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5-Pyrrolidin-2-yltetrazole-Promoted One-Pot Hantzsch Polyhydroquinoline Synthesis Using NH_4HCO_3 as Nitrogen Source

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A straightforward and green synthesis of polyhydroquinoline derivatives was reported via a four-component coupling reaction of aldehydes, dimedone, active methylene compounds, and ammonium bicarbonate in the presence of 5-pyrrolidin-2-yltetrazole under solvent-free conditions. The method offers several advantages including high yields, an environmental friendly procedure, a short reaction time, and easy isolation of products.

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Polyhydroquinoline derivatives are of considerable interest in industry as well as in academia owing to their promising biological activity as calcium channel blockers, vasodilators, bronchodilators, and anti-atherosclerotic, geroprotective, hepatoprotective and antidiabetic agents.[1] Furthermore, recent studies have revealed several other medicinal applications that indicate neuroprotectant and platelet anti-aggregratory activity, cerebral anti-ischemic activity in the treatment of Alzheimer's disease, and as a chemosensitizer in tumour therapy.[2] Thus, the synthesis of this heterocyclic nucleus is of great interest.

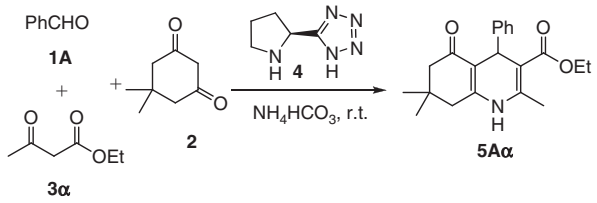
1,4-Dihydropyridines (1,4-DHPs) were first synthesized more than a century ago by heating a mixture of aldehyde, β-keto ester, and ammonia in ethanol and refluxing for several hours.[3] However, the method suffers from drawbacks such as long reaction times, drastic reaction conditions, the use of a large quantity of volatile organic solvents, and providing unsatisfactory yields. Recently, many synthetic methods for preparing these compounds have been reported, including classical conditions, with microwave or ultrasound irradiation, using Lewis acids as well as protic acid promoters such as: microwaves,[4] ionic liquid,[5] high temperature under reflux conditions,[6] iodine,[7] metal triflates,[8] HY-zeolite (acidic molecular sieve),[9] TMSCl–NaI (chlorotrimethylsilane–NaI),[10] ceric ammonium nitrate (CAN),[11] or L-Proline,[12] and a grinding technique.[13] But some of the methods still have their own limitations in terms of yields, the use of high temperatures, catalysts that are harmful to the environment, etc.

Recently, organocatalysis has become an increasingly well-investigated area of organic chemistry, the primary advantage of which is that it avoids the use of metals, which can be both expensive and toxic. Also, organocatalysts can often be used under aerobic conditions, are cheap to use, and in most cases only a small molecule is required to effect a high yield.[14] The proline-derived organocatalyst 5-pyrrolidin-2-yltetrazole **4**, which has been applied in a variety of reactions, displayed great catalytic activity and efficiency.[15] As experimental design using less hazardous solvents or solventless catalytic reactions has received tremendous attention in recent years in the area of green synthesis,[16] in the present paper, aiming at environmentally friendly methodologies for the preparation of 1,4-DHPs, we present our findings about a 5-pyrrolidin-2-yltetrazole-catalyzed four-component Hantzsch reaction without solvent at ambient temperature.

Results and Discussion

First the mixture of benzaldehyde **1A**, 5,5-dimethylcyclohexane-1,3-dione **2**, ethyl acetoacetate **3α**, and ammonium bicarbonate in ethanol were chosen as the model reaction (Scheme 1) to detect whether the use of catalyst **4** was efficient and to investigate the optimal conditions. The results are summarized in Table 1.

As shown in Table 1, it was found that the conditions of no catalyst had a poor effect on the yield of the expected product **5Aα**, indicating a catalyst would be needed for it. Then the condensation reaction of these compounds was tested in the presence of different amounts of catalyst **4**, i.e. 1, 2, 5, 10 mol-% under similar conditions. Fortunately, a significant improvement was observed and the yield of the product **5Aα** was dramatically increased to 56% after workup; also, the reaction time was greatly shortened (Table 1, entry 2). As indicated in Table 1, use of just 2 mol-% of catalyst **4** in ethanol is sufficient to push the reaction forward (Table 1, entry 3). In view of environmentally friendly methodologies, we have discovered that the Hantzsch



Scheme 1.

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reaction proceeds very efficiently by stirring a mixture of neat reactants at room temperature for only 15 min, under solvent-free conditions, and produces polyhydroquinoline derivatives **5Aα** in high yields (Table 1, entry 6). Here, we considered that ammonium bicarbonate is a promising alternative to ammonium acetate or ammonia as nitrogen source, because carbon dioxide that is formed from the decomposition of ammonium bicarbonate can be released directly. Actually, in order to examine effect of acidity of AcOH from the cleavage of ammonium acetate used in traditional method, AcOH was used as catalyst under optimized conditions. In contrast to **4**, the reaction gave a lower yield (Table 1, entry 7).

As **4** has a similar structure and properties to L-proline,[15a] its mechanism as a catalyst for the unsymmetric Hantzsch reaction under solvent-free conditions is proposed (Scheme 2). It might catalyze the Knoevenagel-type coupling of aldehydes with active methylene compounds and then the Michael-type addition of intermediates through either path A or path B to give the 1,4-DHPs.

With good results in hand, we then selected the optimized reaction conditions to examine the universality of this catalyst's application (Scheme 3). As shown in Table 2, aromatic aldehydes carrying either electron donating or withdrawing substituents worked well, giving excellent yields of products with little difference in high purity. Aliphatic or heterocyclic aldehydes under similar conditions also gave medium to good yields (Table 2, entries 11–14). Other active methylene compounds such as methyl acetoacetate or pentane-2,4-dione under similar conditions gave the corresponding products in relative lower yields (Table 2, entries 15–19).

Later, cyclohexane-1,3-dione **6** was used with similar success to provide the corresponding 1,4-DHPs in order to check the versatility of the procedure (Scheme 3). The results (Table 3) also showed a series of aromatic and heterocyclic aldehydes that underwent cyclocondensation to give good to high yields (83–97%) of the products.

Table 1. Optimizing the reaction conditions
All reactions were carried out in ethanol at room temperature and the ratio of **1A**:**2**:**3α**:NH_4HCO_3 was 1:1:1:1.2

Entry	Catalyst [mol-%]	Time	Yield [%][A]
1	None	24 h	12
2	1	4 h	56
3	2	2 h	88
4	5	2 h	85
5	10	2 h	85
6	2	15 min	98[B]
7	20[C]	4 h	48

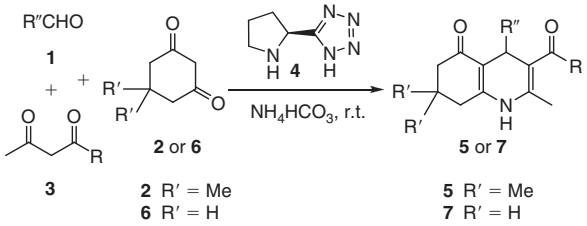
[A]Isolated yields.
[B]Reactions was carried out under solvent-free conditions at room temperature.
[C]AcOH as catalyst.

Conclusions

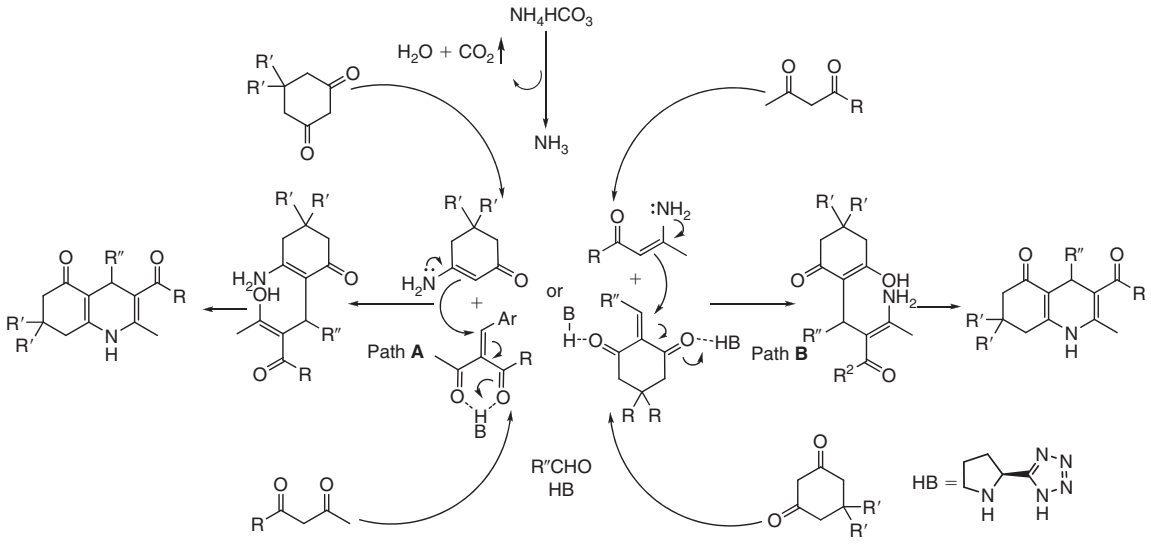
In summary, we have developed a simple, efficient, and green method for the synthesis of 4-substituted-1,4-dihydropyridines with the aid of 5-pyrrolidin-2-yltetrazole at room temperature without solvent. The method offers several advantages including high yields, a short reaction time, and a simple experimental workup procedure, which makes it a useful process for the synthesis of 1,4-dihydropyridines.

Experimental

Melting points were obtained with a capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Thermo Nicolet Avatar 370 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian-400 and Bruker



Scheme 3.



Scheme 2. Proposed mechanism for 5-pyrrolidin-2-yltetrazole-catalyzed polyhydroquinoline synthesis.

Avance DRX-500 using $CDCl_3$ or [D_6]DMSO as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts (δ) are expressed in ppm and coupling constants J are given in Hz. Mass spectra were obtained on a Trace DSQ mass spectrometer. Elemental analysis was performed on a VarioEL-3 instrument. 5-Pyrrolidin-2-yltetrazole used in the current work was prepared according to previously published work;[15i] $[\alpha]_D^{25}$ −9.0 (*c* 0.65, MeOH). δ_H (400 MHz, [D_6]DMSO) 4.78 (m, 1H), 3.30 (m, 2H), 2.36 (m, 1H), 1.98–2.20 (m, 3H). δ_C (100 MHz, [D_6]DMSO) 157.74, 54.97, 44.64, 29.94, 23.17. *m*/*z* (%) 70 ([M^+], 100), 139 (20).

General Procedure for the Synthesis of Polyhydroquinoline Derivatives under Solvent-Free Conditions

To a mixture of aldehyde (2 mmol), dimedone (2 mmol), β-keto ester (2 mmol) and ammonium bicarbonate (2.4 mmol), 5-pyrrolidin-2-yltetrazole (0.04 mmol) was added and the mixture was stirred at room temperature for the given time, monitoring the reaction by TLC. After the completion of the reaction, ethyl acetate (20 mL) was added, and the solution washed with brine and dried over sodium sulfate. After concentration under vacuum, a crude solid was obtained. The pure product was obtained through crystallization from ethanol.

Spectroscopic Data for Selected Products

Ethyl 4-(2-Chloro-6-fluorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate ***5Bα***

Mp 250–253°C. Calc. for $C_{21}H_{23}NO_3$: C 64.4, H 5.9, N 3.6. Found: C 64.5, H 5.9, N 3.5%. ν_{max} (KBr)/cm^{-1} 3288, 3212, 3088, 2956, 1692, 1612. δ_H (400 MHz, $CDCl_3$) 7.05 (m, 2H), 6.87 (t, 1H), 6.44 (s, 1H), 5.64 (s, 1H), 4.03 (q, *J* 7.2, 2H), 2.29–2.08 (m, 7H), 1.14 (t, *J* 7.2, 3H), 1.06 (s, 3H), 0.96 (s, 3H). δ_C (100 MHz, $CDCl_3$) 195.6, 167.5, 150.2, 145.3, 135.3, 135.3, 130.9, 130.7, 127.5, 127.4, 125.7, 114.0, 113.7, 108.7, 102.1, 59.7, 50.6, 40.8, 32.3, 31.2, 29.6, 29.3, 27.1, 19.1, 14.3. *m*/*z* (%) 392.5 ([$M^+ + 1$], 100), 394.5 ([$M^+ + 3$], 37).

Ethyl 4-(2,4-Dimethoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate ***5Cα***

Mp 237−238°C. Calc. for $C_{23}H_{29}NO_5$: C 69.2, H 7.3, N 3.5. Found: C 69.2, H 7.2, N 3.2%. ν_{max} (KBr)/cm^{-1} 3290, 3082, 2953, 2835, 1694, 1648, 1605. δ_H (400 MHz, $CDCl_3$) 7.18 (t, *J* 4.0, 1H), 6.65 (s, 1H), 6.34 (m, 2H), 5.16 (s, 1H), 4.03 (q, *J* 8.0, 2H), 3.75 (s, 3H), 3.72 (s, 3H), 2.26–2.06 (m, 7H), 1.19 (t, *J* 8.0, 3H), 1.04 (s, 3H), 0.91 (s, 3H). δ_C (100 MHz, $CDCl_3$) 195.6, 168.1, 159.1, 158.5, 149.1, 143.2, 131.6, 127.5, 110.7, 105.1, 103.9, 98.4, 59.5, 55.3, 55.2, 50.8, 41.0, 33.0, 32.5, 29.6, 26.8, 19.1, 14.2. *m*/*z* (%) 399.2 ([M^+], 25), 398.1 ([$M^+ - 1$], 100).

Accessory Publication

General experimental details and experimental characterization data for compounds are available from the journal's website.

Table 3. 5-Pyrrolidin-2-yltetrazole-promoted one-pot Hantzsch polyhydroquinoline synthesis using NH_4HCO_3 as nitrogen source
The ratio of **1**:**6**:**3α**:NH_4HCO_3 was 1:1:1:1.2. See Scheme 3 for compounds

Entry	**1**	R″	Time [min]	Products	Yield [%][A]
1	**1A**	C_6H_5	15	**7Aα**	95
2	**1B**	2-F-6-Cl-C_6H_3	20	**7Bα**	90
3	**1C**	2,4-$(OCH_3)_2$-C_6H_3	20	**7Cα**	93
4	**1D**	3-Cl-C_6H_4	15	**7Dα**	93
5	**1E**	3-NO_2-C_6H_4	20	**7Eα**	93
6	**1F**	4-OCH_3-C_6H_4	15	**7Fα**	96
7	**1G**	4-CH_3-C_6H_4	15	**7Gα**	97
8	**1H**	4-Cl-C_6H_4	15	**7Hα**	93
9	**1I**	4-F-C_6H_4	15	**7Iα**	90
10	**1K**	3-F-C_6H_4	20	**7Kα**	92
11[B]	**1L**	4-Methylthiazol-5-yl	30	**7Lβ**	83

[A]Isolated yield.
[B]**3β** as active methylene compound.

Table 2. 5-Pyrrolidin-2-yltetrazole-promoted one-pot Hantzsch polyhydroquinoline synthesis using NH_4HCO_3 as nitrogen source
The ratio of **1**:**2**:**3**:NH_4HCO_3 was 1:1:1:1.2

Entry	**1**	**3**	R″	R	Time [min]	Products	Yield [%][A]
1	**1A**	**3α**	C_6H_5	OC_2H_5	15	**5Aα**	98
2	**1B**	**3α**	2-F-6-Cl-C_6H_3	OC_2H_5	20	**5Bα**	92
3	**1C**	**3α**	2,4-$(OCH_3)_2$-C_6H_3	OC_2H_5	20	**5Cα**	96
4	**1D**	**3α**	3-Cl-C_6H_4	OC_2H_5	15	**5Dα**	93
5	**1E**	**3α**	3-NO_2-C_6H_4	OC_2H_5	20	**5Eα**	93
6	**1F**	**3α**	4-OCH_3-C_6H_4	OC_2H_5	15	**5Fα**	98
7	**1G**	**3α**	4-CH_3-C_6H_4	OC_2H_5	15	**5Gα**	98
8	**1H**	**3α**	4-Cl-C_6H_4	OC_2H_5	15	**5Hα**	92
9	**1I**	**3α**	4-F-C_6H_4	OC_2H_5	15	**5Iα**	92
10	**1J**	**3α**	3-OH-C_6H_4	OC_2H_5	30	**5Jα**	90
11	**1N**	**3α**	Furan-2-yl	OC_2H_5	35	**5Nα**	88
12	**1O**	**3α**	Thiophen-2-yl	OC_2H_5	35	**5Oα**	86
13	**1P**	**3α**	Cyclohexyl	OC_2H_5	40	**5Pα**	82
14	**1Q**	**3α**	Ethyl	OC_2H_5	45	**5Qα**	80
15	**1A**	**3β**	C_6H_5	OCH_3	15	**5Aβ**	92
16	**1F**	**3β**	4-OCH_3-C_6H_4	OCH_3	20	**5Fβ**	88
17	**1G**	**3β**	4-CH_3-C_6H_4	OCH_3	15	**5Gβ**	91
18	**1I**	**3β**	4-F-C_6H_4	OCH_3	15	**5Iβ**	96
19	**1A**	**3γ**	C_6H_5	CH_3	20	**5Aγ**	85

[A]Isolated yield.

Acknowledgements

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