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D,L-Proline-Catalyzed One-Pot Synthesis of Pyrans and Pyrano[2,3-c]pyrazole Derivatives by a Grinding Method under Solvent-Free Conditions

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Abstract: D,L-Proline was found to efficiently catalyze the one-pot condensation of aromatic aldehydes, malononitrile, and dimedone (1,3-cyclohexanedione or 3-methyl-1-phenyl-2-pyrazolin-5-one) 2-Amino-3-cycano-4-aryl-7,7-dimethyl-5,6,7,8-tetrahydrobenzo[b]pyrans and 6-amino-5-cyano-4-aryl-1,4-dihydropyrano[2,3-c]pyrazoles were synthesized by a grinding method under solvent-free conditions. The reaction proceeded cleanly at room temperature to afford the products in good yields.

Keywords: 1,3-cyclohexanedione, 1,4-dihydropyrano[2,3-c] pyrazole, dimedone, D,L-proline, grinding method, malononitrile, 3-methyl-1-phenyl-2-pyrazolin-5-one, solvent free, 5,6,7,8-tetrahydrobenzo[b]pyrans

INTRODUCTION

Synthetic chemistry consumes energy and material. One of the greatest environmentally problematic aspects of organic synthetic chemistry is the use of solvent. The solvent has to be produced in another chemical process, which also consumes energy and resources. Within the reaction, the vast amount of solvent has to be heated or cooled, consuming large amounts of energy, and has to be removed after completion of the

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reaction from the reaction mixture. The best solvent is no solvent.^[1] A move away from the use of solvents in organic synthesis has led in some cases to improved results and milder synthetic procedures, and the solvent-free thermal reactions are more important for practical synthetic processes in industry.^[2]

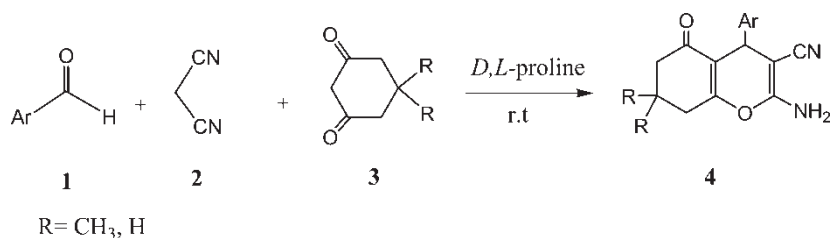
It is well known that 4*H*-pyran and its derivatives are very useful compounds. They have been widely used as medicine intermediates because of their useful biological and pharmacological properties, such as antiallergic^[3] and antitumor agents.^[4] The 4*H*-pyran ring can be transformed to pyridine systems, which relate to pharmacologically important calcium antagonists of the dihydropyridine (DHP) type.^[5] Polyfunctionalized 4*H*-pyrans are a common structural unit in a number of natural products.^[6] 2-Amino-3-cyano-4*H*-pyrans possess photochemical activity.^[7]

The conventional synthesis of 2-amino-3-cyano-4*H*-pyrans use organic solvent, but these solvents make the workup procedure complicated and lead to poor yields of products.^[8] In recent years, 2-amino-3-cyano-4*H*-pyrans have also been synthesized under microwave,^[9] with ultrasound irradiation,^[10] or in aqueous media.^[11,12] Some two-component^[13] and three-component^[11] condensations have been introduced for the synthesis of 2-amino-3-cyano-4*H*-pyrans. Each of these methods has its own merit, with at least one of the limitations of low yields, long reaction time, effluent pollution, harsh reaction conditions, and tedious workup procedures.

The amino acid proline is a remarkable molecule, which has become important in asymmetric catalysis, where it can act as a ligand in asymmetric transition-metal catalysis, a chiral modifier in heterogeneously catalyzed hydrogenations, and most important, can itself be an effective organocatalyst of several powerful asymmetric transformations, such as aldol,^[14] Michael,^[15] and Knoevenagel reactions.^[16] Proline is an abundant bifunctional molecule that is inexpensive and available in both enantiomeric forms. These two functional groups can act as both acid and base and can also facilitate chemical transformations in concert, similar to enzymatic catalysis.^[17]

The grinding method has increasingly been used in organic synthesis in recent years. Compared with traditional methods, this method is more efficient and selective. A large number of organic reactions can be carried out in high yields with mild conditions and simplicity in process and handling by the grinding method.^[11,18]

All of these reasons spur us to study the possibility of synthesis of 2-amino-3-cyano-4-aryl-7,7-dimethyl-5,6,7,8-tetrahydrobenzo[*b*]pyrans (**4**) and 6-amino-5-cyano-4-aryl-1,4-dihydropyrano[2,3-*c*]pyrazoles (**6**) under solvent-free conditions. In this manuscript, we report a highly efficient procedure for the synthesis of these compounds via a one-pot grinding method under solvent-free conditions using an inexpensive and commercially available *D,L*-proline as catalyst (Schemes 1 and 2).

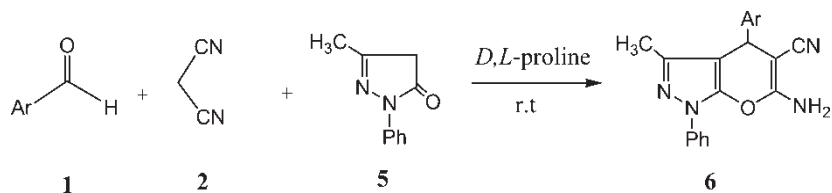


Scheme 1.

RESULTS AND DISCUSSION

In a typical general experimental procedure, aromatic aldehydes (**1**), malononitrile (**2**), dione [1,3-cyclohexanedione (**3**) or 3-methyl-1-phenyl-2-pyrazolin-5-one (**5**)], and a catalytic amount of *D,L*-proline are added to a mortar. The mixture is ground by mortar and pestle at room temperature for a period. The solid product is obtained from an intermediate melt and then is laid up at room temperature for 0.5 h. The mixture is transferred to ice water and then is filtered off. The crude products are purified by recrystallization by ethanol (95%) to afford the products (**4** or **6**) in good yields. The authenticity of the products was established by comparing their melting points, IR spectra, and ¹H NMR spectra with literature.^[8–12]

In the first instance, 4-chlorobenzaldehyde, malononitrile, and dione were ground in the presence of *D,L*-proline under solvent-free conditions. The appropriate reaction conditions were investigated with the results summarized in Table 1. Without catalyst, 2-amino-3-cyano-4-(4-chlorophenyl)-7,7-dimethyl-5,6,7,8-tetrahydrobenzo[*b*]pyran was not obtained for 40 min using the grinding method. The solid compound was not obtained from the intermediate melt. Increasing the amount of the proline to 5 mol%, 10 mol%, 15 mol%, 20 mol%, and 25 mol% results in accelerating the reaction. The yields of product were 75%, 81%, 90%, 94%, and 94% respectively, and the solidified time was 15 min, 10 min, 5 min, 5 min, and 5 min respectively. Use of 20 mol% proline was sufficient to push the reaction forward. Higher amounts of the catalyst did not improve the results to a



Scheme 2.

Table 1. Effects of the reaction conditions on the yields of 2-amino-3-cyano-4-(4-chlorophenyl)-7,7-dimethyl-5,6,7,8-tetrahydrobenzo[b]pyran

| Entry | Catalyst (mol%) | Grinding time (min) | Yield (%) ^a |
|----------|-----------------|---------------------|------------------------|
| 1 | 0 | 40 | 0 |
| 2 | 5 | 15 | 75 |
| 3 | 10 | 10 | 81 |
| 4 | 15 | 5 | 90 |
| 5 | 20 | 5 | 94 |
| 6 | 25 | 5 | 94 |

^aIsolated yields.

greater extent. So, proline was an efficient catalyst, and 20 mol% proline was chosen as a quantitative catalyst for the reactions.

As the appropriate reaction conditions had been established, the generality of the reaction was examined with the results summarized in Table 2. The three-component cyclocondensation reaction proceeded smoothly to give the corresponding products **4**. The property of substituents on the aromatic ring showed strongly obvious effects in terms of yields and grinding time under this reaction condition. Benzaldehyde and other aromatic aldehydes containing electron-withdrawing groups (such as nitro group, halide) (**4a–4h**) reacted better to give the corresponding products in higher yields than aromatic aldehydes containing electron-donating groups (such as alkyl group, alkoxy group) (**4i–4k**).

In addition, the position of substituents in the benzene ring had no obvious effects on the yields of product. The aromatic aldehydes with *ortho*-, *meta*-, and *para*-position substituents in the benzene ring all gave the corresponding products (**4b–4g**) in good yields (91–95%).

On the other hand, aromatic aldehyde reacted with **2** and 1,3-cyclohexanedione to afford the corresponding products (**4l**) and (**4m**) for 5 min using the grinding method in 92% and 90% yields respectively. 1,3-Cyclohexanedione and dimeone had similar reactivity in terms of yields and grinding time under this reaction condition.

It can easily be seen that the reaction of aromatic aldehydes with **2** and dimeone were carried out in good yields by the grinding method under solvent-free conditions using proline as catalyst. For example, compounds **4a**, **4b**, and **4e** were previously prepared in 77%, 63%, and 85% yields respectively using piperidine as catalyst in ethanol.^[9b] These compounds also were previously prepared in 71%, 81%, and 72% yields respectively catalyzed by KF-Al₂O₃ in DMF at room temperature for 1–3 h,^[8b] whereas the present procedure offered them in 91%, 94%, and 92% yields respectively. It was apparent that this method can accelerate this reaction.

Table 2. Synthesis of 2-amino-3-cyano-4-aryl-7,7-dimethyl-5,6,7,8-tetrahydro benzo[b]pyrans by a grinding method

| Entry | Ar | R | Grinding time (min) | Yield (%) ^a | Mp (°C) | |
|-----------|---|-----------------|---------------------|------------------------|---------|----------------------------|
| | | | | | Found | Reported ^[Lit.] |
| 4a | C ₆ H ₅ | CH ₃ | 5 | 91 | 228–230 | 228–230 ^[8b] |
| 4b | 4-ClC ₆ H ₄ | CH ₃ | 5 | 94 | 207–209 | 207–209 ^[8b] |
| 4c | 3-ClC ₆ H ₄ | CH ₃ | 5 | 91 | 230–232 | 230–232 ^[10] |
| 4d | 2-ClC ₆ H ₄ | CH ₃ | 5 | 92 | 214–215 | 215–216 ^[12b] |
| 4e | 4-NO ₂ C ₆ H ₄ | CH ₃ | 5 | 92 | 180–181 | 177–178 ^[8e] |
| 4f | 3-NO ₂ C ₆ H ₄ | CH ₃ | 15 | 95 | 208–210 | 210–212 ^[9b] |
| 4g | 2-NO ₂ C ₆ H ₄ | CH ₃ | 5 | 92 | 229–231 | 224–226 ^[11a] |
| 4h | 4-BrC ₆ H ₄ | CH ₃ | 3 | 91 | 197–199 | 196–198 ^[9c] |
| 4i | 4-CH ₃ C ₆ H ₄ | CH ₃ | 8 | 80 | 220–221 | 220–222 ^[12b] |
| 4j | 4-OHC ₆ H ₄ | CH ₃ | 10 | 81 | 205–206 | 206–208 ^[10] |
| 4k | 3-OH-4-CH ₃ OC ₆ H ₃ | CH ₃ | 10 | 88 | 232–233 | 228–230 ^[10] |
| 4l | 4-ClC ₆ H ₄ | H | 5 | 92 | 226–228 | 226–229 ^[12a] |
| 4m | 4-NO ₂ C ₆ H ₄ | H | 5 | 90 | 235–236 | 234–235 ^[12a] |

^aIsolated yields.

D,L-Proline was also found to efficiently catalyze the one-pot condensation of **1**, **2**, and **5**. Compounds **6** were synthesized by the grinding method under solvent-free conditions.

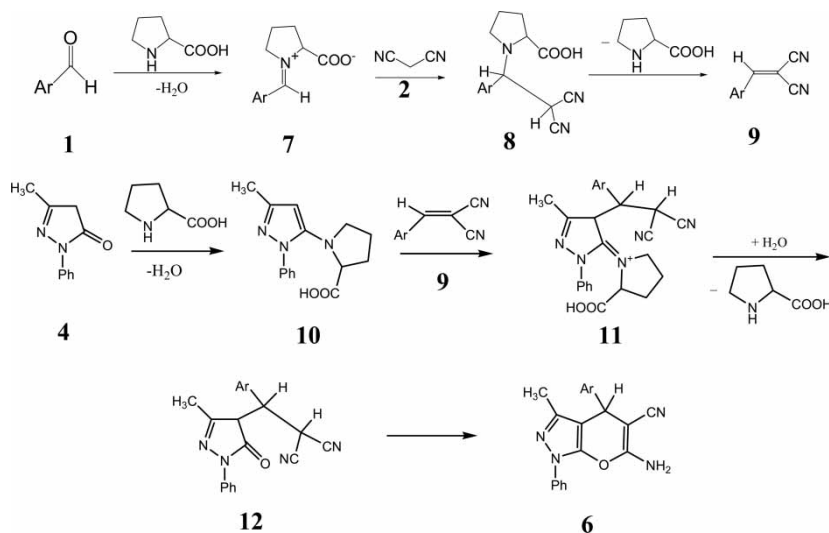
Benzaldehyde and other aromatic aldehydes containing electron-withdrawing groups (such as nitro group, halide), **2**, and **5** were ground under this reaction condition to afford the corresponding products **6** with good yields (95%–99%) in Table 3. The reaction of aromatic aldehydes containing electron-donating groups (such as alkyl group, alkoxy group) with **2** and **5** can also give the corresponding products in good yields (85–99%). The property of substituents on the aromatic ring did not show strongly obvious effects in terms of yields under this reaction condition. The reaction using the aromatic aldehydes containing electron-donating groups as substituents required longer grinding time to give the corresponding products than benzaldehyde and other aromatic aldehydes containing electron-withdrawing groups. The solidified products **6a**–**6h** were obtained for 5 min from the intermediate melt. The solidified products **6i**–**6k** was obtained for 10–20 min from the intermediate melt. The aromatic aldehydes containing electron-donating groups had higher reactivity than the aromatic aldehydes containing electron-withdrawing groups.

It was apparent that the grinding method can accelerate this reaction using proline as catalyst under solvent-free conditions. For example, compounds **6a**, **6b**, **6e**, and **6f** were previously prepared in 61%, 91%, 75%, and 73% yields respectively using piperidine as catalyst in ethanol.^[9b] These compounds also were previously prepared in 99%, 99%, 89%, and 90% yields respectively catalyzed by triethylbenzyl ammonium chloride (TEBA) in water at room temperature for 6–10 h.^[12c] The present procedure offered them in 99%, 96%, 97%, and 98% yields respectively within 20 min. It was a highly efficient procedure for

Table 3. Synthesis of 6-amino-5-cyano-4-aryl-1,4-dihydropyrano [2,3-*c*] pyrazoles by a grinding method

| Entry | Ar | Grinding time (min) | Yield (%) ^a | Mp (°C) | |
|-----------|---|---------------------|------------------------|---------|----------------------------|
| | | | | Found | Reported ^[Lit.] |
| 6a | C ₆ H ₅ | 5 | 99 | 161–163 | 168–170 ^[12c] |
| 6b | 4-ClC ₆ H ₄ | 5 | 96 | 172–174 | 174–175 ^[9b] |
| 6c | 3-ClC ₆ H ₄ | 5 | 96 | 148–150 | 158–159 ^[11b] |
| 6d | 2-ClC ₆ H ₄ | 5 | 95 | 144–146 | 144–146 ^[11b] |
| 6e | 4-NO ₂ C ₆ H ₄ | 5 | 97 | 187–188 | 192–194 ^[12c] |
| 6f | 3-NO ₂ C ₆ H ₄ | 5 | 98 | 193–194 | 190–191 ^[11b] |
| 6g | 4-BrC ₆ H ₄ | 5 | 96 | 176–177 | 183–184 ^[9d] |
| 6h | 2,4-Cl ₂ C ₆ H ₃ | 5 | 95 | 182–184 | 182–184 ^[12c] |
| 6i | 4-CH ₃ C ₆ H ₄ | 10 | 90 | 174–175 | 176–178 ^[12c] |
| 6j | 4-OHC ₆ H ₄ | 20 | 85 | 206–207 | 211–212 ^[11b] |
| 6k | 4-CH ₃ OC ₆ H ₄ | 10 | 99 | 171–173 | 170–172 ^[9d] |

^aIsolated yields.



Scheme 3.

the preparation of compounds **6** by proline-catalyzed three-component condensations via a one-pot grinding method under solvent-free conditions.

We propose the possible following mechanism to account for the condensation of **1**, **2**, and **5** (Scheme 3). The step (1 → 9) can be regarded as a fast Knoevenagel condensation. In this mechanism, *D,L*-proline is an effective catalyst for the formation of the cyano-olefin (**9**). The condensation proceeds via iminium ion (**7**) and intermediate (**8**). Proline also catalyzes the formation of intermediate (**12**), which affords the products **6** via addition and elimination of water. The condensation of **1**, **2**, and dimedone (or 1,3-cyclohexanedione) possesses the resemble mechanism.

CONCLUSION

In conclusion, we have described a highly efficient procedure for the preparation of pyrans and pyrano[2,3-c]pyrazole derivatives by a three-component condensation via a one-pot grinding method using *D,L*-proline as catalyst under solvent-free conditions. Moreover, the procedure offers several advantages including high yields, operational simplicity, cleaner reaction, minimal environmental impact, and low cost, which make it a useful and attractive process for the synthesis of these compounds.

EXPERIMENTAL

Melting points are uncorrected. 5,5-Dimethyl-1,3-cyclohexane-dione was purchased from Fluka and was used without further purification. IR spectra

were recorded on Bio-Rad FTS-40 spectrometer (KBr). ^1H NMR spectra were measured on a Bruker Avance 400 (400-MHz) spectrometer in CDCl_3 using TMS as internal standard.

General Procedure

Aromatic aldehydes **1** (2 mmol), malononitrile **2** (2 mmol), dimedone (1,3-cyclo-hexanedione or 3-methyl-1-phenyl-2-pyrazolin-5-one **5** (2 mmol), and *D,L*-proline (20 mol%) are added to a mortar. The mixture is ground by mortar and pestle at room temperature (25°C) for a period. The solid product is obtained from an intermediate melt and then is laid up at room temperature for 0.5 h. The mixture is transferred to ice water and then is filtered off. The crude product is purified by recrystallization by ethanol (95%).

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