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Molecular iodine-catalyzed one-pot synthesis of 4-substituted-1,4-dihydropyridine derivatives via Hantzsch reaction

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Abstract—A simple, inexpensive and efficient one-pot synthesis of 1,4-dihydropyridine derivatives at room temperature using catalytic amount of iodine were reported with excellent product yields. An easy access to various substituted 1,4-dihydropyridine derivatives quantitatively using commercially available iodine as a catalyst.

In recent years, an increasing interest has been focused on the synthesis of 1,4-dihydropyridyl compounds owing to their significant biological activity.[1] In particular, dihydropyridine drugs such as nifedipine, nicardipine, amlodipine and others are effective cardiovascular agents for the treatment of hypertension.[2] 4-Aryl-1,4-dihydropyridines have been explored for their calcium channel activity and the heterocyclic rings are found in a variety of bioactive compounds such as vasodilator, bronchodilator, antiatherosclerotic, antitumour, antidiabetic, geroprotective and heptaprotective agents.[3] Moreover studies have discovered that these compounds exhibit diverse medical functions such as neuroprotectants, compounds with platelet antiaggregators, cerebral antiischaemic agents and chemosensitizers.[4] The remarkable drug activity of these compounds not only attracted many chemists to synthesize this heterocyclic nucleus but also became an active research area of continuing interest. It has been mostly reported that there are many methods to synthesize 1,4-dihydropyridine derivatives, in view of the biological importance associated with these compounds. The classical method involves the mixing of aldehyde with ethyl acetoacetate, and ammonia in acetic acid or in refluxing alcohol.[5] However, this method suffers from several disadvantages such as longer reaction times, excess of organic solvent, lower product yields and harsh refluxing conditions. Starting from Hantzsch[6] more than a century ago, there are several efficient methods developed for the synthesis of 1,4-dihydropyridines, which comprise the use of microwave,[7] ionic liquid,[8] at high temperature in refluxing solvent,[9] TMSCl–NaI[10] and metal triflates.[11] However, the use of high temperatures, expensive metal precursors and spending longer reaction times limiting these methods. Thus, the development of a simple, efficient and versatile method for the preparation of 1,4-dihydropyridine derivatives is an active area of research and there is a scope for further improvement towards milder reaction conditions and higher product yields.

In recent times, the use of molecular iodine[12] has received 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 enhanced its usage in organic synthesis to realize several organic transformations using stoichiometric levels to catalytic amounts. Owing to numerous advantages associated with this eco-friendly element, iodine has been explored as a powerful catalyst for various organic transformations.[13] As the 1,4-dihydropyridines are important biologically active compounds, which have profound medical applications, development of a reaction that uses catalytic amounts of mild toxic and readily available iodine should greatly contribute to the creation of environmentally benign processes.

As part of our ongoing interest in the iodine catalyzed reactions for various organic transformations,[14] we had the opportunity to further explore its catalytic activity towards the synthesis of 1,4-dihydropyridines.

Keywords: Hantzsch reaction; Synthesis of 1,4-dihydropyridine; Simple and efficient; Molecular iodine; Catalytic amounts.
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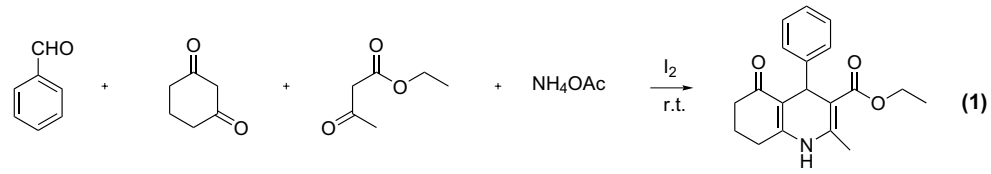
Table 1. Optimizing the reaction conditions[a]



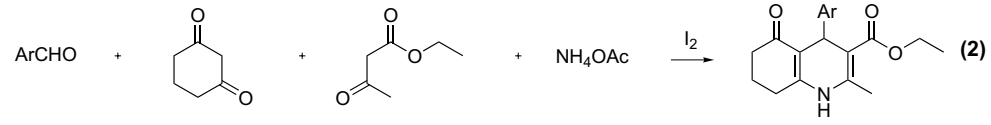
1a **2** **3** **4** **5a**

Entry	Iodine (mol %)	Time (h)	Yield (%)[b]
1	0	4	56
2	15	4	99
3	30	2.5	99
4	50	1.5	70

[a] Benzaldehyde:1,3-cyclohexanedione:ethyl acetoacetate:ammonium acetate = 1:1:1:1.
[b] Crude isolated yields.

Herein, we wish to report a novel synthesis of 1,4-DHPs promoted by the catalytic amount of iodine under ambient conditions with excellent yields. In an initial endeavour, benzaldehyde **1a**, 1,3-cyclohexanedione **2**, ethyl acetoacetate **3** and ammonium acetate **4** were stirred at room temperature in a few drops of ethanol. After 4 hours, only 56% of product **5a** was realized after recrystallization of the crude product from ethanol (entry 1 of Table 1). To improve the product yields and to optimize the reaction condition, iodine was used in catalytic amount (15 mol %) and a reaction was carried out under similar conditions. To our surprise, a significant improvement in the yield of the product **5a** (99% Y) was observed (entry 2). With this optimistic result in hand, we further investigated for the best reaction conditions. In this connection, we investigated the reaction outcome using different amounts of iodine. The increase in the quantity of iodine from 15 to 30 mol % not only lessens the reaction time from 4 to 2.5 h, but also enhanced the product yield from 56% to 99% (entry 3). Similarly, using 50 mol % of iodine as catalyst the reaction time further reduced to 1.5 h along with a decrease in the yield of the product **5a** (70% Y). At little elevated temperature (40 °C) using 15 mol % of iodine also gave better results in terms of both yield and reaction time (Table 1).

Table 2. Iodine catalyzed the synthesis of 1,4-dihydroquinoline derivatives through Hantzsch reaction

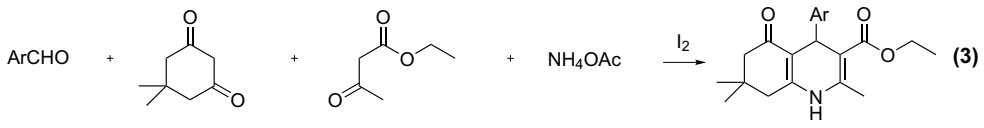


1 **2** **3** **4** **5**

Entry	1	Ar	I_2 (mol %)	Temperature (°C)	Time	Product	Yield (%)[a]	Mp (°C)[b]
1	**1a**	C_6H_5	30	25	2.5 h	**5a**	99	240–241
2	**1a**		15	40	30 min	**5a**	93	
3	**1b**	*p*-MeC_6H_4	30	25	1.5 h	**5b**	90	241–242
4	**1b**		15	40	35 min	**5b**	99	
5	**1c**	*P*-$OMeC_6H_4$	30	25	4 h	**5c**	97	193–195
6	**1c**		15	40	40 min	**5c**	87	
7	**1d**	*p*-FC_6H_4	30	25	3.25 h	**5d**	91	243–244
8	**1d**		15	40	35 min	**5d**	87	
9	**1e**	*p*-ClC_6H_4	30	25	6 h	**5e**	99	234–235
10	**1e**		15	40	40 min	**5e**	90	
11	**1f**	*p*-HOC_6H_4	30	25	2.5 h	**5f**	99	220–222
12	**1f**		15	40	45 min	**5f**	92	
13	**1g**	*o*-$NO_2C_6H_4$	30	25	1.5 h	**5g**	94	190–191
14	**1g**		15	40	25 min	**5g**	91	
15	**1h**	*m*-$NO_2C_6H_4$	30	25	1.5 h	**5h**	99	198–200
16	**1h**		15	40	25 min	**5h**	92	
17	**1i**	*p*-$NO_2C_6H_4$	30	25	3 h	**5i**	99	204–205
18	**1i**		15	40	25 min	**5i**	85	
19	**1j**	Isopropyl	30	25	5 h	**5j**	99	180–182
20	**1j**		15	40	40 min	**5j**	99	

[a] Crude isolated yields.
[b] After recrystallization.

Table 3. Iodine catalyzed the synthesis of 1,4-dihydroquinoline derivatives through Hantzsch reaction



1 6 3 4 7

Entry	1	Ar	I_2 (mol %)	Temperature (°C)	Time	Product	Yield (%)[a]	Mp (°C)[b]
1	**1a**	C_6H_5	30	25	1.5 h	**7a**	93	209–210
2	**1a**		15	40	30 min	**7a**	93	
3	**1c**	*p*-$OMeC_6H_4$	30	25	2 h	**7c**	93	243–245
4	**1c**		15	40	35 min	**7c**	90	
5	**1e**	*p*-ClC_6H_4	30	25	2.5 h	**7e**	92	230–232
6	**1e**		15	40	35 min	**7e**	99	
7	**1f**	*p*-HOC_6H_4	30	25	2.5 h	**7f**	99	237–238
8	**1f**		15	40	35 min	**7f**	97	

[a] Crude isolated yields.
[b] After recrystallization.

Based on these observations, we have also conducted the reaction using 15 mol % of iodine at elevated temperature (40 °C). As expected, the reaction completed within 30 min with excellent product yield is another significant finding regarding these reactions. In order to evaluate the efficiency of iodine as a catalyst, a range of aryl- and alkyl aldehydes **1b–j** were subjected to react with **2**, **3** and **4** in the presence of either 30 or 15 mol % of iodine to generate **5** and the results are summarized in Table 2.[15] For example, with 30 mol % of iodine as catalyst *p*-chlorobenzaldehyde (Table 2, entries 9 and 10) takes 6 h to complete, whereas the same reaction takes place within 40 min at 40 °C without significant loss yields. In general, the yields are little less with 15 mol % of catalyst and the reaction times are also short. Both aliphatic and aromatic aldehydes react equally good to give the products with excellent yields. The aryl group substituted with different groups and same groups located at different positions of the aromatic ring has not shown much effect on the formation of the final product.

Next, we investigated the effect of substitution in 1,3-cyclohexanedione system such as 5,5-dimethyl-1,3-cyclohexanedione. Aromatic aldehydes such as benzaldehyde and different substituted benzaldehydes reacts with dione **6**, ethyl acetoacetate and ammonium acetate in the presence of iodine to afford the products in excellent yields. Interestingly, we have not observed much difference in the product yields either with 30 mol % at ambient temperature or with 15 mol % at higher temperature (40 °C). The reduced reaction times with all substrates using **6** may be due to the more reactivity of 5,5-dimethyl-1,3-cyclohexanedione over **2** (Table 3).

In conclusion, we have successfully developed an easy and efficient method to prepare a variety of 4-substituted-1,4-dihydropyridines from the reaction of different aryl or alkyl aldehydes, 1,3-cyclohexanedione, ethyl acetoacetate and ammonium acetate in the presence of catalytic amount of iodine at room temperature. The catalytic activity of iodine is remarkable and the use of low cost, commercially available iodine as catalyst for the synthesis of 1,4-DHPs in excellent yields is also significant under the aspect of environmentally benign processes. The advantages such as shorter reaction times, milder conditions, simplicity of the reaction, excellent product yields, the easy procedures to carry out the reaction makes the inexpensive and commercially available iodine as a powerful catalyst for the synthesis of 1,4-DHPs.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.05.148.

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14. Unpublished results.
15. A typical experimental procedure for the preparation of **5a**: A 10 mL round-bottomed flask charged with benzaldehyde **1a** (0.106 g, 1.0 mmol), 1,3-cyclohexanedione **2** (0.112 g, 1.0 mmol), ethyl acetoacetate **3** (0.130 g, 1.0 mmol), ammonium acetate **4** (0.077 g, 1.0 mmol) and iodine (0.076 g, 0.3 mmol) followed by few drops (5–6 drops) of ethanol. The mixture was then stirred at room temperature until the reaction was completed (2.5 h, monitored by TLC). The reaction mixture was treated with aq $Na_2S_2O_3$ solution, extracted into ethyl acetate (2×20 mL) and the crude product (99%) was recrystallized from ethanol to give the product **5a** as a yellow solid (0.304 g, 98% Y) (mp: 240–241 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.18 (t, 3H, $J = 6.8$ Hz), 1.80–2.10 (m, 2H), 2.30–2.44 (m, 7H), 4.05 (q, 2H, $J = 6.8$ Hz), 5.09 (s, 1H), 6.07 (s, 1H), 7.10 (t, 1H, $J = 7.6$ Hz), 7.20 (t, 2H, $J = 7.6$ Hz), 7.30 (d, 2H, $J = 7.6$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.16, 19.34, 21.01, 27.46, 36.38, 37.00, 59.78, 106.06, 113.46, 125.99, 127.90, 127.98, 143.30, 147.12, 149.58, 167.41. HRMS calcd for $C_{19}H_{21}NO_3$ (M^+) 311.1521, found: 311.1526.