTP/SiO_2, Multicomponent reactions, 4-Thiazolidinones, Green synthesis

Introduction:

Heterocyclic compounds have attracted a lot of attention due to their number of biological activities. Specifically, five-membered heterocycles with two heteroatomshave received particular attention, having proven utility in medicinalchemistry. Among them, 4-thiazolidinones represent avery important class of fivemeberedheterocycles. Some of the thiazolidinones are found to possess good biological activities such as anticancer, anti-HIV, antimalarial, antibacterial,tuberculostatic,antihistaminic, anticonvulsant and antiarrythmic activity **[1-9]**. Etozoline, pioglitazone,ralitoline, and thiazolidomycin have this heteryl ring and arealready in the market as medicaments.This diversity in the biological responseprofile has attracted much attention from many researchers to explore this skeletonfor its multiple potential activities.

Furthermore, 4-thiazolidinones derivative have antiproliferative activity against Reh and Nalm6 cells **[10]**, antiapoptotic biocomplex, Cyclin B/CDK1 inhibitor **[11]**,,

MCF-7[12],tumour necrosis factor (TNF) [13] integrin avb3 receptor [14], HT29 colon cancer cell line [15], and breast cancer JSP-1 inhibitor [16]**Figure 1** shows the structure of exemplary bio-active 4-thiazolidinonederivatives.

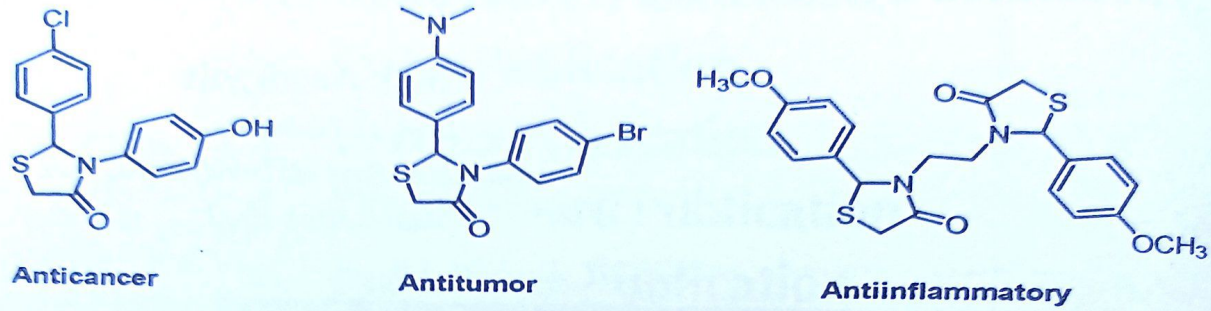


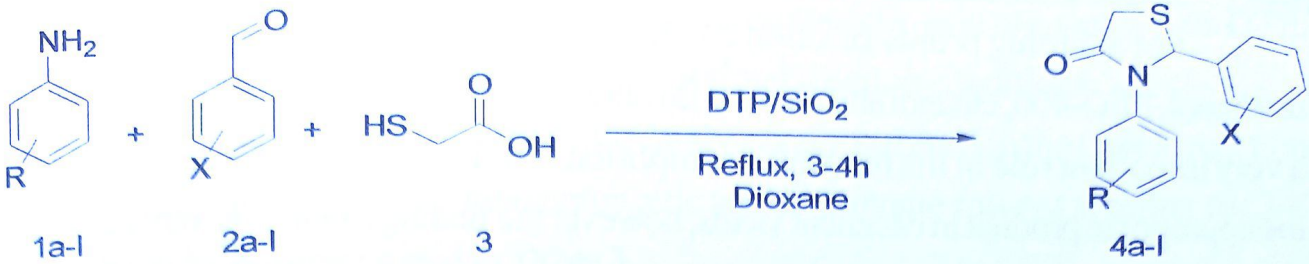
Fig.1. Some bio-active 4-thiazolidinones derivatives.

Literature survey show that due to wide range of pharmacological activity number of catalytic protocol have been established including,N,N'-dicyclohexylcarbodiimide (DCC),[17]O-(benzotriazol-yl)-N,N,N',N'-tetramethyluronium hexafluoro phosphate (HBTU),[18]ferrite,[19]$ZnCl_2$,[20]sodium sulfate,[21][bmim][PF_6][22],activated fly ash.[23]The use of microwave heating,[24]solidphase,[25]polymer supported[26]acetic acid [27] and ammonium persulfate [28] etc.

However above-mentioned protocol has one or more drawbacks including, acetic acid is hazardous in naturewhile most of them require heating condition as well as longer reaction time. Considering above facts here report the first-time synthesis of 4-thiazolidinone derivatives using DTP/SiO_2 as a catalyst to give good to prominent yields, easy workup, no column chromatography is benifit of this protocol.

Results and discussion

The reaction between substituted aniline(0.001 mmol), benzaldehyde (0.001 mmol) and mercaptoacetic acid (0.001 mmol) in dioxane in the presence of Silica Supported Dodecatungstophosphoric Acid (DTP/SiO_2) as a catalyst. The product was synthesized after refluxing the reaction mixture for 3-4 Hours. 4-thiazolidone derivatives**(4a-l)** were obtainedwith high purity and better yields, as shown in**Scheme 1.**



R= 4-CH_3, 4-OCH_3, 4-Br, 4-Cl, H, 4-F.
X= 4-Cl, H,4-CH_3, 4-OCH_3, 4-NO_2,

Scheme1. Synthesis of 4-thiazolidinone using DTP/SiO_2

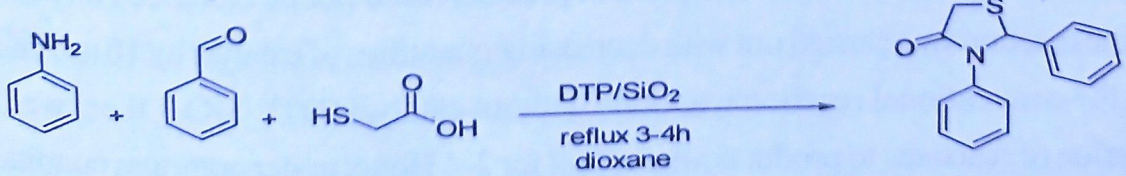
Table 1:

DTP/SiO_2 catalyzed synthesis of 4-thiazolidinones in dioxane[a]

Entry	R	X	Product	Yield[b](%)
1	4-Cl	4-CH_3	4a	86
2	4-Br	H	4b	88
3	4-OCH_3	H	4c	85
4	4-CH_3	4-Cl	4d	89
5	H	H	4e	85
6	4-CH_3	4-CH_3	4f	84
7	4-F	H	4g	90
8	H	4-OCH_3	4h	83
9	4-CH_3	H	4i	90
10	H	4-CH_3	4j	86
11	4-Cl	4-NO_2	4k	84
12	4-Cl	H	4l	87

[a]Reaction conditions: aryl aldehyde (1 mmol), aryl amine (1 mmol), thioglycolicacid (1mmol), and DTP/SiO_2 (10%) in dioxane (5mL) reflux, 3-4h.[b]Isolated yields.

Optimization of the reaction parameters was performed bymodel reaction of substituted aniline, benzaldehyde and mercaptoacetic acidas shown below.



Scheme 2. Model reaction for Synthesis of 4-thiazolidone.

For attaining proper reaction conditions some solvents are tested such water, methanol, PEG-400, ethanol and dioxane. In optimization it is observed that solventsplays a very important role in the reaction's complition. The reaction with dioxane produced the appropriate product in excellent yields, however the findings with some other solvents such as methanol, PEG-400, ethanol produced the product ina reduced amount of quantities, and in water conversion of reactant to product was minimum. Furthermore, it was determined that dioxane was the most promising and suitable solvent for this conversion.

Table 1. Screening of reaction conditions with respect to solvent and catalyst loading **4a[a].**

Entry	Solvent	Catalyst(mol%)	Yield[b](%)
1	Water	10% DTP/SiO_2	12
2	Methanol	10% DTP/SiO_2	51
3	Ethanol	10% DTP/SiO_2	49
4	PEG-400	10% DTP/SiO_2	58
5	Dioxane	5% DTP/SiO_2	82
6	Dioxane	10% DTP/SiO_2	90
7	Dioxane	15% DTP/SiO_2	88
8	Dioxane	No catalyst	09

[a]Reactionconditions:

aniline (1 mmol), benzaldehyde (1mmol) and mercaptoacetic acid (1mmol), DTP/SiO_2 (10%) in dioxane (5mL) reflux, 3-4h.[b]Isolated yields, NR: No Reaction.

The effect of catalyst loading was also tested in the model reaction. According to the study, a catalyst concentration of 10 mol% was an very good choice for this reaction. Increasing the catalyst concentration by 10 to 15 mol% had a very feweffect on yield and should not be again increased. The yield of productcould not be enhanced any further when the reaction was carried out with decreasing quantities of catalyst by 10 to 5 mol%. When the conventional reaction was done without catalyst (DTP/SiO_2), there was less conversion of reactants to products after reflux for 3-4 Hours under optimum conditions.

This finding prompts us to develop protocol for synthesising 4-thiazolidone from

substituted aromatic aldehydes, anilines, and mercaptoacetic acid utilising a 10% DTP/SiO_2 catalyst and dioxane as a solvent under optimal reaction conditions.

The recyclability of the DTP/SiO_2 catalyst was examined in the typical reaction of aniline, benzaldehyde , and mercaptoacetic acid in dioxane solvent at reflux for 3-4 hours. Results are summarized in **Table 3**.

Table 3. The recyclability of DTP/SiO_2 Catalyst.

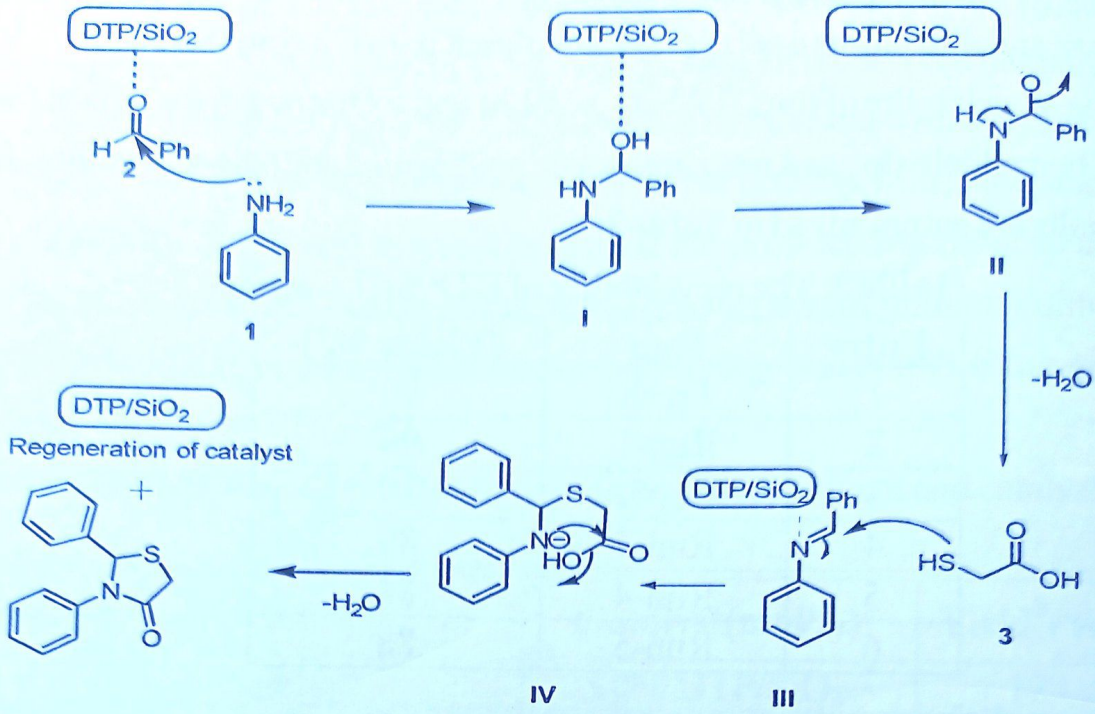
Entry	Run	(Yields %[b])
1	Fresh	90
2	Run-1	90
3	Run-2	89
4	Run-3	89
5	Run-4	88
6	Run-5	88

[a]**Reaction conditions:**

aniline(0.001mmol), benzaldehyde (0.001mmol), and mercaptoacetic acid (0.001mmol),), DTP/SiO_2 (10%) in dioxane (5mL) reflux, 3-4h, [b]Isolated yields.

The catalyst was collected and washed with water. After drying, the recovered catalyst was used for the next cycle. In each of the four reactions, the catalyst was reused, and the target compounds were synthesized in high yields (90% to 88%) within their respective reaction times and condition.

DTP/SiO_2catalyzed reaction mechanism for the synthesis of 4-thiazolidinones. In the first step, benzaldehyde is activated, then aniline is nucleophilically substituted, results in the formation of **I** intermediate. The next step is to remove water molecules from intermediates **I** using DTP/$SiO_2$to produce imine product **II**. Intermediate **III** reacts with mercaptoaceticacid to produce cycloaddition product **IV** in the third stage. Regeneration of the catalyst and further intramolecular cyclization to generate the final product via elimination of the H_2O molecule. **Scheme 3** explains the reaction mechanism in detail.



Scheme 3. Plausible mechanism for the synthesis of 4-thiazolidinones.

Conclusion

Finally, we devised a mild, efficient, approach for synthesising4-thiazolidinones (4a-l) from substituted aniline, benzaldehyde and mercaptoacetic acidusingSilica Supported Dodecatungstophosphoric Acid (DTP/SiO_2) as recyclable acid catalyst. The protocol's major features are simple reaction conditions, no side reactions, and high yield product formation. The current approach is an alternative to traditional for synthesis of 4-thiazolidinonesproduction procedures. The catalyst was retrieved multiple times without loss of catalytic activity, resulting in a cost-effective method.

Experimental

General experimental procedure for the synthesis of4-thiazolidone

In a dry and clean 50ml round bottom flask, a mixture of substituted aniline(0.001mmole) benzaldehyde (0.0011mmol),and mercaptoaceticacid (0.001mmol),wasrefluxed in 5 ml dioxane as a solvent along with DTP/SiO_2(10mole%) as a catalyst for 3-4 Hours. The progress of the reaction was monitored by thin-layer chromatography. After completion of reaction, reaction mixture was diluted with ethyl acetate and catalyst was recovered by filtration. The filtrate was washed with aqueous

$NaHCO_3$ and then with water followed by separation of aqueous layer and organic layer. The organic layer is dried over anhydrous Na_2SO_4 and concentrate in vacuum to gives the crude product. The crude product was purified by crystallization using ethanol to afford the pure 4-thiazolidone.The melting points of the products isolated in this study were found to be in good agreement with those reported in literature.

Spectral data of some synthesized compounds :

2-(4-chlorophenyl)-3-(p-tolyl)thiazolidin-4-one (4a):

As yellow solid; Mp: 163-164 °C; Yield: 89%; ^{1}H NMR (400 MHz, $CDCl_3$, ä ppm): 2.29 (s, 3H, CH_3),3.85 (d, 1H, J = 16 Hz), 3.99 (d, 1H, CH_2, J = 16 Hz), 6.05 (s, 1H, S-CH-N), 7.02 (dd, J = 8.2, 2.8 Hz, 2H), 7.09 (d, J = 6.2 Hz, 2H) and 7.25 (dd, J = 8.0, 4.4 Hz, 4H); ^{13}C NMR (101 MHz, cdcl$_3$) ä 20.31, 32.72, 64.30, 124.96, 128.32, 129.19, 132.88, 134.00, 135.11, 137.44 and 171.16.

3-(4-bromophenyl)-2-phenylthiazolidin-4-one (4b):

As white solid; Mp: 113-114°C ; Yield: 85%; ^{1}H NMR (400 MHz, $CDCl_3$, ä ppm): 3.85 (d, 1H, J = 16 Hz), 3.96 (d, 1H, CH_2, J = 16 Hz), 6.08 (s, 1H, S-CH-N), 7.11 (dd, J= 6.6, 4.7 Hz, 2H) and 7.38-7.41 (m, 7H).

3-(4-methoxyphenyl)-2-phenylthiazolidin-4-one (4c):

As yellow solid; Mp: 61-62 °C ; Yield: 90%; ^{1}H NMR (400 MHz, $CDCl_3$, ä ppm): 3.81 (d, 1H, J = 16 Hz), 3.85 (s, 3H, , CH_3), 3.95 (d, 1H, CH_2, J = 16 Hz), 6.11 (s, 1H, S-CH-N), 7.24-7.13 (m, 5H), 7.46 (d, J = 8.4 Hz, 2H) and 7.81 (d, J = 8.2 Hz, 2H).

2,3-Diphenylthiazolidin-4-one(4e):

As white solid; Mp: 128-130 °C; Yield: 87%; ^{1}H NMR (400 MHz, $CDCl_3$, ä ppm): 3.82 (d, 1H, J = 16 Hz), 3.96 (d, 1H, J = 16 Hz), 6.08 (s, 1H, S-CH-N), 7.24 (d, J = 7.9 Hz, 3H) and 7.28 (dd, J = 9.6, 4.9 Hz, 7H).

2,3-di-p-tolylthiazolidin-4-one (4f):

As white solid; Mp: 122-123 °C ; Yield: 90%; ^{1}H NMR (400 MHz, $CDCl_3$, ä ppm): 2.31 (s, 6H, CH_3), 3.85 (d, 1H, J = 16 Hz), 3.95 (d, 1H, CH_2, J = 16 Hz), 6.13 (s, 1H, S-CH-N), 7.54 (d, J = 8.1 Hz, 4H) and 7.85 (d, J = 8.2 Hz, 4H).

3-(4-fluorophenyl)-2-phenyl thiazolidin-4-one (4g):

As white solid; Mp: 114-116 °C ; Yield: 84%; ^{1}H NMR (400 MHz, $CDCl_3$, ä ppm): 3.77 (d, 1H, J = 16 Hz), 3.82 (d, 1H, CH_2, J = 16 Hz), 6.08 (s, 1H, S-CH-N), 6.96 (dd, J = 24.1, 6.9 Hz, 2H) and 7.21-7.05 (m, 7H).

2-(4-methoxyphenyl)-3-phenylthiazolidin-4-one (4h):

As white solid; Mp: 99-101 °C ; Yield: 90%; ^{1}H NMR (400 MHz, $CDCl_3$, ä ppm): 3.84 (s, 3H, -OCH_3), 3.98 (d, 1H, J = 16 Hz), 4.11 (d, 1H, CH_2, J = 16 Hz), 6.10 (s, 1H, S-CH-N), 7.40-7.26 (m, 5H), 7.65 (d, J = 8.3 Hz, 2H) and 7.88 (d, J = 8.1 Hz, 2H).

2-phenyl-3-(p-tolyl)thiazolidin-4-one (4i):

As white solid; Mp: 111-113 °C; Yield: 89%; ^{1}H NMR (400 MHz, $CDCl_3$, ä ppm): 2.28 (s, 3H, CH_3), 3.90 (d, 1H, J = 16 Hz), 3.97 (d, 1H, CH_2, J = 16 Hz), 6.05 (s, 1H, S-CH-N), 7.16 (m, 2H), 7.25 (d, J = 8.3 Hz, 2H) and 7.38-7.26 (m, 5H).

3-Phenyl-2-(p-tolyl)thiazolidin-4-one (4j):

As brown solid; Mp: 116-118 °C; Yield: 87%; ^{1}H NMR (400 MHz, $CDCl_3$, ä ppm): 2.39 (s, 3H, CH_3), 3.89 (d, 1H, J = 16 Hz), 4.02 (d, 1H, CH_2, J = 16 Hz), 6.05 (s, 1H, S-CH-N), 7.15 (dt, J = 6.4, 5.1 Hz, 4H) and 7.30-7.35 (m, 5H).

3-(4-chlorophenyl)-2-(4-nitrophenyl)thiazolidin-4-one (4k):

As white solid; Mp: 148-150 °C; Yield: 84%; ^{1}H NMR (400 MHz, $CDCl_3$, ä ppm): 3.84 (d, 1H, J = 16 Hz), 4.02 (d, 1H, CH_2, J = 16 Hz), 6.17 (s, 1H, S-CH-N), 7.13 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 7.55 (d, J = 8.6 Hz, 2H) and 8.18 (d, J = 8.2 Hz, 2H).

3-(4-Chlorophenyl)-2-phenylthiazolidin-4-one (4l):

As white solid; Mp: 108-110 °C; Yield: 84%; ^{1}H NMR (400 MHz, $CDCl_3$, ä ppm): 3.80 (d, 1H, J = 16 Hz), 3.88 (d, 1H, CH_2, J = 16 Hz), 5.99 (s, 1H, S-CH-N), 7.17-7.01 (m, 5H), 7.31-7.27 (m, 2H) and 7.41-7.27 (m, 2H).