One-pot Synthesis of 3,4-dihydropyrimidin-2-(1*H*)-one / thiones bearing Sugar Side Chain Using Samarium Chloride as a Catalyst

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A simple one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-one / thiones sugar derivatives, using samarium chloride as a catalyst, from sugar aldehydes, 1.3-dicarbonyl compounds and urea or thiourea in ethanol was described. This new method has the advantage of excellent yields (76-83%) and short reaction time.

Keywords: dihydropyrimidine, sugar aldehydes, samarium chloride, thioureea, Biginelli reaction

It is well known that 3,4-dihydropyrimidin-2-(1*H*)-ones and related compounds exhibit a wide range of biological activities such as antiviral, antitumor, antibacterial, cardiovascular activities and antiinflammatory properties [1]. The 2-oxodihydropyrimidine-5-carboxylate core unit is found in nature [2] and in potent HIVgp-120-CD_4 inhibitors. In addition, several functionalized derivatives are used as calcium channel modulators, antihypertensive agents and α_{1a}-antagonists [3].

So, currently the original cyclocondensation reaction has been extended to include variations in all three components allowing access to a large number of multifunctionalized dihydropyrimidine derivatives, and many publications and patents deal with their synthesis [3,4].

The most simple and straightforward procedure, first reported by Biginelli, involves the one-pot cyclo-condensation of a β-ketoester with an aldehyde and urea under strongly acidic conditions [4, 5]. One major drawback of this so-called Biginelli reaction is the moderate yields (25-60%) that are frequently encountered when using substituted aromatic and aliphatic aldehydes [4-7]. Although high yields could be achieved by complex multi-step procedures, these methods lack the simplicity of original *one–pot* Biginelli protocol [4,7,8]. Within the past few years several modified and improved procedures for the one-step synthesis of dihydropyrimidines have been published. Hu [4] and Kappe [9] reported the use of BF_3.OEt_2/CuCl and PPE (polyphosphate ester)-mediated variations of the Biginelli reaction, giving high yields of dihydropyrimidines, but the reaction requires 15-18h of reaction time. More recently, montmorillonite-KSF [10], iron(III) [11], and Nafion-H [12] have been employed for this transformation. In addition, there are some other methods such as microwave-assisted [12] and solid-phase synthesis [13]. However, in spite of their potential utility, some methods suffer from drawbacks like longer reaction times, unsatisfactory yields, lower selectivity, and cumbersome product isolation procedures.

Very recently, we found that the Biginelli reaction can occur more smoothly under microwave irradiation in the presence of ferric chloride or TsOH as the catalyst [14]. Here in, we would like to report a simple effective approach to the Biginelli reaction products by using Samarium chloride catalyst. In a typical experimental procedure, a solution of β-ketoester, sugar aldehyde and urea or thiourea in ethanol was heated under reflux in the presence of a catalytic amount of $SmCl_3$.6 H_2O and one drop of conc. HCl for a certain period of time as required to complete the reaction (TLC).

Experimental part

General

Solvent were purified and dried in the usual way. The boiling range of the petroleum ether used was 40-60 °C. Thin layer chromatography (TLC): silica gel 60 F_{254} plastic plates (E. Merck, layer thickness 0.2 mm) detected by UV absorption. Melting points were determined on a Buchi 510 melting-point apparatus and the values are uncorrected. NMR spectra were measured with Bruker (600 MHz and 250 MHz). If was used TMS (0.00 ppm) as internal standard. Microanalyses were performed at the Microanalytical Center, Chemistry Department, Konstanz University, Germany.

General procedure of dihydropyrimidine

A solution of methyl acetoacetate (0.58 g, 5 mmol), sugar aldehydes (1.39 g, 5 mmol), urea or thiourea (10 mmol), $SmCl_3$.6 H_2O (0.36 g, 1 mmol) and conc. HCl (one drop) in EtOH (15 mL) was heated under reflux for 8 h. After cooling, the reaction mixture was dried under high vacuo. The residue was purified by flash chromatography (chloroform/methanol 1/8).

Methyl-6-methyl-4-(1-*O*-benzyl-2:3-*O*-isopropylidene-a-D-xylofuranose)-2-oxo-1,2,3,4-tetrahydropyrimidin-5-carboxylate (6a). White crystals (1.59 g, 76%); m.p. 165 °C; ^{1}HNMR (600 MHz, $CDCl_3$): δ 1.29 (3H, s, CH_3), 1.45 (3H, s, CH_3), 2.25 (3H, s, CH_3), 3.67 (3H, s, OCH_3), 4.07 (1H, d, $J_{3,4}$ = 4.6 Hz, 3-H), 4.27 (1H, d, $J_{4,3}$ = 4.6 Hz, 4-H), 4.48 (1H, d, J_{gem} = 11.6 Hz, CHPh), 4.57 (1H, s, CHNH), 4.62 (1H, d, $J_{2,1}$ = 3.7 Hz, 2-H), 4.77 (1H, d, J_{gem} = 11.6 Hz, CHPh), 5.60 (1H, s, NH), 6.00 (1H, d, $J_{1,2}$ = 3.7 Hz, 1-H), 7.39-7.25 (5 H, m, Ar-H), 7.79 (1H, s, NH),; ^{13}CNMR (150 MHz, $CDCl_3$): δ 19.3 (CH_3), 26.2 (CH_3), 26.9 (CH_3), 51.2 (OCH_3), 51.7 (CHNH), 71.9 (CH_2Ph), 81.7 (4-C), 82.6 (2-C), 84.7 (3-C), 105.4 (1-C), 111.8, 127.8, 128.1, 128.2, 128.3, 128.7, 136.6, 149.1 (C-Ar), 154.6 (CO), 166.4 (CO). (MALDI, positive mode, Matrix: DHB): m/z = 440.1

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$(M+Na)^+$, 457.0 $(M+K)^+$. Anal. Calcd for $C_{21}H_{26}N_2O_7$ (418.17): C, 60.28 %; H, 6.26 %; N, 6.69 %; Found: C, 60.01 %; H, 6.45 %; N, 6.68 %.

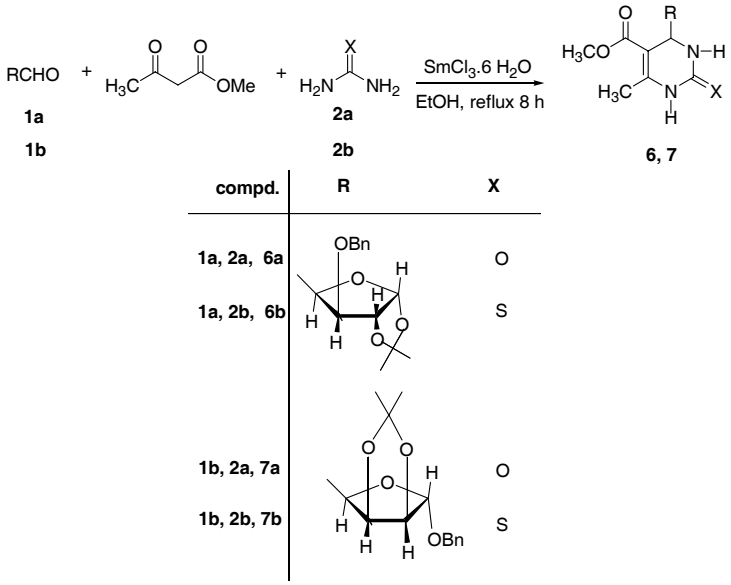
Methyl-6-methyl-4-(1-*O*-benzyl-2:3-*O*-isopropylidene-a-D-xylofuranose)-2-thio-1,2,3,4-tetrahydropyrimidin-5-carboxylate (6b). White crystals (1.80 g, 83%); m.p. 141 °C; ^{1}HNMR (600 MHz, $CDCl_3$): δ 1.31 (3H, s, CH_3), 1.43 (3H, s, CH_3), 2.26 (3H, s, CH_3), 3.69 (3H, s, OCH_3), 4.13 (1H, d, $J_{3,4}$ = 5.2 Hz, 3-H), 4.30 (1H, d, $J_{4,3}$ = 5.2 Hz, 4-H), 4.51 (1H, d, J_{gem} = 11.9 Hz, CHPh), 4.54 (1H, d, J = 2.3 Hz, CHNH), 4.66 (1H, d, $J_{2,1}$ = 3.6 Hz, 2-H), 4.83 (1H, d, J_{gem} = 11.9 Hz, CHPh), 6.04 (1H, d, $J_{1,2}$ = 3.6 Hz, 1-H), 7.19 (1H, s, NH), 7.26-7.41 (5 H, m, Ar-H), 7.60 (1H, s, NH); ^{13}CNMR (150 MHz, $CDCl_3$): δ 19.1 (CH_3), 26.4 (CH_3), 27.1 (CH_3), 51.5 (OCH_3), 52.6 (CHNH), 72.3 (CH_2Ph), 82.6 (4-C), 83.0 (2-C), 84.4 (3-C), 105.4 (1-C), 112.2, 127.7, 128.4, 128.9, 136.4, 145.4 (C-Ar), 166.0 (CO), 177.0 (CS). (MALDI, positive mode, Matrix: DHB): m/z = 473.0 $(M+K)^+$. Anal. Calcd for $C_{21}H_{26}N_2O_6S$ (434.15): C, 58.05 %; H, 6.03 %; N, 6.45 %; Found: C, 57.76 %; H, 6.04 %; N, 6.31 %.

Methyl-6-methyl-4-(1-*O*-benzyl-2:3-*O*-isopropylidene-a-D-lyxofuranose)-2-oxo-1,2,3,4-tetrahydropyrimidin-5-carboxylate (7a). White powder (1.65 g, 79%); m.p. 136 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.31, 1.59 (6H, 2s, $2CH_3$), 2.32 (3H, s, CH_3), 3.69 (1H, s, OCH_3), 3.90 (1H, d, J = 3.7 Hz, 3-H), 4.44 (1H, d, J_{gem} = 11.7 Hz, CHPh), 4.57 (1H, d, J_{gem} = 11.7 Hz, CHPh), 4.63 (1H, m, 4-H), 4.77 (2H, m, CHNH, 2-H), 5.18 (1H, s, 1-H), 5.85 (1H, s, NH), 7.24-7.37 (5H, m, Ar-H), 8.70 (1H, s, NH); ^{13}CNMR (150 MHz, $CDCl_3$): δ 19.0 (CH_3), 26.6 (CH_3), 26.8 (CH_3), 51.2 (OCH_3), 52.1 (CHNH), 72.5 (CH_2Ph), 82.1 (4-C), 83.3 (2-C), 84.9 (3-C), 101.3 (1-C), 112.0, 126.7, 128.6, 128.9, 137.4, 145.9 (C-Ar), 155.2 (CO), 165.3 (CS). (MALDI, positive mode, Matrix: DHB): m/z = 457.0 $(M+K)^+$. Anal. Calcd for $C_{21}H_{26}N_2O_7$ (418.17): C, 60.28 %; H, 6.26 %; N, 6.69 %; Found: C, 59.81 %; H, 6.34 %; N, 6.66 %.

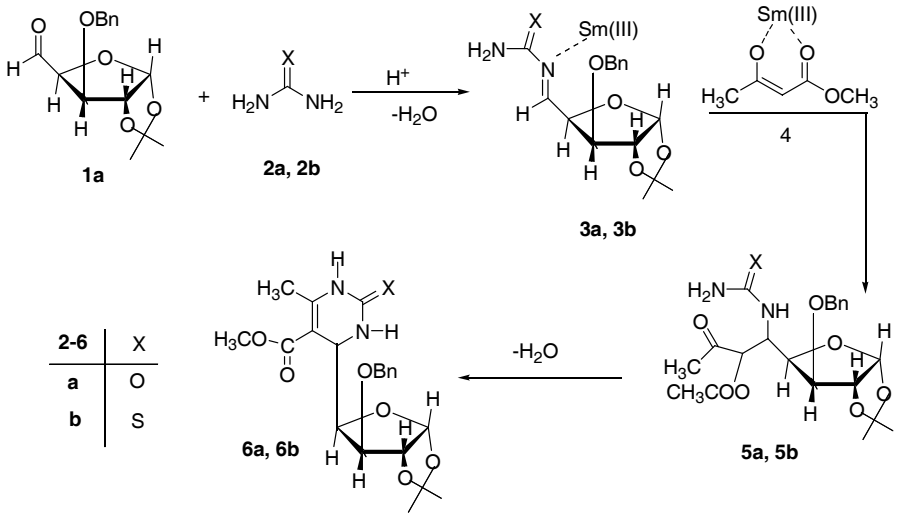
Methyl-6-methyl-4-(1-*O*-benzyl-2:3-*O*-isopropylidene-a-D-lyxofuranose)-2-thio-1,2,3,4-tetrahydropyrimidin-5-carboxylate (7b). White powder (1.63 g, 75%); m.p. 98°C; ^{1}H NMR (600 MHz, $CDCl_3$): d 1.29, 1.68 (6H, 2s, $2CH_3$), 2.30 (3H, s, CH_3), 3.69 (1H, s, OCH_3), 3.88 (1H, d, J = 3.9 Hz, 3-H), 4.60 (1H, d, J_{gem} = 12.2 Hz, CHPh), 4.77 (2H, m, CHPh, 4-H), 4.75 (2H, m, CHNH, 2-H), 5.19 (1H, s, 1-H), 7.21-7.33 (5H, m, Ar-H), 7.42 (1H, s, NH), 8.61 (1H, s, NH); ^{13}CNMR (150 MHz, $CDCl_3$): δ 19.4 (CH_3), 26.1 (CH_3), 27.6 (CH_3), 51.0 (OCH_3), 52.9 (CHNH), 73.4 (CH_2Ph), 82.1 (4-C), 82.8 (2-C), 83.9 (3-C), 103.3 (1-C), 113.1, 128.3 128.7 128.9, 137.5, 146.1 (C-Ar), 165.6 (CO), 176.8 (CS). (MALDI, positive mode, Matrix: DHB): m/z = 473.0 $(M+K)^+$. Anal. Calcd for $C_{21}H_{26}N_2O_6S$ (434.15): C, 58.05 %; H, 6.03 %; N, 6.45 %; Found: C, 57.78 %; H, 5.96 %; N, 6.41 %.

Results and discussions

As a part of our program towards synthesis of dihydropyrimidine sugar derivatives, samarium chloride catalyzed one pot three component condensation reactions of a sugar aldehydes, 1,3-dicarbonyl compounds and urea or thiourea led to to 3,4-dihydropyrimidin-2-(1H)-one/thions (scheme 1).



Scheme 1



Scheme 2

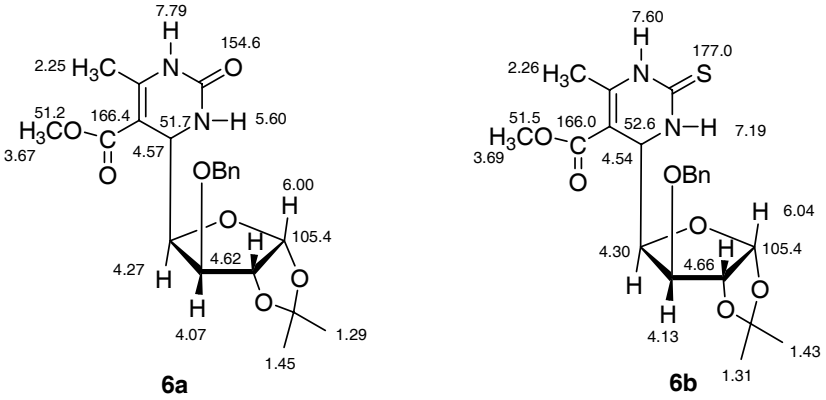


Fig. 1. Selected ^{1}H and ^{13}C NMR data of 6a and 6b

Although the detailed mechanism of the reaction presented in scheme 1 has been reported by Xuesen F., [15] in which the first step, the acid-catalyzed formation of an acyl imine intermediate (**5**) formed by reaction of the sugar aldehyde (**1a**, **1b**) with ureea (**2a**) or thiourea (**2b**), is the key rate-limiting step. Interception of the iminium ion by methyl acetoacetate (**4**) produces an open-chain ureide (**5a**, **5b**) which subsequently cyclized to the 3,4-dihydropyrimidin-2-(1H)-one (**6a**, **6b**) (scheme 2). Due to the empty orbital in the samarium ion, a complex of **1** and **5** with samarium(III) may be formed through a coordinative bond and so be stabilized by samarium.

The structure assignment of the 3,4-dihydropyrimidin-2-(1H)-one/thiones sugar derivatives is based on ^{1}H NMR spectral and physicochemical analysis, (fig. 1). The structures of **6a** and **6b** were established through the ^{1}H NMR spectra [**6a**: 7.79 (1H, s, NH), 6.00 (1H, d, $J_{1,2}$ = 3.7 Hz, 1-H), 5.60 (1H, s, NH), 4.57 (1H, s, CHNH), 3.67 (3H, s, OCH_3); **6b**: 7.60 (1H, s, NH), 7.19 (1H, s, NH), 6.04 (1H, d, $J_{1,2}$ = 3.6 Hz, 1-H), 4.54 (1H, d, J = 2.3 Hz, CHNH), 3.69 (3H, s, OCH_3)].

Conclusions

In conclusion, the present procedure of the synthesis of 3,4-dihydropyrimidine-2-(1H)-one/thiones sugar derivatives by $SmCl_3.6\ H_2O$ catalyzed condensation of β-keto ester, sugar aldehyde and urea or thiourea provides an efficient and much improved modification of Biginelli's reaction. With its simplicity and milder reaction conditions, this procedure will offer an easy access to substituted dihydropyrimidine-2-(1H)-ones and thiones with various sugars in high yields.

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