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Synthesis of some new bis-3,4-dihydropyrimidin-2(1H)-ones by using silica-supported tin chloride and titanium tetrachloride

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Abstract

Silica-supported tin chloride and titanium tetrachloride were prepared by the reaction of tin chloride and titanium tetrachloride with activated silica gel in refluxing toluene. These solid acids have been employed as the catalysts for the synthesis of bisdihydropyrimidin-2(1H)-ones from aromatic dialdehydes, 1,3-dicarbonyl compounds and urea at 90 °C under solvent-free conditions.

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Heterogenization of homogeneous catalysts has been an interesting area of research from the industrial point of view; this could provide an ideal method for combining the advantages of homogeneous catalysts (high activity and selectivity, etc.) with the engineering advantages of heterogeneous catalysts (easy catalyst separation, long catalytic life, easy catalyst regenerability, thermal stability and recycle) [1]. Therefore, attachments of the Lewis acids on solid supports have received much attention. One way to convert corrosive strong Lewis acids into environmentally friendlier catalysts is to heterogenize soluble Lewis acids used in liquid-phase reactions by supporting them on high-surface-area solids, such as graphite, Al_2O_3 , SiO_2 , zeolites, clays, etc. Basically, the support has to be thermally and chemically stable during the reaction process and has to provide accessibility and a good dispersion of the active sites [1,2]. In the continuation of our studies on the design and application of solid acid catalysts in organic transformations [3], herein, we wish to report the preparation of silica-supported tin tetrachloride and titanium tetrachloride by the reaction of tin chloride and titanium tetrachloride with activated silica gel in refluxing toluene (Scheme 1). These solid acids have been used as catalyst in a one-pot three component reaction of β -dicarbonyl compounds, aromatic dialdehydes and urea under solvent-free conditions for the synthesis of bis-3,4-dihydropyrimidin-2(1*H*)-ones.

Dihydropyrimidinone derivatives (DHPMs) have been taken into considerable interest in recent years because these types of compounds exhibit attractive pharmacological profiles as calcium channel blockers, antihypertensive agents, α 1-antagonists and neuropeptide Y (NPY) antagonists [4]. In addition, several marine alkaloids containing the dihydropyrimidinone-5-carboxylate motifs also showed interesting biological properties [5]. The Biginelli reaction,

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Scheme 1. Probable structure of covalently anchored silica-supported tin or titanium tetrachloride.

first described more than a century ago and recently reviewed [6], consists of the acid-catalyzed cyclocondensation reaction of ethyl acetoacetate, benzaldehyde and urea. A major drawback of the classical Biginelli reaction is the poor to moderate yields, particularly when substituted aromatic aldehydes were employed. Therefore, several improved procedures for the preparation of Biginelli compounds' have been reported during the last two decades [7], including microwave irradiation, Lewis acids, ionic liquids, solid acids and supported catalysts [8–12].

However, attention has so far been mainly paid to the synthesis of mono-3,4-dihydropyrimidinones, while synthesis of bis-3,4-dihydropyrimidin-2(1H)-ones has been seldom reported [13,14].

Herein, we would like to use silica-supported tin chloride and titanium tetrachloride as catalyst for the synthesis of bis-3,4-dihydropyrimidin-2(1H)-ones. We have synthesized these bifunctional compounds containing two dihydropyrimidinone units (4), by using terephthaldicarbaldehyde and isophthal-dicarbaldehyde as the precursor (Schemes 2 and 3).

It can be seen that by this protocol bis-dihydropyrimidinones **4a–e** were synthesized in very good yields (70–79%) by the reaction of dicarbaldehyde (1 mmol), 1,3-dicarbonyl compounds (2 mmol), and urea (3 mmol) in the presence of SiO_2-SnCl_{4-n} and SiO_2-TiCl_{4-n} (0.2 g) at 90 °C under solvent-free conditions and the results are shown in Table 1. Also, the reaction of 1,3-cyclohexadione with terephthaldicarbaldehyde, and urea under this condition afforded bis-dihydropyrimidinone **5** in 70% yield after 70 min heating at 90 °C (Scheme 3, Table 1).

It should be noted that, these reactions catalyzed by $SnCl_4$ and $TiCl_4$ in lower yields and longer reaction times. For example, bis-dihydropyrimidinone **4a**, was synthesized in 45-50% yield by the reaction of terephthaldehyde (1 mmol), ethyl acetoacetate (2 mmol), and urea (3 mmol) in the presence of $SnCl_4$ or $TiCl_4$ (0.25 mmol) at 90 °C after 30 min under solvent-free conditions.

In conclusion, we prepared some of the new bis-dihydropyrimidinone by using SiO_2 - $SnCl_{4-n}$ and SiO_2 - $TiCl_{4-n}$ as a catalyst in good yields under solvent-free conditions.



Scheme 2. Synthesis of bis-dihydropyrimidinones in the presence of SiO_2-MCl_{4-n} (M = Sn, Ti).



Scheme 3. Synthesis of bis-dihydropyrimidinones by using 1,3-cyclohexadione in the presence of SiO_2-MCl_{4-n} (M = Sn, Ti).

SiO_2 - $SnCl_{4-n}$ (I) and SiO_2 - $TiCl_{4-n}$ (II) catalyzed condensation reaction of 1,3-dicarbonyl compounds, dialdehydes and urea.						
Entry	Aldehyde	R ₂	Time (min) I (II)	Yield $(\%)^a \mathbf{I} (\mathbf{II})^b$	MP ($^{\circ}$ C) found	MP (°C) reported
4 a	онсСно	OEt	20 (20)	79 (75)	>300	>300 [13]
4b	ОНСССНО	OEt	20 (20)	72 (70)	260–261	>300 [13]
4c	онсСно	OMe	30 (35)	71 (72)	>300 (dec.)	-
4d	OHC, CHO	OMe	30 (35)	76 (71)	243–244	_

70 (73)

70 (71)

>300 (dec.)

>300 [13]

>300

30 (35)

70 (70)

^a Isolated yield.

4e

5

Table 1

^b The yields and times of catalyst **II** are written in paranthesis.

Me

1,3-Cyclohexadione

1. Catalyst preparation

Silica gel 60 (0.063–0.200 mesh) was washed with 1 mol/L HCl, followed by deionized water, 30% H₂O₂, and then again deionized water. After being washed, the silica was dried overnight at 373 K in vacuum to give preconditioned silica gel [1,15].

4.0 g of preconditioned silica was first refluxed in toluene for 2 h. Then tin chloride (5.5 mL) was added to the stirring mixture. This mixture was allowed to react for 1 day under refluxing condition. Then, the mixture was filtered. and washed three times with absolute ethanol and dried at 373 K to give 5.137 g of product.

2.2 g of preconditioned silica was first refluxed in toluene for 2 h. Then titanium tetrachloride (2.3 mL) was added to the stirring mixture. This mixture was allowed to react for 1 day under refluxing condition. Then, the mixture was filtered, and washed three times with absolute ethanol and dried at 373 K to give 3.3 g of product.

2. General procedure, synthesis of bis-dihydropyrimidinones 4a-4e, and 5

A mixture of dialdehyde (terphthaldehyde or isophthaldehyde) (0.134 g, 1 mmol), 1,3-dicarbonyl compounds (2 mmol), urea (0.18 g, 3 mmol) and SiO₂-SnCl_{4-n} or SiO₂-TiCl_{4-n} (0.2 g) were finely mixed together. The reaction mixture in a screw-capped vial containing a magnetic stirring bar was heated at 90 °C in a preheated oil batch (Table 1). After completion of the reaction, the mixture was washed with hot ethanol (2×20 mL). The ethanol solution was poured onto crushed ice (40 g) and stirred for 5-10 min. The solid separated was filtered under suction, washed with cold water (40 mL) and then recrystallized from hot ethanol to afford the pure product.

3. ¹H & ¹³C NMR data of compounds

Compound **4a**: ¹H NMR (300 MHz, DMSO-d₆): δ 1.08 (t, 6H, J = 5.20 Hz), 2.22 (s, 6H), 3.96 (q, 4H, J = 5.20 Hz), 5.09 (s, 2H), 7.16 (s, 4H), 7.70 (s, 2H), 9.18 (s, 2H). ¹³C NMR (75 MHz, DMSO-d₆): δ 14.51, 18.22, 54.14, 59.68, 126.29, 130.37, 144.40, 148.76, 152.58, 165.78. Compound **4b**: ¹H NMR (500 MHz, DMSO-d₆): δ 1.05–1.10 (m, 6H), 2.23 (s, 6H), 3.92–3.99 (m, 4H), 5.12 (s, 2H), 7.14 (d, 1H, J = 6.8 Hz), 7.18 (s, 2H), 7.28 (t, 1H, J = 7.2 Hz), 7.67 (s, 1H), 7.71 (s, 1H), 9.13 (d, 2H, J = 6.8 Hz). ¹³C NMR (125 MHz, DMSO-d₆): δ 14.92, 18.55, 18.63, 54.51, 54.80, 60.02, 60.09, 126.18, 127.15, 144.74, 145.88, 149.15, 149.18, 152.95, 153.01, 166.11, 166.22. Compound 4c: IR (KBr): 3231, 3112, 1700 cm⁻¹. ¹H NMR (500 MHz, DMSO-d₆): δ 2.24 (s, 6H), 3.54 (s, 6H), 5.12 (d, 2H, J = 3.2 Hz), 7.12 (s, 4H), 7.70 (s, 2H), 9.19 (s, 2H). ¹³C NMR (125 MHz, DMSO-d₆): δ 18.69, 51.70, 54.39, 127.17, 130.79, 144.63, 149.56, 153.04, 166.68. MS (m/z %): 414 [M⁺] (1.50), 368 (59.39), 349 (base peak), 313 (29.32), 273 (27.06), 236 (33.08), 169 (63.15), 137 (29.32), 111 (30.82), 97 (56.39), 83 (65.41), 69 (72.18), 57 (93.98), 43 (84.96). Anal. Calcd for C₂₀H₂₂N₄O₆: C: 57.96; H: 5.35; N: 13.51; Found, C: 57.70; H: 5.20; N: 13.33. Compound **7d**: IR (KBr): 3314, 3227, 1697 cm⁻¹. ¹H NMR (500 MHz, DMSO-d₆): δ 2.24 (s, 6H), 3.54 (s, 6H), 5.11 (s, 2H), 7.13 (s, 2H), 7.15 (s, 1H), 7.29 (t, 1H, J = 7.5 Hz), 7.73 (s, 1H), 7.76 (s, 1H), 9.20 (d, 2H, J = 9.19 Hz). ¹³C NMR (125 MHz, DMSO-d₆): δ 18.61, 18.63, 51.56, 54.58, 54.69, 124.76, 124.82, 126.06, 129.45, 145.75, 145.89, 149.38, 149.44, 153.01, 166.58. MS (m/z %): 414 [M⁺] (42.51), 382 (16.53), 349 (33.07), 339 (34.64), 323 (26.77), 245 (22.83), 169 (base peak), 137 (73.22), 110 (11.02), 96 (8.66), 42 (20.47). Anal. Calcd for C₂₀H₂₂N₄O₆: C: 57.96; H: 5.35; N: 13.51; Found, C: 57.67; H: 5.18; N: 13.31. Compound **7e**: IR (KBr): 3398, 3230, 1695 cm⁻¹. ¹H NMR (500 MHz, DMSO-d₆): δ 2.11 (s, 6H), 2.30 (s, 6H), 5.22 (s, 2H), 7.19 (s, 4H), 7.75 (s, 2H), 9.14 (s, 2H). ¹³C NMR (125 MHz, DMSO-d₆): δ 19.77, 31.25, 54.36, 54.41, 127.42, 130.78, 144.29, 148.93, 152.98, 195.03. MS (m/z %): 382 [M⁺] (3.14), 368 (26.77), 349 (59.05), 313 (24.40), 273 (14.96), 258 (25.98), 236 (31.49), 169 (11.81), 153 (29.92), 111 (29.13), 99 (66.14), 83 (59.84), 71 (65.35), 57 (98.42), 43 (base peak). Anal. Calcd for C₂₀H₂₂N₄O₄: C: 62.81; H: 5.79; N: 14.65; Found, C: 62.63; H: 5.63; N: 14.34. Compound **5**. ¹H NMR (300 MHz, DMSO-d₆): δ 1.93–2.49 (m, 12H), 5.05–5.11 (m, 2H), 7.01–7.19 (m, 4H), 7.69 (s, 2H), 9.45 (s, 2H).

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