Communication

Sodium Tetrafluoroborate as a New and Highly Efficient Catalyst for One-pot Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones and Thiones

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Sodium tetrafluoroborate ($NaBF_4$) is found to catalyze the three component condensation 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. This method is very useful for the synthesis of a wide range of 3,4-dihydropyrimidin-2(1*H*)-ones and thiones from aromatic, heterocyclic, α,β-unsaturated aldehydes and aliphatic aldehydes.

Keywords: Sodium tetrafluoroborate; Aldehyde; 1,3-Dicarbonyl compound; Urea; Thiourea.

INTRODUCTION

Dihydropyrimidinones and their derivatives have emerged as the integral backbones of several calcium channel blockers, α_{1a}-adrenergic antagonists, antihypertensives, and neuropeptide Y (NPY) antagonists.[1] 3,4-Dihydropyrimidinones and their sulfur analogues were found to exhibit a wide spectrum of biological activities such as antiviral, antitumor, antibacterial and antiinflammatory behavior.[2] Furthermore, several alkaloids containing the dihydropyrimidine core structure have been isolated from marine sources, which also exhibit interesting biological properties. Most notably, among these are the batzelladine alkaloids that are found to be potent HIV gp-120-CD_4 inhibitors.[3] Therefore, the synthesis of this heterocyclic core unit is of much current importance. The simplest and direct procedure originally reported by Biginelli[4] involves three-component one-pot condensation of an aldehyde, β-ketoester, and urea under strongly acidic conditions. However, this method often suffers from low yields of products particularly in the case of substituted aromatic and aliphatic aldehydes.[5] This has led to the disclosure of multi-step synthetic strategies, which produce relatively higher yields but lack the simplicity of the original one-pot-Biginelli protocol.[6] Recently several methods have been reported for preparing dihydropyrimidinones using different Lewis acids such as $BF_3.OEt_2$, $LaCl_3$, $La(OTf)_3$, $Yb(OTf)_3$, $InCl_3$, $InBr_3$, $ZrCl_4$, $BiCl_3$, $Bi(OTf)_3$, LiBr, $LiClO_4$, $Mn(Oac)_3$, CAN, $FeCl_3.6H_2O$, $NiCl_2.6H_2O$, *N*-butyl-*N*,*N*-dimethyl-α-phenylethylammonium bromide, etc.[7]as well as protic acids such as H_2SO_4, HOAc, conc. HCl, etc.[8] as promoters. Many other methods including microwave irradiation, ionic liquids, and clays[9] have also been reported. However, many of these methods are associated with disadvantages like expensive and toxic reagents, stoichiometric amounts of catalysts, strongly acidic conditions, long reaction times, unsatisfactory yields, incompatibility with other functional groups and involve difficult product isolation procedures. Moreover, some of the methods are only practical for aromatic aldehydes.[7a,k,9c] Thus a practical and more efficient alternative using an inexpensive and environment friendly reagent is still of interest for one-pot synthesis of dihydropyrimidinones and thiones under mild conditions.

Fluoroboric acid (HBF_4) and its salt, particularly lithium tetrafluoroborate ($LiBF_4$), have been used widely as Lewis catalysts in a variety of reactions.[10] However, HBF_4 is a strong acid and $LiBF_4$ is very expensive and moisture sensitive. On the other hand, sodium tetrafluoroborate is readily available and inexpensive. However, attention has so far been mainly paid to using HBF_4 and $LiBF_4$ as a catalyst for various transformations, while the use of sodium tetrafluoroborate has been seldom reported in the literature in association with other reagents.[11] The literature survey reveals that the potentiality of this reagent uniquely for organic transformations has not been explored. Thus we thought to employ this reagent for organic transformations and found that sodium tetrafluoroborate is able to catalyze the synthesis of dihydropyrimidinones and thiones. Moreover, no additive or protic/Lewis acid is necessary in this procedure.

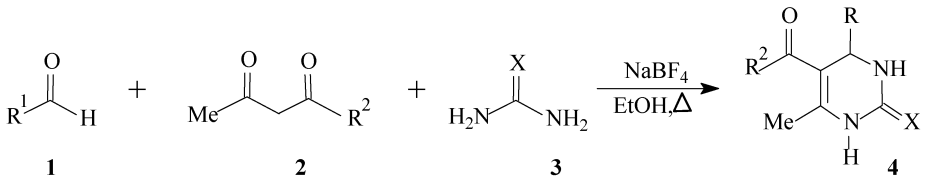
RESULTS AND DISCUSSION

In this report, we would like to disclose our economic approach for the synthesis of dihydropyrimidinones and thiones by a three-component one-pot condensation of an aldehyde, β-keto ester and urea employing sodium tetrafluoroborate as a novel promoter. The catalyst is mild, inexpensive and highly efficient for open chained 1,3-dicarbonyl compounds. The method is highly efficient and free from the aforesaid drawbacks. The reaction of aldehydes, β-keto ester and urea/thiourea using $NaBF_4$ in ethanol proceeded smoothly to afford the corresponding dihydropyrimidinones and thiones in high yields (Scheme I).

The results presented in Table 1 indicate the scope and generality of the method, which is efficient, not only for urea or thiourea but also for a wide range of substrates including aromatic, aliphatic, heterocyclic and α,β-unsaturated aldehydes. Most importantly, aromatic aldehydes carrying either electron donating or withdrawing substituents reacted well under the reaction conditions to give the corresponding dihydropyrimidinones in good to excellent yields with high purity. The important feature of the present methodology is the ability to tolerate the variations in all the three components as well as the survival of a variety of functional groups such as olefins, ethers, nitro, and halide under the reaction conditions. In comparison to earlier methods, which are only practical for aromatic aldehydes,[6a,b,7a,b,k] the present method is found to be superior as it is even effective with aliphatic aldehydes (Table 1, Entries 23, 24, and 25). Furthermore, the present protocol affords the excellent yield of corresponding dihydropyrimidinone when α,β-unsaturated aldehyde reacted with 1,3-dicarbonyl compound and urea, which normally show extremely low conversion in the Biginelli reaction (Table 1, Entry 30). Thiourea has been used with similar success to produce the corresponding thio-derivatives of dihydropyrimidinones which are also of much interest with respect to their biological activities (Table 1, Entries 13, 14, 15, 16, 17, 22 and 29).[2a] Besides the β-keto esters, 1,3-diketone was employed to produce a dihydropyrimidinone (Table 1, Entries 27, 28 and 29). It has been found that methanol or ethanol is a much better solvent in terms of conversion than all the other tested solvents, which included acetonitrile, dichloromethane and tetrahydrofuran. Furthermore, the use of just 20 mol% of $NaBF_4$ in ethanol is sufficient to promote the reaction and no additives such as HCl or CH_3COOH[7e] are required for this conversion. Thus, the present protocol provides an easy access to the preparation of substituted dihydropyrimidinones with a wide range of substitution patterns on all three components.

In conclusion, we have developed a simple and general method for the synthesis of biologically significant aryl-substituted dihydropyrimidinones by means of a three-component condensation of an aldehyde, 1,3-dicarbonyl compound and urea or thiourea in a one-pot operation using sodium tetrafluoroborate as a novel catalyst. This method is applicable for a wide range of substrates including aromatic, aliphatic, α,β-unsaturated and heterocyclic aldehydes and provides a variety of biologically relevant dihydropyrimidinones in good to excellent yields. Even though Lewis acids and other protic acids are known to catalyze this reaction, this is the first report using sodium tetrafluoroborate as a catalyst. The catalyst is inexpensive, mild and commercially available and also offers several advantages including cleaner reactions, higher yields of the products as well as a simple experimental and isolation procedure which makes it a useful and attractive process for the synthesis of biologically relevant dihydropyrimidinones.

Scheme I



1 **2** **3** **4**

R^1 = Alkyl and Aryl
R^2 = Alkyl -O and Alkyl
X = O,S

Table 1. Sodium tetrafluoroborate catalyzed synthesis of dihydropyrimidinones and thiones

Entry	Product	R^1	R^2	X	Time (h)	Yield[a,b] (%)	Ref.
1	4a	C_6H_5	OEt	O	3	85	7a
2	4b	4-ClC_6H_4	OEt	O	4	92	7e
3	4c	4-$NO_2C_6H_4$	OEt	O	4	90	7e
4	4d	4-MeC_6H_4	OEt	O	4.5	89	7e
5	4e	4-$OMeC_6H_4$	OEt	O	4	87	7e
6	4f	2-$(OH)C_6H_4$	OEt	O	5	88	7m
7	4g	3,4-$(OMe)_2C_6H_3$	OEt	O	4.5	90	7j
8	4h	3,4-(O-CH_2-O)C_6H_3	OEt	O	4	83	7m
9	4i	2,5-$(OMe)_2C_6H_3$	OEt	O	5	86	7p
10	4j	4-BrC_6H_4	OEt	O	5	84	7p
11	4k	4-FC_6H_4	OEt	O	5	83	7a
12	4l	3-(OMe)-4$(OH)C_6H_3$	OEt	O	5	84	7m
13	4m	C_6H_5	OEt	S	4.5	89	7e
14	4n	4-$OMeC_6H_4$	OEt	S	5	90	7e
15	4o	4-$NO_2C_6H_4$	OEt	S	5	91	7e
16	4p	4-ClC^6H_4	OEt	S	5	90	7e
17	4q	3-$(OH)C_6H_4$	OEt	S	5.5	88	7n
18	4r	4-$NO_2C_6H_4$	OMe	O	4	87	7e
19	4s	4-ClC_6H_4	OMe	O	4	86	7e
20	4t	3-$OMeHC_6H_4$	OMe	O	4.5	85	7e
21	4u	C_6H_5	OMe	O	3.5	88	7e
22	4v	C_6H_5	OMe	S	3.5	86	7o
23	4w	$(CH_3)_2CH$	OEt	O	5	81	7m
24	4x	$CH_3(CH_2)_4$	OEt	O	5,5	80	8b
25	4y	$CH_3(CH_2)_5$	OEt	O	5.5	78	7l
26	4z	2-Furyl	OEt	O	4	80	7e
27	4a	4-$NO_2C_6H_4$	Me	O	4.5	90	7c
28	4b	4-$OMeC_6H_4$	Me	O	4	89	7c
29	4c	C_6H_5	Me	S	4	88	7d
30	4d	C_6H_5CH=CH	OEt	O	4	86	7e

[a] Yields are of pure isolated products. [b] Products are characterized by their physical constants and spectral analysis.

EXPERIMENTAL

Melting points were measured using a Buchi R-535 apparatus. IR spectra were recorded on a Bomem MB FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Varian Gemini-200 spectrometer. Mass spectra were recorded on a VG Micromass-7000 H (70 eV). CHN analyses were recorded on a Vario EL analyser.

Experimental Procedure

A mixture of aldehyde (1 mmol), β-keto ester (1 mmol), urea or thiourea (1.5 mmol) and $NaBF_4$ (0.2 mmol) in ethanol (10 mL) was refluxed for a certain period of time as required to complete the reaction. The progress of the reaction was monitered by TLC. On completion, the solvent was removed under reduced pressure and the resulting product was washed with water, filtered and recrystallized from hot ethanol to afford pure dihydropyrimidinone.

Spectral Data of Some Compounds

Compound **4a**: Solid; m.p. 200-202 °C; IR (KBr): 1595, 1650, 1710, 1725, 2920, 2950, 3125, 3250 cm.$^{-1}$ ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.15 (t, 3H, *J* = 7.0 Hz), 2.35 (s, 3H), 4.10 (q, 2H, *J* = 7.0 Hz), 5.25 (s, 1H), 7.12-7.30 (m, 6H), 8.95 (br. s, NH); EIMS: *m/z* = 260 (M^+).

Compound **4d**: Solid; m.p. 171-172 °C; IR (KBr): 1650, 1660, 1690, 3115, 3245 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.23 (t, 3H, *J* = 7.0 Hz), 2.35 (s, 3H), 2.45 (s, 3H), 4.15 (q, 2H, *J* = 7.0 Hz), 5.45 (d, 1H, *J* = 2.4 Hz), 6.95-7.22 (m, 4H), 7.75 (br. s, NH), 9.10 (br. s, NH); EIMS: *m/z* = 274 (M^+).

Compound **4u**: solid; m.p. 206-207 °C; IR (KBr):

1655, 1650, 1695, 3110, 3245 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 2.30 (s, 3H), 3.45 (s, 3H), 5.20 (s, 1H), 7.25-7.30 (m, 5H), 7.75 (br. s, NH), 9.20 (br. s, NH).

Compound **4z**: Solid; m.p. 205-207 °C; IR (KBr): 1485, 1590, 1690, 1710, 3110, 3245 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.15 (t, 3H, *J* = 7.0 Hz), 2.33 (s, 3H), 4.20 (q, 2H, *J* = 7.0 Hz), 5.30 (d, 1H, *J* = 2.2 Hz), 6.15 (d, 1H, *J* = 2.2 Hz), 6.35 (s, 1H), 7.35 (m, 1H), 7.80 (br. s, NH), 9.20 (br. s, NH); EIMS: *m/z* = 250 (M^+).

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