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New synthesis of flavanones catalyzed by L-proline☆

S. Chandrasekhar,* K. Vijeender and K. Venkatram Reddy

Indian Institute of Chemical Technology, Hyderabad 500 007, India

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Abstract—L-Proline is utilized as an efficient organocatalyst for the synthesis of substituted flavanones and chalcones in good yields. The efficiency of the catalyst was proved with a variety of substrates ranging from electron-deficient to electron-rich aryl aldehydes and 2-hydroxyacetophenones.

There is a resurgence in research activity in the flavanoid class of molecules due to excellent biological profiles reported in the recent times. This class of New Chemical Entities show activity in cancer, AIDS, bacterial and inflammatory diseases.

The methodology most widely used to prepare flavanones involves the isomerization of appropriately substituted 2-hydroxy chalcones, in turn obtained by an aldol condensation reaction between a 2-hydroxyacetophenone and an aldehyde. These cyclizations have been carried out under numerous conditions using acids,[1] bases,[2] silica gel,[3] heat,[4] light,[5] electrolysis,[6] Ni/Zn/K halides[7] and others.[8] Other alternative procedures to synthesize flavanones include oxidation of flavan-4-ol.[9] Reacting benzaldehydes with 1-(2-hydroxyphenyl)-3-phenyl propane-1,3-diones in basic medium[10] and transformation of 3-bromo-1-phenylprop-2-ynyl aryl ethers in the presence of mercury(II) trifluoroacetate.[11]

As part of an exploration of the possibility of utilizing L-proline as organocatalyst[12] for aldol and related reactions, herein we disclose syntheses of flavanones from aryl aldehydes and substituted 2-hydroxyacetophenones in one step. Also, the synthesis of spiroflavanones were achieved from ketones and substituted 2-hydroxyacetophenones in the presence of L-proline (30 mol %) in DMF as solvent. In the case of aldehydes, mixtures of flavanones and chalcones were isolated with ease, whereas in the case of ketones spirocyclic flavanones were the exclusive products.

In the first instance, 2-hydroxyacetophenone and benzaldehyde in equimolar quantities were stirred together in the presence of L-proline (30 mol %) in DMF (0.02 M) at 80 °C for 18 h. The usual work up viz extracting with ether followed by a water wash and chromatography furnished flavanone **1** along with chalcone in a 7:3 ratio with combined yield of 70%. To further substantiate this result, various substituted aldehydes and substituted 2-hydroxy acetophenones were subjected to L-proline catalysis and good yields of flavanones and chalcones were obtained. The various aldehydes included benzaldehyde (Table 1, entries 1–3), 4-nitrobenzaldehyde (entry 4), 4-chlorobenzaldehyde (entry 5), mono- and dimethoxy benzaldehydes (entries 6–10), *p*-tolualdehyde (entry 11), pyridine aldehydes (entries 12–14) and furfuraldehyde (entry 14). The substituted 2-hydroxy acetophenones are represented by 2-hydroxyacetophenone (entries 1, 4, 5, 6, 11, 12, 14 and 15), 5-chloro-4-methyl-2-hydroxyacetophenone (entries 2, 7 and 9) and 3-methoxy 2-hydroxyacetophenone (entries 3, 8, 10 and 13). In total, 15 flavanones and 15 chalcones were synthesized (Scheme 1).

Next, cyclohexanone was used as partner in the flavanone synthesis (Scheme 2). The unsubstituted (Table 2, entries 1–3) mono- (entry 4) and disubstituted (entry 5) 2-hydroxyacetophenones underwent very easy spirocyclization to generate novel tricyclic flavanones in very high yields.

In conclusion, L-proline has been shown to be an efficient organocatalyst for the synthesis of various substituted

Keywords: L-Proline; Flavanone; Chalcone; 2′-Hydroxyacetophenone; Isomerization.

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* Corresponding author. Tel.: +91 40 27193434; fax: +91 40 27160512; e-mail addresses: srivaric@iict.res.in; srivaric@gmail.com

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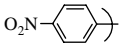
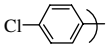
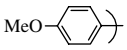
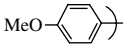
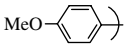
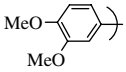
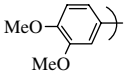
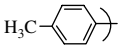
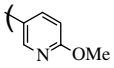
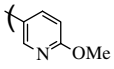
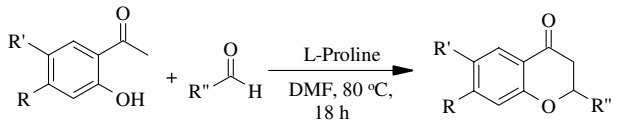
Table 1. L-Proline catalyzed synthesis of flavanones[a]

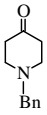
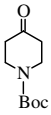
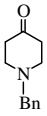
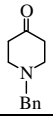
Entry	R′	R	R″	Ratio of flavanone/ chalcone	Combined yield[b] (%)
1	H	H		7/3	70
2	Cl	CH_3		7/3	68
3	H	OCH_3		7/3	65
4	H	H		8/2	73
5	H	H		8/2	72
6	H	H		7/3	60
7	Cl	CH_3		7/3	63
8	H	OCH_3		6/4	65
9	Cl	CH_3		7/3	62
10	H	OCH_3		6/4	60
11	H	H		7/3	64
12	H	H		6/4	63[c]
13	H	OCH_3		6/4	61[c]
14	H	H		7/3	65[c]
15	H	H		6/4	67

[a] All the compounds were characterized by ^1H NMR and mass spectral data.
[b] Isolated yields after column chromatography.
[c] The optical purity of products was found to be less than 5% ee and was not checked for other products.



Scheme 1.

Table 2. Synthesis of spiroflavanones

Entry	R′	R	Ketone	Flavanone[a] (%)
1	H	H		80[b]
2	H	H		93
3	H	H		95
4	H	OCH_3		96
5	Cl	CH_3		92

[a] Isolated yields after column chromatography.
[b] Reaction carried out for 20 h.

flavanones and chalcones. The biological application of these flavanones as aldose reductase inhibitors will be described elsewhere.

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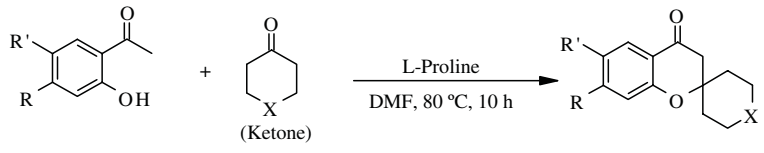

X=CH_2, NBn, NBoc

Scheme 2.

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