Titanium(IV) chloride catalyzed one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and thiones

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Titanium(IV) chloride catalyses efficiently the three-component condensation reaction of an aldehyde, 1,3-dicarbonyl compound and urea or thiourea to afford the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones and thiones in high yields.

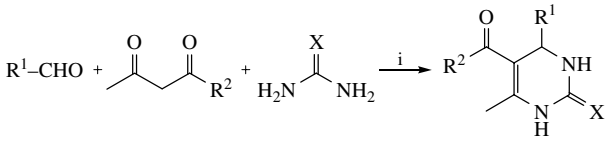
Dihydropyrimidinones and their sulfur analogues are pharmacologically important because of their antibacterial, antitumour and antiinflammatory properties.[1] Many of these compounds act as antihypertensive agents, as well as calcium channel blockers, α-1a-antagonists and neuropeptide Y antagonists.[2] The biological activity of recently isolated alkaloids has also been attributed to the presence of a dihydropyrimidinone moiety in the molecule.[3] The most important compounds of this type are batzelladine alkaloids, which are potent HIV gp 120-CD4 inhibitors.[4]

In 1893, Biginelli[5] reported the first synthesis of 3,4-dihydropyrimidin-2(1*H*)-one by refluxing a mixture of an aldehyde, a β-ketoester and urea under strongly acidic conditions. However, it suffers from low yields of the product, particularly in the case of substituted aromatic and aliphatic aldehydes. Recently, several methods have been reported for preparing 3,4-dihydropyrimidin-2(1*H*)-ones and thiones using Lewis acids[6] or protic acids such as H_2SO_4, HOAc and HCl[7] as promoters. Other methods including microwave irradiation, ionic liquids and clay[8] are also reported. However, many of these methods are associated with expensive and toxic reagents, stoichiometric amount of catalyst, longer reaction times, unsatisfactory yields, incompatibility with other functional groups and difficult product isolation procedures. Moreover, some of the methods are only practical for aromatic aldehydes.[6(a),(k),9] Thus, there is still a need for a simple and general procedure for the one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and thiones under mild conditions.

Titanium(IV) chloride is a moderately strong Lewis acid, which is used in the conversion of ketones to N-alkylimines, aldol condensation of aryl ketones with aryl aldehydes, Michael addition of silyl enol ethers to α,β-enones, conjugate allylation of α,β-enones *etc*.

Here, we report a simple and efficient synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and thiones using $TiCl_4$ as a catalyst.† The three-component mixture of an aldehyde, a 1,3-dicarbonyl compound and urea or thiourea was refluxed in ethanol in the presence of a catalytic amount of $TiCl_4$ for 2–3 h to give corresponding 3,4-dihydropyrimidin-2(1*H*)-ones or thiones in 85–95% yield. Most importantly, aromatic aldehydes carrying either electron donating or electron withdrawing substituents reacted very well to give the desired product in excellent yield (Table 1). Even aliphatic aldehydes, which normally show poor yield in the Biginelli reaction, afforded the product in high yield (Table 1). The procedure is equally effective for urea and thiourea.

In conclusion, a simple and general method for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and thiones by the Biginelli reaction using $TiCl_4$ as a catalyst is developed. The compatibility



1 **2** **3** **4a–s**

Scheme 1 *Reagents and conditions*: 0.2 equiv. $TiCl_4$, EtOH, 80 °C.

Table 1 Physical data of 3,4-dihydropyrimidin-2(1*H*)-ones and thiones.

Entry	R^1	R^2	X	*t*/min	Yield (%)	mp/°C found	mp/°C reported
4a	Ph	EtO	O	130	91	202–203	200–202[10]
4b	4-$NO_2C_6H_4$	EtO	O	100	95	208–209	205–207[10]
4c	4-ClC_6H_4	EtO	O	90	95	214	210–212[12]
4d	4-HOC_6H_4	EtO	O	140	94	230–231	228[11]
4e	*n*-Butyl	EtO	O	130	86	160–162	157–158[12]
4f	3-$NO_2C_6H_4$	EtO	O	140	93	228–230	225–227[10]
4g	4-pyridyl	EtO	O	130	90	186–187	—
4h	2-ClC_6H_4	EtO	O	130	88	218–220	216–218[10]
4i	2-furyl	EtO	O	90	94	204–205	203–205[12]
4j	4-$CF_3C_6H_4$	EtO	O	100	93	173–174	—
4k	Ph	MeO	O	90	91	212–214	209–216[15]
4l	4-$NO_2C_6H_4$	MeO	O	95	90	238–240	235–237[15]
4m	4-ClC_6H_4	Me	O	70	89	231–232	233–235[13]
4n	4-HOC_6H_4	Me	O	140	94	230–231	230[11]
4o	3-$NO_2C_6H_4$	Me	O	120	84	267–268[a]	267–269[a,15]
4p	3-$NO_2C_6H_4$	MeO	O	110	90	239–240[a]	240–241[a,15]
4q	2-ClC_6H_4	MeO	O	120	88	225–227	226–229[15]
4r	2-furyl	Me	O	90	94	216–217	217–219[13]
4s	Ph	EtO	S	120	91	209–212	208–210[14]

[a]With decomposition.

with various functional groups, mild reaction conditions, high yields and application of inexpensive, mild, readily and easily available $TiCl_4$ as a catalyst are the advantages of this procedure.

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† A mixture of aldehyde **1** (10 mmol), 1,3-dicarbonyl compound **2** (10 mmol), urea or thiourea **3** (15 mmol) and $TiCl_4$ (2 mmol) in ethanol was heated at 80 °C for an appropriate time as mentioned in Table 1. The reaction was monitored by TLC. After completion of reaction, the reaction mixture was poured into ice water and the precipitated solid was collected by filtration, washed with water and dried. The crude product obtained was recrystallised from ethanol to give pure compound as a white solid. All the synthesised compounds were characterised by ^{1}H NMR and ^{13}C NMR spectroscopy, mass spectrometry (ES-MS), elemental analysis and melting points. Elemental analyses were recorded on an EA 1108 CHNS-O Fisons instrument and are within ±0.4% of calculated values.

Ethyl 6-methyl-4-(4-pyridyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **4g**: ^{1}H NMR (200 MHz, [$^2H_6$]DMSO) δ: 9.38 (s, 1H, NH), 8.50 (d, 2H_{arom}), 7.85 (s, 1H, NH), 7.20 (d, 2H_{arom}), 5.15 (d, 1H, H-4, *J* 3.3 Hz), 4.00 (q, 2H, OCH_2), 2.27 (s, 3H, Me), 1.09 (t, 3H, Me, *J* 7.2 Hz). ^{13}C NMR (50 MHz, [$^2H_6$]DMSO) δ: 14.2, 14.9, 49.5, 61.7, 106.4, 124.3, 124.3, 146.5, 147.3, 149.9, 149.9, 150.3, 167.2. MS, *m/z*: 260 (M – H). Found (%): C, 59.97; H, 5.81; N, 16.01. Calc. for $C_{13}H_{15}N_3O_3$ (%): C, 59.76; H, 5.79; N, 16.08.

Ethyl 6-methyl-4-(4-trifluoromethylphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **4j**: ^{1}H NMR (200 MHz, [$^2H_6$]DMSO) δ: 9.35 (s, 1H), 7.85 (s, 1H), 7.70 (dd, 2H), 7.45 (dd, 2H), 5.25 (d, 1H), 3.97 (q, 2H), 2.25 (s, 3H), 1.10 (t, 3H). ^{13}C NMR (50 MHz, [$^2H_6$]DMSO) δ: 14.2, 14.9, 49.5, 61.7, 106.4, 124.2, 125.1, 125.1, 127.3, 127.3, 129.1, 146.5, 147.3, 150.3, 167.2. MS, *m/z*: 327 (M – H). Found (%): C, 55.10; H, 4.63; N, 8.56. Calc. for $C_{15}H_{15}F_3N_2O_3$ (%): C, 54.88; H, 4.61; N, 8.53.

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