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SYNTHESIS OF 5-UNSUBSTITUTED -3,4-DIHYDROPYRIDINE-2-(1H)- ONES USING NBS AS A CATALYST UNDER SOLVENT FREE CONDITIONS

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ABSTRACT

The development of efficient and versatile catalytic system for one pot multicomponent reaction is an active ongoing research area for further improvement towards milder reaction conditions, N-bromosuccinimide (NBS) has been used an efficient catalyst for the synthesis of 5-unsubstituted-3,4-dihydropyrimidin-2-(1*H*)-ones at room temperature under solvent free conditions.

Keywords. Dihydropyrimidine derivatives, Enolizable ketones, Aldehydes, Multicomponent, N-Bromosuccinimide, Solvent-free

INTRODUCTION

At the beginning of the new century, with the increasing environmental concerns and the regulatory constrains faced in the chemical and pharmaceutical industries, development of environmentally benign organic reactions has become a crucial and demanding research area in modern organic chemistry[1]. Recently Wender defined the 'ideal synthesis' as one in which the target components is produced in one step, in quantitative yield from readily available and inexpensive starting materials in resource-effective and environmentally acceptable[2]. The one-pot multicomponent condensation reactions offer significant advantages over conventional linear type synthesis to provide products with the required diversity. Biginelli reported a cyclo-condensation reaction[3] between active methylene compound, aldehydes and urea under strongly acidic conditions. Dihydropyrimidone derivatives are found as core units in many marine alkaloids (batzelladine and crambine), which are potent HIVgp-120CD_4 inhibitors[4]. In recent years, these compounds are known to exhibit a wide range of biological activities such as antiviral, antitumer, antibacterial and anti-inflammatory[5], consequently, synthesis of these compounds has gained importance and plethora of improved synthetic methodologies has been recently reported. Most commonly Lewis acids[6] such as $InCl_3$, $BF_3.OEt_2$, $BiCl_3$, $ZnCl_4$, $LiClO_4$, La $(OTf)_3$, $NiCl_2.6H_2O$ or $FeCl_3.6H_2O$, $Zn(OTf)_2$, $Mn(OAc)_3.H_2O$, CAN, $Bi(OTf)_3$, LiBr, $Yb(OTf)_3$ and ionic liquids have been used. However, some of these methods require toxic reagents in combination with Bronsted acids such as HCl, acetic acid. Recently acidic montmorrillonite-KSF and microwave irradiation have been reported[7]. Thus the development of efficient and versatile catalytic system for multicomponent reaction is an active ongoing research area for further improvement towards milder reaction conditions, variations of substituents in all these components. Herein, we report N-bromosuccinimide (NBS) as an efficient catalyst for the synthesis of 5-unsubstituted-3,4-dihydropyrimidin-2-(1H)-ones at room temperature under solvent free conditions with enhanced reaction rates and high yields. (Scheme-1)

EXPERIMENTAL

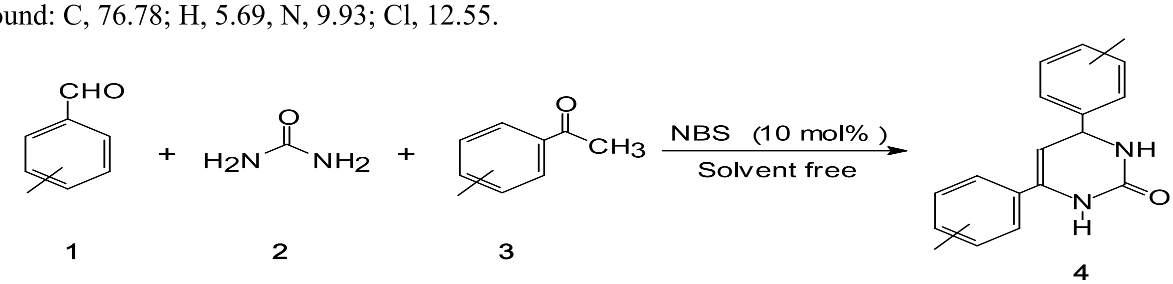
All chemicals were used as AR grade. The reactions were carried out in a borosil beaker of 50 ml capacity at room temperature and monitored by TLC using silica gel 60-120 mesh. Melting points were recorded by open capillary method and are uncorrected. IR spectra were determined on Perkin-Elmer FTIR-240C spectrophotometer on KBr disc. ^{1}H NMR spectra were recorded on 300 MHz spectrometer in DMSO-d_6 using TMS as an internal standard.

Typical Procedure

A mixture of benzaldehyde (530 mg, 5mmol), urea (450 mg 7.5 mmol) and acetophenone (590 mg, 5 mmol) mixed for few minutes at room temperature. To this mixture NBS (10 mmol %) was added. The reaction mixture was ground for 30 minutes and the temperature of mixture was raised up to 50^{0}C and maintained at room temperature for appropriate time (Table 1). After completion of the reaction (monitored by TLC), the reaction mixture was washed with ice-cold water (2 x 20 ml).The resulting solid products were collected by filtration. The crude products were purified by crystallization from ethanol.

Spectroscopic data

(4d), M. P. = 178-180 ^{0}C
IR (KBr) cm^{-1}: 840, 960, 1016, 1078, 1240, 1440, 1444, 1600, 1620, 1655, 3305, 3170.
^{1}H-NMR (200 MHz, DMSO-d_6), δ = 5.1 (s, 1H), 5.3 (s, 1H), 5.5 (s, 1H), 5.8 (s, 1H), 6.8 (d, J = 8.2 Hz, 2H), 7.1(d, J = 8. 2 Hz, 2H), 7.3- 7.4 (m, 5H).
Elemental Analysis for $C_{17}H_{16}N_2O$; Calcd. C, 77.25; H, 6.09; N, 10.59.
Found: C, 77.32; H, 6.24, N, 10.24.
(4g), M. P. = 148-150 ^{0}C
IR (KBr) cm^{-1}: 846, 964, 1016, 1068, 1240, 1440, 1590, 1621, 3315, 3180, 1655,
^{1}H-NMR (200 MHz, DMSO-d_6), δ = 5.2 (s, 1H), 5.5 (s, 1H), 5.5 (s, 1H), 5.8 (s, 1H), 7. 0 (d, J = 8 Hz, 2H), 7.2 (d, J = 8. 0 Hz, 2H), 7.3- 7.4 (m, 5H).
Elemental Analysis for $C_{16}H_{13}N_2OCl$; Calcd. C, 76.72; H, 5.65, N, 9.83; Cl, 12.45.
Found: C, 76.78; H, 5.69, N, 9.93; Cl, 12.55.



Scheme 1.

RESULTS AND DISCUSSION

At present there are very few articles describing the synthesis of certain 5-unsubstituted 3,4-dihydropyrimidin-2-(1H)-ones. And these methods have typically accomplished to the synthesis of 5-unsubstituted 3,4-dihydropyrimidin-2-(1H)-ones in a multistep fashion via the saponification of the C-5 ester followed by the thermal decarboxyllation with low yields. The use of ketones instead of β-keto esters or β-diketones gave us the opportunity to prepare corresponding new -5-unsubstituted 3,4-dihydropyrimidin-2-(1H)-ones. The Biginelli type reaction of ketones with single carbonyl group provide a useful 5-unsubstituted 3,4-dihydropyrimidin-2-(1H)-ones.

All the results are summarized in table 1. Aromatic aldehydes carrying electron withdrawing groups (entry, b, c, e, g, h, j, k, m, and n) or electron donating groups (entry, d, f, i, l) afforded high yields of 5-unsubstiruted-3, 4-dihydropyrimidin-2- (1*H*)-ones. The enolizable ketones carring electron donating groups (entry, h, k, l, m, and n) and electron withdrawing groups (i and j) affords the high yields of 5-unsubstiruted-3, 4-dihydropyrimidin-2- (1*H*)-ones. It is also observed that the enolizable ketone carring electron donating groups (entry h, k, l, m, and n) reacts more slowly as compared to the simple enolizable ketones. The important feature of this procedure is the survival of a variety of functional groups such as nitro, hydroxyl, halides, etc. under the reaction conditions. The aliphatic aldehydes and aliphatic ketones as well as α, β-unsaturated aldehydes and ketones do not undergo multi-component cyclocondensation reaction under the same reaction conditions for a longer period. This method is very simple, clean, and the product precipitates out as a solid in nearly all cases.

In conclusion, we have developed a simple and general method for the synthesis of 5- -unsubstituted-3, 4-dihydropyrimidin-2- (1*H*)-ones using highly inexpensive and easily available N-bromosuccinimide as a catalyst. This protocol offers several advantages including mild reaction conditions, elevated product yields, enhanced reaction time and simple workup procedure, which makes it a useful process for the synthesis of 5-unsubstituted-3, 4-dihydropyrimidin-2- (1*H*)-ones.

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Table. 1: Synthesis of 5-Unsubstituted-3,4-Dihydropyrimidin-2- (1H) -ones.

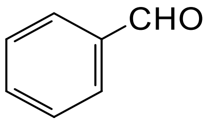
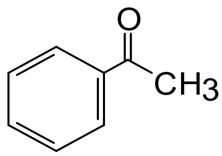
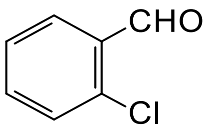
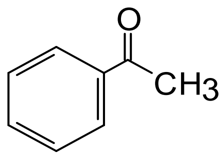
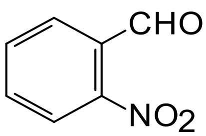
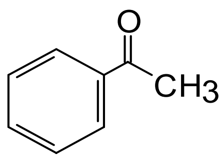
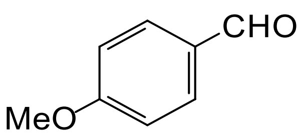
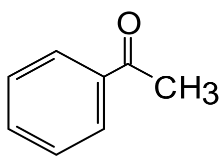
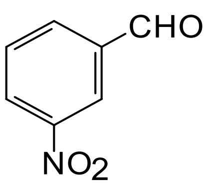
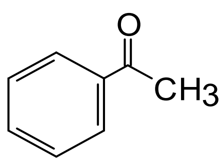
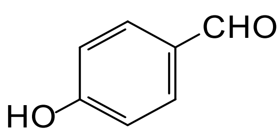
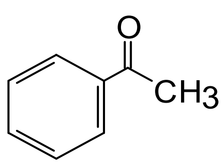
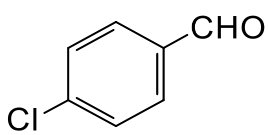
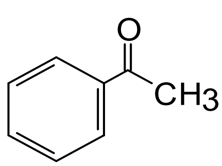
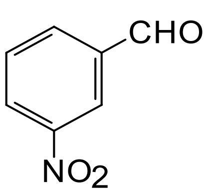
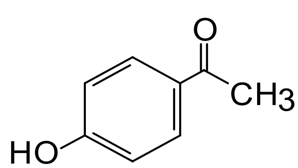
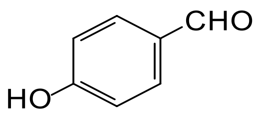
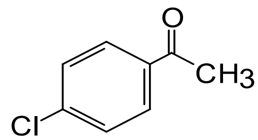
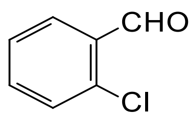
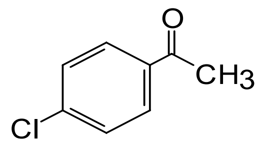
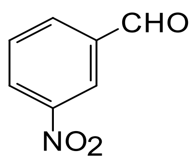
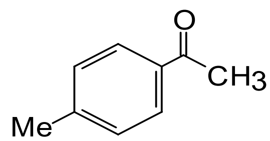
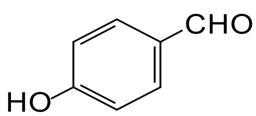
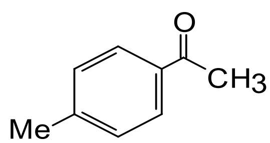
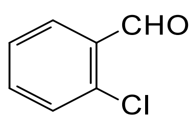
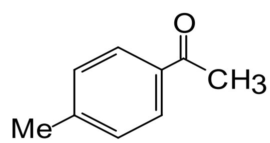
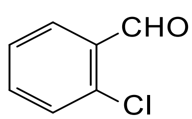
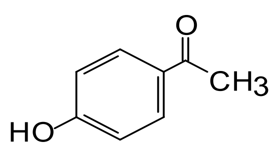
Entry	Aldehydes 1	Ketones 2	Product 4	Time (min.)	Yields [a,b] (%.)	MP (^0C)
a			4a	28	81	232-234
b			4b	24	94	202-204
c			4c	24	76	126-217
d			4d	29	88	----c
e			4e	25	80	196-197
f			4f	33	71	166-167
g			4g	24	92	----c
h			4h	33	88	196-197

Table. 1: Continued.....

Entry	Aldehydes 1	Ketones 2	Product 4	Time (min.)	Yields [a,b] (%.)	MP (^0C)
i			4i	23	74	167-168
j			4j	24	91	182-184
k			4k	29	88	189-190
l			4l	32	70	166-167
m			4m	32	92	196-197
n			4n	29	90	203-205

[a] Products were characterised by IR and ^1H NMR spectra and compared with authentic samples.

[b] Isolated and purified yields.

[c] Newly synthesized and spectroscopic data is given.

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