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ORIGINAL PAPER

Three-components condensation catalyzed by molecular iodine for the synthesis of 2,4,6-triarylpyridines and 5-unsubstituted-3,4-dihydropyrimidin-2(1*H*)-ones under solvent-free conditions

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Abstract One-pot, three-components synthesis of 2,4,6-triarylpyridines and 5-unsubstituted-3,4-dihydropyrimidin-2(1*H*)-ones was performed under solvent-free conditions using molecular iodine as the catalyst in moderate to good product yields.

Keywords Molecular iodine · Solvent-free · 2,4,6-Triarylpyridines · 5-Unsubstituted-3,4-dihydropyrimidin-2(1*H*)-ones

Introduction

The *N*-heterocyclic compounds, such as pyridines and dihydropyrimidinones, are very useful intermediates for the development of molecules of pharmaceutical or biological interest. Pyridines show variable biological activities, such as antimalarial, anticonvulsant, anesthetic, antioxidant, antibacterial, and antiparasitic properties [1–3]. In addition, dihydropyrimidinones have also attracted much attention in previous years due to the large range of biological activities leading to calcium channel blockers, antiviral, antitumor, and anti-inflammatory drugs [4, 5].

Owing to their wide range of pharmacological activity and industrial and synthesis applications, a number of methods have been reported for the synthesis of Kröhnke-type pyridines [6]. Traditionally, Kröhnke-type pyridines have been synthesized through the reaction of *N*-phenacylpyridinium salts with α,β-unsaturated ketones in the presence of ammonium acetate [6, 7], but the pyridinium salts and unsaturated ketones have to be synthesized first, which has let this method appear to be relatively expensive. The same compounds have also been synthesized by the condensation of 1,5-diketones with formamide-ammonium formate [8] and by other synthesis procedures [6]. However, most of the established methods suffer from some disadvantages, such as multi-step procedures, long reaction times, and use of toxic reagents and organic solvents. More recently, one-pot syntheses of 2,4,6-triarylpyridines by three-components condensation of aromatic ketones, aldehydes, and ammonium acetate have been reported [9–13]. The process consists of two or more synthesis steps, which are carried out without isolation of any intermediate and, thus, reduce time, saving money, energy, and raw materials. In addition, via the Biginelli reaction, the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones has received renewed interest, and several improved procedures have recently been reported. However, the scope of substrates for the Biginelli reaction is limited to aromatic aldehydes, acetoacetate (or acetylacetone) and urea or thiourea. The first Biginelli-like reaction, reported by Wang et al. [14], was conducted in CH_3CN by condensation of aldehydes, ketones, and urea, using $FeCl_3{\cdot}6H_2O$ and TMSCl as catalysts, which remarkably broadened the Biginelli reaction. Since then, the Biginelli-like reaction has been applied and improved by several authors [15–17].

In recent years, the usage of molecular iodine has drawn considerable attention as an inexpensive, nontoxic, readily available catalyst for various organic transformations to afford the corresponding products in excellent yields with high selectivity. The mild Lewis acidity associated with iodine enhances its usage in organic synthesis to realize several organic transformations using stoichiometric levels or even catalytic amounts [18–27]. As a part of our studies

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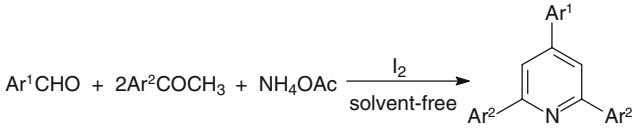
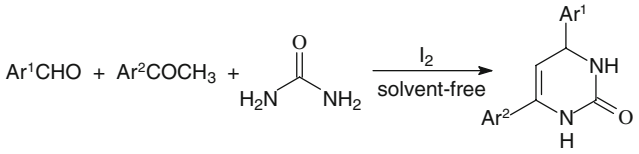


Scheme 1



Scheme 2

to explore the utility of iodine-catalyzed reactions [28–30], we proceeded to examine the synthesis of 2,4,6-triarylpyridines and 5-unsubstituted-3,4-dihydropyrimidin-2(1*H*)-ones in the presence of molecular iodine under solvent-free conditions (Schemes 1, 2).

Results and discussion

Initially, we explored the synthesis of 2,4,6-triphenylpyridine in order to identify optimal reaction conditions. The reactions were carried out under solvent-free conditions (Table 1, entries 1–10). Table 1 shows that the appreciable amount of I_2 for synthesis of 2,4,6-triphenylpyridine was 20 mol% (referred to benzaldehyde) under solvent-free conditions. An increase in the amount of I_2 did not lead to an improvement in yield. A reaction temperature of 120 °C was found to be optimal (Table 1, entry 4). The reaction medium had an influence on the reaction; the results showed that solvent-free conditions provided better yield than if solvents were used.

In order to explore the scope of our reagent system, we synthesized a series of 2,4,6-triarylpyridines via three-components condensation of aromatic ketones, aldehydes, and ammonium acetate (Table 2). Table 2 shows that both electron-deficient and electron-rich aromatic aldehydes were converted to the corresponding 2,4,6-triarylpyridines in moderate yields. Moreover, it is important to note that, in all cases, 2,4,6-triarylpyridines were precipitated upon dilution of the reaction mixture with *EtOH* and were isolated by simple filtration. The products thus obtained showed a single spot on TLC and were pure enough for all practical purposes.

According to Heravi et al. [9] and Razdanand colleagues [31], urea can also used as the ammonium source in the synthesis of 2,4,6-triarylpyridines. However, if we applied the established protocol of a 1/2/1.3 ratio of benzaldehyde/acetophenone/urea, we received, to our surprise, 3,4-dihydro-4,6-diphenylpyrimidin-2(1*H*)-one in good yield by a Biginelli-like reaction. Previously, molecular iodine had been explored as a powerful catalyst for the Biginelli reaction, in CH_3CN [32] and toluene [33], or under microwave irradiation [34]. However, the scope of substrates was limited to 1,3-dicarbonyl compounds in the above-reported methods. We herein report the synthesis of 5-unsubstituted-3,4-dihydropyrimidin-2(1*H*)-ones by one-pot three-components condensation of aromatic aldehydes

Table 1 Studies on the synthesis of 2,4,6-triphenylpyridine using iodine as catalyst

Entry	$c(I_2)$/mol%	Solvent	*T*/°C	Yield[a]/%
1	0	–	120	Trace
2	5	–	120	35
3	10	–	120	41
4	20	–	120	56
5	30	–	120	51
6	40	–	120	45
7	20	–	80	21
8	20	–	110	37
9	20	–	130	52
10	20	–	140	45
11	20	EtOH	78	22
12	20	CH_3CN	82	17
13	20	DMF	140	9
14	20	CH_2Cl_2	40	10
15	20	Et_3N	90	Trace
16	20	PhMe	110	11

Millimole ratio of benzaldehyde/acetophenone/NH_4OAc was 5.0/10.0/6.5. The reaction time was 6 h

[a] Isolated yields

Table 2 I_2-catalyzed solvent-free synthesis of 2,4,6-triarylpyridines

Entry	Ar^1	Ar^2	Yield[a]/%	m.p./°C	m.p./°C [Ref.]
1	C_6H_5	C_6H_5	56	133–134	134–135 [3]
2	4-$NO_2C_6H_4$	C_6H_5	61	195–196	195–197 [3]
3	4-ClC_6H_4	C_6H_5	57	124–126	125–127 [3]
4	4-MeC_6H_4	C_6H_5	52	119–120	123–124 [3]
5	4-HOC_6H_4	C_6H_5	48	182–184	184–185 [36]
6	C_6H_5	4-ClC_6H_4	52	126–128	126–127 [11]
7	C_6H_5	4-MeC_6H_4	54	156–157	157–158 [3]
8	4-Cl C_6H_4	4-ClC_6H_4	57	264–265	269–270 [36]

Millimole ratio of aldehyde/ketone/NH_4OAc/I_2 was 5.0/10.0/6.5/1.0. The reaction was accomplished under solvent-free conditions at 120 °C in 6 h

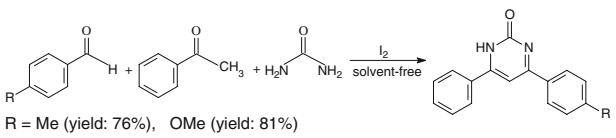
[a] Isolated yields

Table 3 I_2-catalyzed solvent-free synthesis of 5-unsubstituted-3,4-dihydropyrimidin-2(1*H*)-ones

Entry	Ar^1	Ar^2	Time/min	Yield[a]/%	m.p./°C	m.p./°C [Ref.]
1	C_6H_5	C_6H_5	30	78	229–230	228–230 [35]
2	4-ClC_6H_4	C_6H_5	20	75	265–266	267–269 [17]
3	2-ClC_6H_4	C_6H_5	40	70	264–265	260–263 [17]
4	4-HOC_6H_4	C_6H_5	30	68	257–258	255–257 [17]
5	3-BrC_6H_4	C_6H_5	25	79	258–259	256–258 [17]
6	C_6H_5	4-MeC_6H_4	30	73	173–174	174–175 [15]
7	4-$NO_2C_6H_4$	4-MeC_6H_4	25	80	215–217	214–215 [15]
8	C_6H_5	4-ClC_6H_4	25	77	221–222	223–224 [15]

Millimole ratio of aldehyde/ketone/urea/I_2 was 5.0/5.0/10.0/2.5. The reaction was accomplished under solvent-free conditions at 140 °C

[a] Isolated yields



Scheme 3

with aromatic ketones and urea, using iodine as the catalyst, under solvent-free conditions (Scheme 2). The results are summarized in Table 3.

In a preliminary study, we had found that 50 mol% of catalyst to aldehyde was sufficient to mediate the reaction toward the formation of the corresponding 5-unsubstituted-3,4-dihydropyrimidin-2(1*H*)-ones in good yields within the given reaction time. Table 3 shows that various aromatic aldehydes and several aromatic ketones were converted to the corresponding products in good yields and in short time. However, the dehydrogenated products were obtained when aromatic aldehydes with electron-donating groups, such as methoxy, methyl, were used (Scheme 3).

In conclusion, the method of synthesis described here represents a simple and inexpensive path to 2,4,6-triarylpyridines and 5-unsubstituted-3,4-dihydropyrimidin-2(1*H*)-ones. The advantages of our method are the avoidance of metals, organic solvents, and toxic reagents and operational simplicity. Further studies on the synthesis applications of 2,4,6-triarylpyridines and 5-unsubstituted-3,4-dihydropyrimidin-2(1*H*)-ones are now in progress.

Experimental

Reagents were obtained from commercial sources. Products were all known compounds and were identified by the comparison of their physical and spectra data with those reported in literature.

Typical procedure for the synthesis of 2,4,6-triphenylpyridine

To a mixture of 0.53 g benzaldehyde (5 mmol), 1.20 g acetophenone (10 mmol), and 0.50 g NH_4OAc (6.5 mmol) were added 0.25 g I_2 (1 mmol) at room temperature. Then, the mixture was stirred at 120 °C. After 6 h, the mixture obtained was treated with EtOH. A precipitate formed, which was collected by filtration, washed with EtOH, dried, and recrystallized from EtOH to afford the pure product, 2,4,6-triphenylpyridine. M.p. 133–134 °C ([3] 134–135 °C).

Typical procedure for 3,4-dihydro-4,6-diphenylpyrimidin-2(1H)-one

To a mixture of 0.53 g benzaldehyde (5 mmol), 0.60 g acetophenone (5 mmol), and 0.60 g urea (10 mmol) were added 0.63 g I_2 (2.5 mmol) at room temperature. Then, the mixture was stirred at 140 °C. After 30 min, the solid produced was treated with EtOH. A precipitate was formed, which was then filtered, washed with EtOH, dried, and recrystallized from EtOH to afford the pure product, 3,4-dihydro-4,6-diphenylpyrimidin-2(1*H*)-one. M.p. 229–230 °C ([35] 228–230 °C).

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