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Vanadium Hydrogen Sulfate Catalyzed Solvent-Free Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones and Bis-(indolyl) methanes

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3,4-Dihydropyrimidin-2(1*H*)-ones and their derivatives have attracted increasing interest due to their wide range of therapeutical and pharmacological properties, such as antiviral, antitumor, antibacterial, and antiinflammatory properties.[1] Some of them have been successfully used as calcium channel blockers, antihypertensive agents, and α1a-antagonists.[2] Moreover, several marine alkaloids whose molecular structures contain the dihydropyrimidinone core also exhibit interesting biological activities.[3] Therefore, synthesis of these type of compounds is still of great importance.

In 1893, Biginelli reported that DHPMs can be prepared *via* one-pot three-component condensation of an aldehyde, β-ketoester and urea or thiourea in the presence of an acid catalyst.[4] This so-called Biginelli reaction, suffer from long reaction times, acidic reaction conditions, low yields of the desired products (20 - 40%) particularly in the case of substituted aldehydes and loss of sensitive functional groups during the reaction. Although, during the past years, many improved methods have been reported for the preparation of DHPMs,[5-21] the practical application of most of them suffer from disadvantages such as the use of expensive or less easily available reagents, long reaction times, unsatisfactory yields, vigorous reaction conditions, and tedious manipulations to isolate the products. Therefore, a need still exist for efficient and simple protocols whereby DHPMs may be obtained under milder conditions.

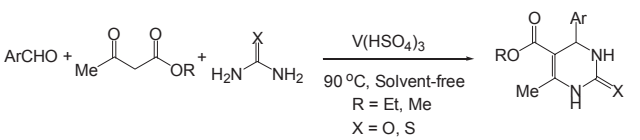
Bis-(indolyl) methanes, as important derivatives of indole, are widely presented in bioactive metabolites of terrestrial and marine origin. [22] These type of compounds are also known to promot estrogen metabolism in both woman and men and expected to have an application in prevention of breast cancers.[23] Therefore, a wide variety of methods for the synthesis of bis-(indolyl) methanes by the reaction of indole with aldehydes in the presence of different catalysts have bee reported.[24-34] However, some of the reported methods suffer from disadvantages such as need to use of a large or stoichiometric amount of catalysts, long reaction times, low yields of the products, drastic conditions for catalyst preparation, tedious work-up leading to the generation of large amount of toxic waste and use of an additional microwave or ultrasound irradiation. Therefore, introduction of new methods and catalysts for the preparation of BIMs is still in demand.

In recent years, the organic reactions under solvent-free conditions have attracted considerable attention because of their enhanced selectivity, milder reaction conditions, much improved reaction rates, formation of cleaner products, and associated ease of manipulation.[35]

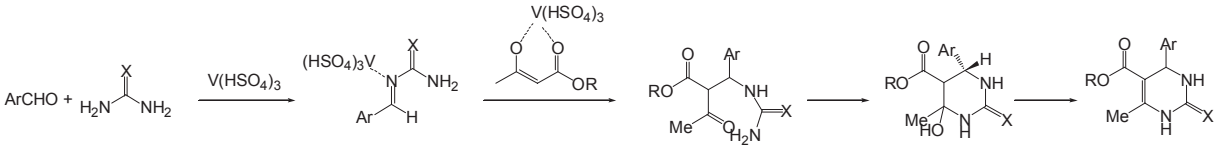
In continuation of our ongoing research program on the development of the applications of hydrogen sulfate salts in organic reactions,[36-39] we have found that $V(HSO_4)_3$, as a newly prepared hydrogen sulfate salt,[40,41] is efficiently able to improve the Biginelli condensation reaction under solvent-free conditions (Scheme 1).

Optimization of the reaction conditions is carried out by the condensation of benzaldehyde, ethyl acetoacetate, and urea under solvent-free conditions. The best result was achieved by carring out the reaction of benzaldehyde, ethyl acetoacetate, and urea (with 1: 1.2 : 1.3 mol ratio) in the presence of 0.2 mol of $V(HSO_4)_3$ at 95 °C for 20 min under solvent-free conditions (Table 1, entry 1). Other aromatic aldehydes, were also reacted under the same reaction conditions to produce the corresponding DHPMs in good to high yields (Table 1). Methyl acetoacetate and thiourea were also used with similar success to provide the corresponding 3,4-dihydropyrimidin-2(1*H*)-thiones.[42]

A plausible mechanism for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and thiones using this method, is shown in Scheme 2 based on literature, [43] our observations and obtained results.



Scheme 1



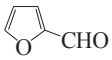
Scheme 2

Table 1. Synthesis of DHPMs under solvent-free conditions[a,b]

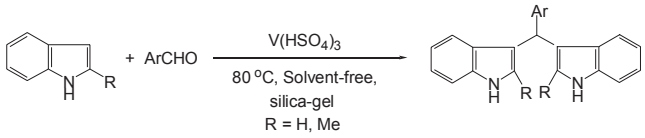
Entry	Ar	R	X	Time (min)	Yield (%)	mp (°C) Found	mp (°C) Reported
1	Ph	Et	O	20	90	205 - 207	206 - 207[20]
2	2-Cl-Ph	Et	O	30	85	210 - 213	215 - 218[20]
3	3-Cl-Ph	Et	O	30	90	190 - 192	192 - 193[20]
4	4-Cl-Ph	Et	O	20	80	213 - 214	213 - 215[20]
5	4-MeO-Ph	Et	O	40	80	200 - 202	201 - 203[20]
6	4-Me-Ph	Et	O	20	90	213 - 214	214 - 215[20]
7	2-Furyl	Et	O	60	85	207 - 209	203 - 205[15]
8	Ph	Et	S	20	85	205 - 207	206 - 207[20]
9	2-Cl-Ph	Et	S	70	80	165 - 168	168 - 169[43]
10	3-Cl-Ph	Et	S	30	80	190 - 192	192 - 196[43]
11	4-Cl-Ph	Et	S	40	75	190 - 192	192 - 195[13]
12	4-MeO-Ph	Et	S	50	80	150 - 152	152 - 153[15]
13	4-Me-Ph	Et	S	35	80	187 - 190	189 - 192[45]
14	2-Furyl	Et	S	70	75	180 (dec)	183 (dec)[46]
15	Ph	Me	O	30	90	205 - 207	207 - 210[17]
16	4-Cl-Ph	Me	O	50	80	204 - 206	203 - 205[17]
17	4-MeO-Ph	Me	O	50	80	190 - 192	192 - 194[17]
18	4-Me-Ph	Me	O	30	82	200 - 202	204 - 206[47]
19	2-Furyl	Me	O	70	80	210 - 212	214 - 216[48]

[a]Products were characterized by comparison with authentic samples and IR and NMR spectroscopy. [b]Isolated yields.

Table 2. Solvent-free synthesis of BIMs[a,b]

Entry	R	Aldehyde	Time (min)	Yield (%)	mp (°C) Found	mp (°C) Reporetd
1	H	Ph-CHO	20	90	120 - 122	124 - 126[33]
2	H	4-NO_2-Ph-CHO	20	90	218 - 220	217 - 220[31]
3	H	3-NO_2-Ph-CHO	40	85	255 - 257	261 - 263[33]
4	H	4-Cl-Ph-CHO	40	85	83 - 85	87 - 89[33]
5	H	2-Cl-Ph-CHO	60	75	75 - 77	70 - 71[31]
6	H	4-Me-Ph-CHO	25	80	96 - 98	95 - 97[33]
7	H	4-MeO-Ph-CHO	35	75	190 - 192	191 - 193[33]
8	H	4-HO-Ph-CHO	50	80	118 - 120	122 - 124[33]
9	H		60	70	> 300	> 300[31]
10	Me	Ph-CHO	20	90	240 - 245	247 - 248[31]
11	Me	4-NO_2-Ph-CHO	20	90	238 - 240	240 - 242[32]
12	Me	4-Me-Ph-CHO	20	85	168 - 170	174 - 175[31]
13	Me	4-HO-Ph-CHO	60	75	234 - 236	237 - 239[30]

[a]Products are characterized by IR, NMR, elemental analysis and comparison with authentic samples. [b]Isolated yield.



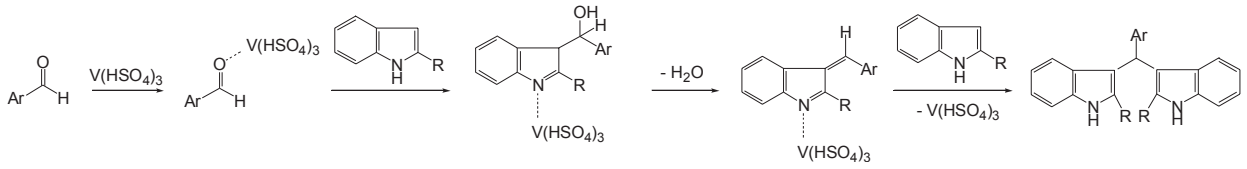
Scheme 3

Over investigations clarified that the electrophilic substitution reactions of indoles with various aromatic aldehydes can also be catalyzed in the presence of $V(HSO_4)_3$. All reactions were preformed in the absence of solvent at 80 °C in good to high yields (Scheme 3, Table 2). Because of the formation of a sticky mixture during the course of the reaction, SiO_2 is needed to use for the suitable mixing of the reactants.

A reasonable pathway of the reaction of indoles with aldehydes conducted in the presence of $V(HSO_4)_3$ is presented by Scheme 4.

The efficiency of the present method is shown by the comparison of the results with some of those reported in the literature (Table 3).[13,15,21,31,34]

In conclusion, we have developed a mild, simple and efficient method for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/



Scheme 4

Table 3. Comparison of some of the results obtained by the present method (I) with some of those reported by trichloroisocyanuric acid (II),[13] 12-tungstophosphoric acid (III),[15] $Al(HSO_4)_3$ in the absence of solvent (IV),[21] methanol (V)[31] and 12-tungstophosphoric acid supported on zirconia (VI).[34]

Entry	Product	Time (min) / Yield (%) I	II	III	IV	V	VI
1	Table 1, Entry 1	20 / 90	120 / 90	6-7 (**h**) / 75	15 (**h**) / 90	----	----
2	Table 1, Entry 12	50 / 80	120 / 85	6-7 (**h**) / 50	12 (**h**) / 80	----	----
3	Table 1, Entry 15	30 / 90	120 / 90	6-7 (**h**) / 70	20 (**h**) / 80	----	----
4	Table 2, Entry 1	20 / 90	----	----	----	12 (**h**) / 70	30 / 90
5	Table 2, Entry 10	20 / 90	----	----	----	2.5 (**h**) / 90	30 / 90

thiones and bis-(indolyl) methanes catalyzed by $V(HSO_4)_3$.

Based on our studies, this method offers several adavantages including mild reaction conditions, good to high yields of the products, short reaction times, solvent-free reaction conditions and simple experimental procedure.

Experimental

General procedure for the synthesis of DHPMs under solvent-free conditions. A mixture of aldehyde (1 mmol), β-keto-ester (1.2 mmol), urea or thiourea (1.3 mmol) and $V(HSO_4)_3$ (0.2 mmol) was heated in an oil bath (90 ^oC) for the appropriate time (Table 1). After completion (monitored by TLC), the reaction was cooled to room temperature and ethanol was added and filtered. The filterate was concentrated followed by addition of water. The resulting precipitate was filtered and recrystallized from ethyl acetate or ethanol to afford the corresponding DHPMs in good to high yields.

General procedure for the synthesis of BIMs under solvent-free conditions. A mixture of 1 mmol of aromatic aldehyde, 2 mmol of indole derivative, 0.1 g silica-gel and 0.1 mmol of $V(HSO_4)_3$ was magnetically stirred in a round-bottomed flask at 80 ^oC for the appropriate time according to Table 2. The progress of the reaction was monitored by TLC. Upon completion of the reaction, the mixture was cooled to room temperature. Then acetone (5 mL) was added, the mixture was filtered and filterate was washed with acetone (2 × 3 mL). After evaporation of the solvent under reduced pressure, the crude product was obtained. Column chromatography on a short silica-gel column gives highly pure products.

Selected spectral data.

Table 1, entry 1: IR (KBr): υ 3245, 3118, 2978, 1725, 1701, 1649 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 1.06 (t, 3H, J = 6.84), 2.24 (s, 3H), 3.94 (q, 2H, J = 6.75), 5.13 (d, 1H, J = 3.06), 7.21-7.37 (m, 5H), 7.37 (brs, 1H), 9.19 (brs, 1H).

Tabe 1, entry 5: IR (KBr): υ 3436, 3247, 3113, 2929, 1724, 1705, 1649 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 1.10 (t, 3H, J = 7.08), 2.17 (s, 3H), 3.71 (s, 3H), 3.96 (q, 2H, J = 7.14), 5.07 (d, 1H, J = 2.97), 6.85 (d, 2H, J = 8.49), 7.12 (d, 2H, J = 8.55), 7.67 (brs, 1H), 9.15 (brs, 1H).

Table 1, entry 7: IR (KBr): υ 3342, 3242, 3117, 2985, 1700, 1645 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 1.05 (t, 3H, J = 7.08), 2.22 (s, 3H), 3.98 (q, 2H, J = 6.99), 5.19 (d, 1H, J = 3.0), 6.08 (d, 1H, J = 2.94), 6.35 (s, 1H), 7.55 (s, 1H), 7.76 (brs, 1H), 9.25 (brs, 1H).

Table 2, entry 2: IR (KBr): υ 3422, 3052, 1507, 1456, 1340 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.00 (s, 1H), 6.07 (s, 2H), 7.00-7.05 (m, 3H), 7.35 (d, 3H, J = 8.0), 7.40 (d, 2H, J = 8.0), 7.52 (d, 2H, J = 8.8), 8.04 (brs, 2H), 8.15 (d, 2H, J = 8.8).

Table 2, entry 6: IR (KBr): υ 3410, 3040, 2930, 1600, 1510, 1215, 1050, 775 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.32 (s, 3H), 5.86 (s, 1H), 6.68 (s, 2H), 7.02 (t, 2H, J = 7.2), 7.1 (d, 2H, J = 7.2), 7.23-7.27 (m, 6H), 7.40 (d, 2H, J = 7.2), 7.93 (brs, 2H).

Table 2, entry 9: IR (KBr): υ 3410, 1715, 1450, 1260 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.95 (s, 1H), 6.90 (s, 2H), 7.03-7.50 (m, 11H), 8.00 (brs, 1H).

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