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Iodine catalyzed one-pot synthesis of flavanone and tetrahydropyrimidine derivatives via Mannich type reaction

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ABSTRACT

A variety of functionalized flavanone derivatives and tetrahydropyrimidine derivatives were achieved under remarkably mild conditions. The combination of good to excellent yields, a simple work-up, and the high compatibility of functional groups makes this an attractive synthetic approach to access flavanone and tetrahydropyrimidine derivatives.

1. Introduction

Mannich reaction is an important carbon–carbon bond-forming reaction, which involves a multi component reaction of a non enolizable aldehyde, amine, and enolizable carbonyl compound in the presence of acid catalyst to afford β-aminocarbonyl compound.[1] It is an important tool for constructing a diverse array of pharmaceutically useful natural products as well as synthetically utilizable substances.[2,3] Further, Mannich reaction is also utilized in the synthesis of *N*-heterocyclic compounds like tetrahydropyridines,[4] imidazolines,[5] pyrazolone derivatives,[6] 1,6-naphthyridine derivative,[7] and many other heterocyclic compounds.[8]

On the other hand, flavanone and its derivatives are important constituents of natural products and found in many fruits and vegetables. For instance, hesperetin, naringenin are important natural products, possessing immense importance in the field of pharmaceuticals.[9] Moreover, flavanone derivatives display important biological activities, such as aldose reductase inhibitors, iron chelators of redox inhibition HIV, cancer, chemoprevention of breast cancer, bacterial and inflammatory diseases.[10] Apart from these, flavanones also serve as important intermediates in the synthesis of many biologically active compounds.[11]

In general, the synthesis of flavanones could be achieved from the isomerization of an appropriately substituted 2′-hydroxychalcone. These cyclizations can be carried out under various conditions using acid catalysts,[12] bases,[13] thermal, photochemical, and electrochemical transformations.[14]

Other alternative procedures for the synthesis of flavanones include the oxidation of flavan-4-ol,[15] reaction of aldehydes with 1,3-diones in basic medium,[16a] the transformation of phenyl alkenyl aryl ethers in the presence of $Hg(OCOCF_3)_2$,[16b] intramolecular oxa-Michael addition of activated α,β-unsaturated ketones,[16c] Juliae Kocienski olefination of 2-(benzo[*d*]thiazol-2-ylsulfonyl)-1-phenylethanones with aldehydes in the presence of a base,[16d] and intermolecular C–O addition of carboxylic acids to arynes.[16e] Very recently, flavanone derivatives were achieved from 3-hydroxy-1-(2-hydroxylphenyl)-3-arylpropan-1-ones.[16f] Various synthetic routes for flavanones are depicted in Fig. 1.

Molecular iodine has recently been reported to be a Lewis acid imparting high regio- and chemoselectivity in various transformations. For the last decade the use of iodine as Lewis acid has been increasing exponentially due to its high tolerance to air and moisture, low-cost, ready availability, and high catalytic activity in dilute and highly concentrated conditions as well as under solvent-free reaction conditions.[17] Our group has explored many catalytic reaction of iodine in the last decade.[18] In continuation to our investigations on iodine catalyzed reactions, herein we wish to report iodine catalyzed one-pot synthesis of flavanone and highly substituted pyrimidine derivatives via multi component Mannich reaction.

2. Results and discussions

The three component Mannich reaction of aldehyde, amine, and enolizable ketone to obtain the β-aminocarbonyl compounds has

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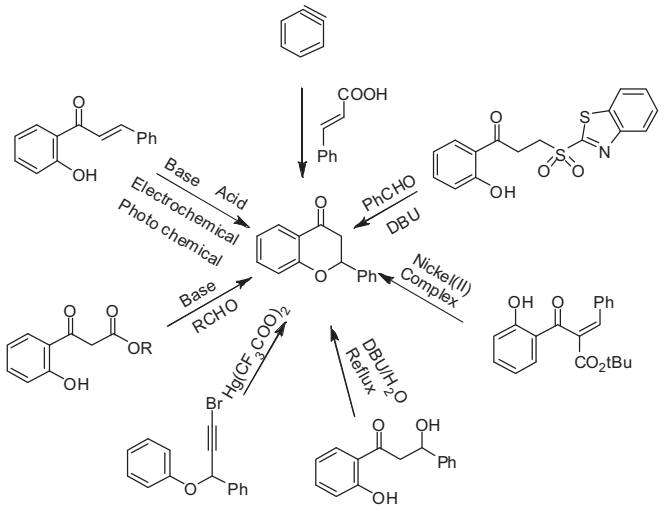
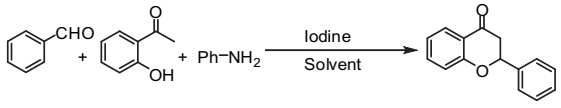


Fig. 1. Important synthetic routes for the flavanone derivatives.

been known for long time.[19] However, none of the report described the use of 2-hydroxyacetophenones as enolizable ketone component in the Mannich reaction. In an attempt to carry out the Mannich reaction of benzaldehyde, aniline, and 2-hydroxyacetophenone in the presence of iodine as catalyst, no trace of β-aminocarbonyl compound is observed however, flavanone was formed as the sole product in moderate yield. This interesting result prompted us to further investigate the reaction (Table 1).

Table 1
Solvent screening

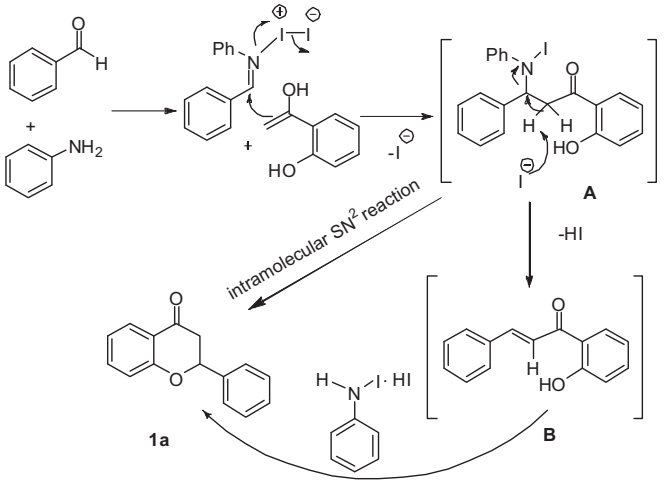


Entry	Solvent	Iodine loading (equiv)	Time (h)	Yield[a,b] (%)
1	Ether	0.1	36	39
2	Ether	0.3	20	63
3	Ether	0.5	10	55
4	Ether	1.0	4.5	36
5	No	0.3	4	42
6	CH_2Cl_2	0.3	22	37
7	$CHCl_3$	0.3	22	35
8	EA	0.3	22	25
9	DMSO	0.3	22	57
10	CH_3OH	0.3	22	82

[a] Isolated yields.
[b] Reactions were performed on 1 mmol scale.

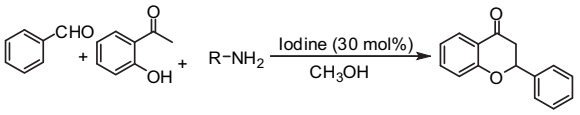
Encouraged by this initial observation, we first focused our attention on optimizing the reaction conditions. When the reaction was carried out in absence of iodine, it was stopped after the formation of imine. In an attempt to evaluate the catalytic efficiency of iodine, we carried out the reaction with benzaldehyde (1 equiv), 2-hydroxyacetophenone (1.2 equiv), and aniline (1.5 equiv) in diethyl ether in the presence of various amounts of iodine at 40 °C. The reaction occurred most efficiently with 30 mol % of iodine. After determining the amount of catalyst, we further screened the reaction with various solvents. The reaction worked in most of the solvents and methanol was found to be the best solvent for conducting this reaction.

The reaction did not work when no amine was used. Hence, to better understand the effect of different amines, we screened the reaction with different primary amines. We found that aliphatic amines were less effective than aromatic amines. It may be attributed to the less efficient 1,2-addition of 2-hydroxyacetophenone derivative at the imine due to the presence of electron donating aliphatic group on nitrogen atom (Scheme 1). Among the aromatic amines, aniline was found to be the most efficient. Less efficient reaction with 4-methoxyaniline is may be due to similar reason as aliphatic amines. Poor yield with 4-chloroaniline is initially appearing to be surprising. Moderate yield with 4-nitroaniline is presumably due to less efficient imine formation. Based on the results obtained from the screening with different amines aniline was chosen as the most suitable amine for this conversion. The reaction trend suggests that the formation of imine as well as the elimination of amine is the key steps involved in the formation of flavanone derivatives (Table 2).



Scheme 1. Plausible mechanistic route for the formation of flavanones.

Table 2
Screening of amine component

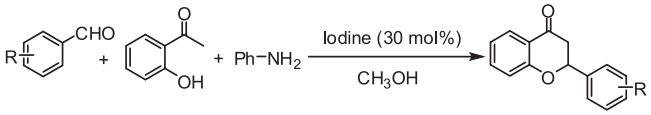


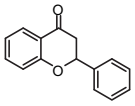
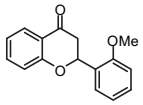
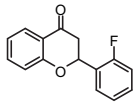
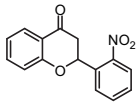
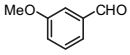
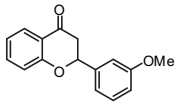
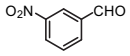
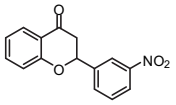
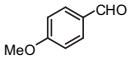
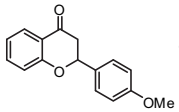
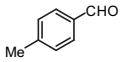
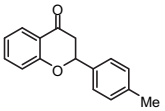
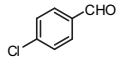
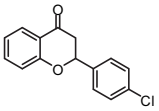
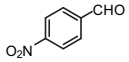
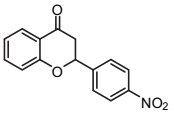
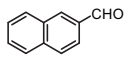
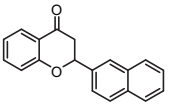
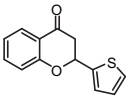
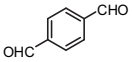
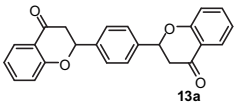
Entry	R	Time (h)	Yield[a,b] %
1	CH_3	20	40
2	$PhCH_2$	20	32
3	Ph	15	88
4	4-OMe–Ph	24	70
5	4-NO_2–Ph	24	80
6	4-Cl–Ph	24	44

[a] Isolated yields.
[b] Reactions were performed on 1 mmol scale.

After optimizing the reaction conditions, in order to evaluate the scopes and limitation of our methodology, we first treated 2-hydroxyacetophenone with different aldehydes (Table 3). Almost all the aldehydes underwent smooth reactions to produce their corresponding flavanone derivatives in good to excellent yields at 40 °C. As shown in Table 3, electronic factor of the substitution at benzaldehyde moiety controls the reaction time, however, it seems to have no effect on the reaction yield. With the *o*-substituted benzaldehyde, the presence of electron-donating methoxy (entry 2) and fluoro (entry 3) functionality renders the reaction time longer than unsubstituted benzaldehyde (entry 1). With *o*-nitrobenzaldehyde (entry 4) the reaction time is shorter than the methoxy and fluoro derivatives, but, comparable to unsubstituted benzaldehyde, may be due to the steric factor. Due to this fact, a trace amount of hydroxyl chalcone was observed in the crude ^1H NMR spectra of the

Table 3
Synthesis of flavanone derivatives using Mannich approach



Entry	Substrate	Product	Time (h)	Yield[a,b] (%)
1		 **1a**	15	88
2[c]		 **2a**	24	68[c]
3[c]		 **3a**	24	65[c]
4[c]		 **4a**	16	73[c]
5		 **5a**	24	77
6		 **6a**	12	76
7		 **7a**	20	83
8		 **8a**	14	82
9		 **9a**	18	82
10		 **10a**	10	86
11[c]		 **11a**	24	72[c]
12		 **12a**	14	67
13		 **13a**	24	53

[a] Isolated yields.
[b] Reactions were performed on 1 mmol scale.
[c] 2′-Hydroxychalcon derivative was detected in crude ^{1}H NMR.

o-functionalized benzaldehyde derivatives. A similar trend of the electronic effect of the substitution was observed with the *m*- (entries 5 and 6) and *p*- (entries 7–10) substituted benzaldehyde. Effect of steric factor is more prominent than the electronic factor in determining the yield of the reaction. *m*-Substituted benzaldehydes (entries 5 and 6) are more efficient for this conversion than the *o*-substituted derivatives (entries 2–4) and *p*-functionalized benzaldehyde derivatives (entries 7–10) are most productive. It is worthy to note that the sterically hindered aldehyde, such as naphthaldehyde also participated in the reaction to furnish the product in good yield. In addition, heteroaromatic aldehydes (2-thiophene carbaldehyde) can also serve as substrates in this reaction, giving the corresponding product in good yield. Further more, our procedure was also applied for the dialdehyde (*p*-terephthaldehyde) to obtain corresponding bis flavanone in moderate yield.

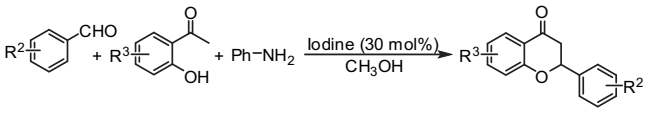
Subsequently, we examined the reaction with other substituted 2-hydroxyacetophenones, we found that the reaction of 2-hydroxyacetophenone containing electron-donating group completed in relatively shorter time to furnish the corresponding flavanones in excellent yields. Moreover, the reactions with 2-hydroxyacetophenone with electron-withdrawing group (Cl) has taken longer time for the completion. It is interesting to note that 1-(1-hydroxynaphthalen-2-yl)ethanone having bulky naphthyl moiety has also participated in the reaction to produce benzo[*h*]chromen-4(3*H*)-one derivative in good yield. However, the reaction failed to form the flavanone products with highly electron-rich (hydroxy functionalized) acetophenones under the present reaction conditions (Table 4).

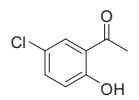
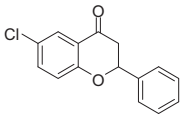
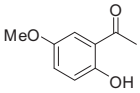
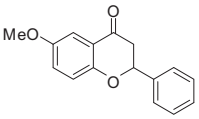
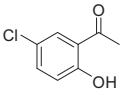
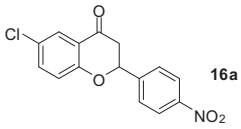
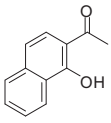
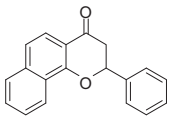
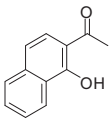
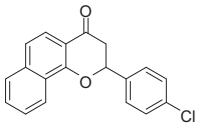
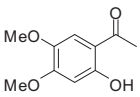
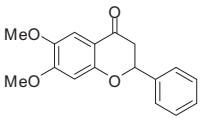
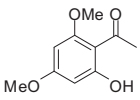
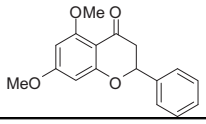
A plausible mechanism for this conversion is postulated in Scheme 1. The initially formed imine is activated by coordination with highly polarizable iodine and the enol form of the 2-hydroxyacetophenone attacks the nucleophilic carbon of imine moiety to form intermediate A. This step is followed by the removal of *N*-iodoaniline and HI to form intermediate B. This intermediate undergoes 1,4-Michael type addition that leads to the cyclization to form the flavanone derivative. This Michael addition is probably catalyzed by the in situ formed *N*-iodoaniline–HI complex. Alternatively[24] the intermediate A in Scheme 1 could gave the flavanone directly via an intramolecular S_N2 reaction. Here the aniline may acted as a leaving group.

During the screening of the reaction conditions with various amines, we conducted this three component Mannich reaction by using ammonia as an amine component. We obtained an interesting five component condensed product (tetrahydropyrimidine derivative), which comprised two aldehyde units, two ammonia molecules, and one 2-hydroxyacetophenone moiety. In fact, the synthesis of these kinds of products was reported in the literature in 1977 by Takajo et al. They synthesized these products by the reaction of *N*,*N*-dibenzylideneaminals with acetophenones in the presence of ammonium acetate.[20] Recently, Chebanov et al. also synthesized these compounds by the reaction of ammonia with chalcones and various ketones.[21] The former method is based on the base mediated two component reaction, whereas the second method is three component reaction starting from chalcones. On the other hand these kind of tetrahydropyrimidine derivatives are known to exhibit several biological activities.[21]

Encouraged by this result, we screened the conditions to optimize reaction for the formation of the pyrimidine derivatives. We found the best conditions for the formation of these compounds is aldehyde (2.4 mmol) and ammonia (0.5 mL 7 M NH_3 in MeOH) and 1 mmol 2-hydroxylacetophenone in methanol as solvent in the presence of 30 mol % iodine. At these conditions the reaction produced pyrimidine compound as major compound along with trace of some unidentified products. The ^{1}H NMR spectrum of the crude product reveals the formation of two diastereoisomers in the ratio of 3:1. Both isomers can be clearly distinguishable by means of four distinct signals of protons at C-2, C-3, and C-6 in their ^{1}H NMR spectra.

Table 4
Synthesis of flavanone derivatives using Mannich approach



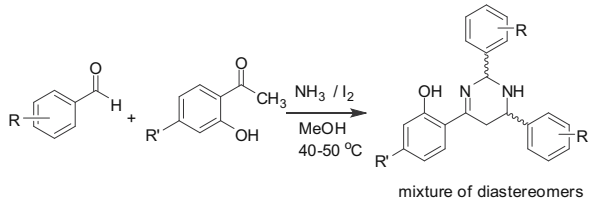
Entry	Substrate	Product	Time (h)	Yield[a,b] %
1		 **14a**	12	82
2		 **15a**	7	87
3		 **16a**	19	63
4		 **17a**	16	78
5		 **18a**	15	76
6		 **19a**	24	—
7		 **20a**	24	—

[a] Isolated yields.
[b] Reactions were performed on 1 mmol scale.

The optimized reaction conditions were applied to different aldehydes and hydroxyacetophenones to obtain their corresponding tetrahydropyrimidine derivatives in good to moderate yield (Table 5). The reaction with electron-donating group contained substrates underwent slow reaction to obtain moderate yield of corresponding product. While other substitution on aldehyde as well hydroxyl phenones showed equal ease to form their corresponding pyrimidine derivative in moderate yield. All pyrimidine derivatives were obtained as a mixture of two diastereomers in 3:1 ratio. The major isomer happens to be trans diastereomer, whereas minor diastereomer is cis. All the major diastereomers were separated in pure form. Unfortunately we could not obtain the minor diastereomers in pure form.

The major isomer (**i**) displayed C-6 proton as triplet at 5.81 ppm, with coupling constant 2.8 Hz. C-2 proton as doublet of doublet at 4.28 ppm with coupling constants 4.0, 10.8 Hz. Two protons at C3

Table 5
One-pot synthesis of tetrahydropyrimidine derivatives via Mannich reaction



Entry	R	R′	Product[c]	Time (h)	Yield[a,b] %
1[d]	H	H	**i**/**i**′	12	78 (82:18)
2	4-Me	H	**ii**/**ii**′	15	75 (79:21)
3[d]	4-OMe	H	**ii**/**ii**′	13	70 (79:21)
4	4-F	H	**iii**/**iii**′	10	74 (76:24)
5[d]	H	Cl	**iv**/**iv**′	16	80 (80:20)
6	H	OMe	**v**/**v**′	18	65 (78:22)

[a] Isolated yields.
[b] Reactions were performed on 1 mmol scale.
[c] Ratio of diastereomers were determined by ^{1}H NMR.
[d] Diastereomers were not separable through column.

carbon displayed two ddd at 3.20 ppm (J=17.5, 4.2, 2.8 Hz) and 2.7 ppm (J=17.5, 10.9, 3.3 Hz). It is well known fact that the tetrahydropyrimidine ring adopts an asymmetric half-chair conformation.[22]

Now based on the coupling constants all the protons can placed in the half-chair confirmation to obtain the relative configuration. Due to the presence of large coupling and small coupling constants of proton at C2 carbon allow us to place the C2 proton in axial position. The alignment of other protons was determined from the standpoint of coupling constant. Here, we first consider the H^{3a} and H^{3e}. The H^4 coupled with H^{3a} and H^{3e} with ^3J value 10.8 and 4.2 Hz. It is very much clear that the higher coupling constant is due to diaxial interaction. So the ^3J value 10.8 Hz corresponds to the coupling with H^{3a} and H^4. ^3J=4.2 Hz is due to interaction between H^{3e} and H^4 (axial equatorial interaction). No coupling was observed between H^4 and H^6. However, H^{3e} couples with H^6 with ^5J=2.8 Hz. It is appearing that H^{3a} couples with H^6 with ^5J=3.3 Hz. Indeed, H^6 appeared as a triplet instead of dd is presumably as two coupling constants are very near to each other (2.8 Hz and 3.3 Hz). The structure of the major diastereomer was confirmed by the single crystal X-RD of **i** (Fig. 2). The relative configuration of the major diastereomer was assigned from crystal structure is 4R*6R*.

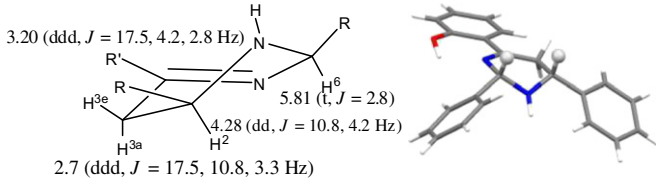


Fig. 2. Crystal structure of **i**.[23]

However, the minor isomer (**ii**′) showed the C-6 proton as a broad singlet at 5.97 ppm, C-2 proton appeared as doublet of doublet at 4.10 ppm with coupling constants 4.8, 9.2 Hz. Unlike major diastereomer, among two protons at C-3 carbon, one proton displayed as doublet of doublet at 3.18 ppm with coupling constants 4.9, 17.8 Hz and another proton as ddd at 2.84 ppm with coupling constants 17.8, 9.2, 1.9 Hz. Similarly, to explain the observed coupling in ^{1}H NMR spectroscopy we place H^4 at the equatorial position. Here H^4 couples with H^{3a} with ^3J value 9.2 Hz, which is little lower than the major isomer. However, coupling constant for H^4 and H^{3e} is little higher (^3J=4.9 Hz). Geminal coupling constant is also higher in this case (17.8 Hz). A coupling constant 1.9 Hz is due to 1,4-axial–equatorial interaction. 1,4 Diequatorial interaction is appearing to be absent here. H^6 is actually appeared as a broad singlet instead of doublet. The structure of the major diastereomer was confirmed by the single crystal X-RD of **ii**′ (Fig. 3). The relative configuration of the minor diastereomer was assigned from crystal structure is 4R*6S*.

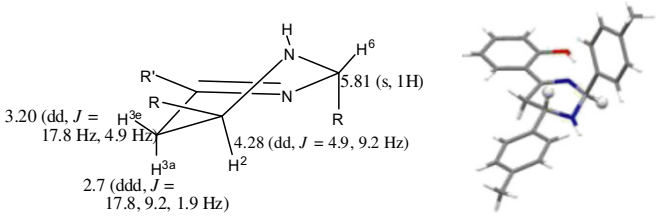
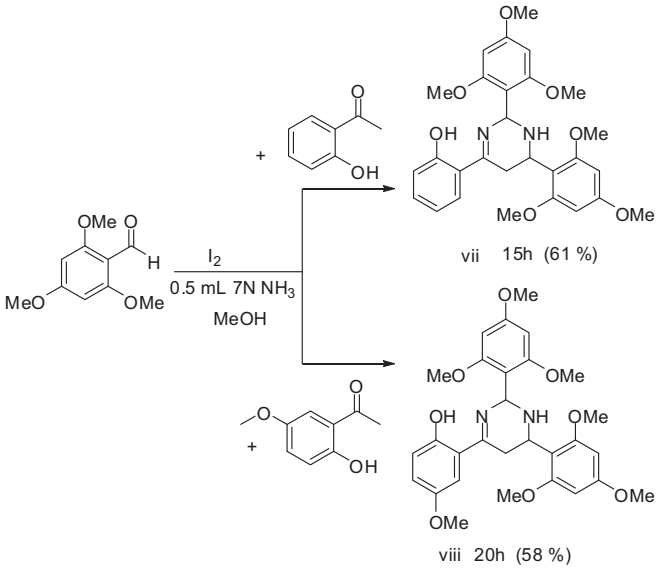


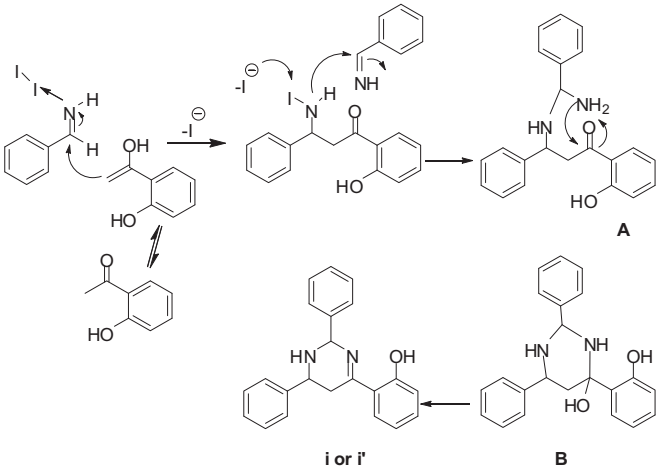
Fig. 3. Crystal structure of **ii**′.[23]

By applying the same procedure, we could synthesize a highly methoxy substituted tetrahydropyrimidines from the reaction of 2,4,6-trimethoxy benzaldehyde with corresponding hydroxyacetophenone in moderate yields (Scheme 2).



Scheme 2. Synthesis of a highly methoxy substituted tetrahydropyrimidines.

Mechanism for the formation of tetrahydropyrimidine is outlined in the Scheme 3. Like the previous mechanism (Scheme 1) the initially formed imine undergoes 1,2-addition with enolized 2-hydroxyacetophenone moiety to form intermediate **A**. The



Scheme 3. Mechanism for the formation of tetrahydropyrimidine derivatives.

intermediate **A** undergoes 1,2-addition with another in situ formed imine to form intermediate **B**. Intermediate **B** undergoes cyclization and removal of water to form the product **D**.

3. Conclusion

In conclusion we have described the synthesis of flavanone and pyrimidine derivatives by utilizing the Mannich reaction. This is highly selective and efficient protocol, which involves the use of a cheap reagent and an easy work-up procedures.

4. Experimental section

4.1. General procedures

Solvents for extraction and chromatography were distilled before use. All chemicals were purchased from Acros Organics and Sigma Aldrich and used directly without any purification. Analytical thin-layer chromatography was performed using E. Merck silica gel 60F glass plates and E. Merck silica gel 60 (230–400 mesh) was used in flash chromatography separations. MS were measured by JEOL JMS-HX110 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with Bruker Advance EX 400. Chemical shifts were reported in parts per million (δ) using TMS as internal standard and coupling constants were expressed in hertz. Melting points were recorded using an electro thermal capillary melting point apparatus and uncorrected.

4.2. Typical experimental procedures for the synthesis of flavanone

The mixture of aldehyde (1.0 mmol), aniline (1.5 mmol), 2-hydroxyacetophenone (1.2 mmol) in methanol (1.0 mL), and iodine (I_2) (0.3 mmol) was added and stirred at 40 °C over a period of time mentioned in Tables 3 and 4. After completion of the reaction (monitored by TLC), the solution was washed with an ice cold saturated $Na_2S_2O_{3(aq)}$ solution (2×10 mL) and then extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were washed sequentially with brine and ice water and dried over anhydrous Na_2SO_4. Evaporation of the organic solvent afforded the crude products, which were purified by recrystallization from hexane and ethyl acetate or by short flash column chromatography.

4.3. Typical experimental procedures for the synthesis of tetrahydropyrimidine derivatives

The mixture of aldehyde (2.4 mmol), ammonia (0.5 mL, 7 N in methanol), 2-hydroxyacetophenone (1 mmol) in methanol (1.0 mL), and iodine (I_2) (0.3 mmol) was added and stirred at 40 °C over a period of time mentioned in Table 5. After completion of the reaction (monitored by TLC), the product was precipitated out, which was collected by simple filtration to obtain the crude products, which were purified by short flash column chromatography (hexane and ethyl acetate).

4.4. Spectral data

*4.4.1. 2,3-Dihydro-2-phenyl-4H-1-benzopyran-4-one (**1a**).* Colorless solid; mp 75–76 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, J=8.12, 1.56 Hz, 1H), 7.53–7.39 (m, 6H), 7.04–7.08 (m, 2H), 5.46 (dd, J=13.32, 2.92 Hz, 1H), 3.06 (dd, J=16.84, 13.36 Hz, 1H), 2.87 (dd, J=16.84, 2.92 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9, 161.6, 138.8, 136.2, 128.9, 128.8, 127.1, 126.2, 121.7, 121.0, 118.20, 79.6, 44.7; MS m/z (relative intensity) 224 (M^+, 100), 223 (65), 147 (49), 120 (93), 92 (34), 77 (14), 64 (9).

*4.4.2. 2,3-Dihydro-2-(2-methoxyphenyl)-4H-1-benzopyran-4-one (**2a**).* Colorless solid; mp: 113–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ=7.94 (dd, J=1.36, 7.8 Hz 1H), 7.63 (dd, J=0.8, 7.5 Hz, 1H), 7.52–7.48 (m, 1H), 7.37–7.32 (m, 1H), 7.08–7.034 (m, 3H), 6.94 (d, J=8.3 Hz, 1H), 5.87 (dd, J=13.40, 3.96 Hz, 1H), 3.84 (s, 3H), 3.00–2.92 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=192.9, 162.3, 156.0, 136.2, 129.6, 127.7, 126.6, 121.6, 121.2, 121.1, 118.3, 110.7, 74.9, 55.5, 43.9. MS m/z (relative intensity) 254 (M^+, 39), 223 (100), 134 (25), 119 (66), 91 (52), 77 (16), 59 (49).

*4.4.3. 2,3-Dihydro-2-(2-fluorophenyl)-4H-1-benzopyran-4-one (**3a**).* Yellow solid, mp 147–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.96 (dd, J=8.56, 1.0 Hz, 1H), 7.72–7.64 (m, 1H), 7.53–7.49 (m, 1H), 7.39–7.34 (m, 1H), 7.25–7.22 (m, 1H), 7.13–7.02 (m, 3H), 5.78 (dd, J=13.24, 2.96 Hz, 1H), 3.06 (dd, J=16.88, 13.24 Hz, 1H), 2.90 (dd, J=16.88, 3.08 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.76, 161.7, 159.9 (J_{C-F}=246 Hz), 136.4, 130.4 (J_{C-F}=9.0 Hz), 127.6 (J_{C-F}=4.0 Hz), 126.4, 126.3, 122.8 (J_{C-F}=4 Hz), 122.0, 118.3, 115.9 (J_{C-F}=21 Hz), 77.0 (J_{C-F}=3 Hz), 43.72.

*4.4.4. 2,3-Dihydro-2-(2-nitrophenyl)-4H-1-benzopyran-4-one (**4a**).* Colorless solid; mp: 121–122 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (dd, J=8.20, 1.0 Hz, 1H), 8.01 (d, J=8.20 Hz, 1H), 7.96 (dd, J=7.8, 1.64 Hz, 1H), 7.77 (m, 1H), 7.58–7.49 (m, 1H), 7.11–7.07 (m, 1H), 7.02 (d, J=8.0 Hz, 1H), 6.08 (dd, J=13.12, 2.66 Hz, 1H), 3.22 (dd, J=16.92, 2.56 Hz, 1H), 2.94 (dd, J=16.88, 13.12 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.9, 161.3, 147.5, 136.5, 134.9, 134.2, 129.5, 128.4, 127.4, 125.0, 122.3, 121.2, 118.2, 75.8, 44.6.

*4.4.5. 2,3-Dihydro-2-(3-methoxyphenyl)-4H-1-benzopyran-4-one (**5a**).* Colorless solid; mp: 110–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (dd, J=8.24, 1.64 Hz, 1H), 7.53–7.49 (m, 1H), 7.35 (t, J=8.4 Hz, 1H), 7.07–7.04 (m, 4H), 6.93–6.90 (m, 1H), 5.44 (dd, J=13.28, 2.40 Hz, 1H), 3.87 (s, 3H), 3.07 (dd, J=16.88, 13.28 Hz, 1H), 2.87 (dd, J=16.88, 2.96 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.13, 161.57, 159.91, 136.07, 130.72, 127.67, 126.96, 121.45, 120.86, 118.07, 114.14, 79.27, 55.28, 44.38. MS m/z (relative intensity) 254 (M^+, 63), 147 (35), 134 (100), 91 (16), 77 (5), 57 (8).

*4.4.6. 2,3-Dihydro-2-(3-nitrophenyl)-4H-1-benzopyran-4-one (**6a**).* Pale yellow solid; mp: 139–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (s, 1H), 8.06 (dd, J=8.28, 1.0 Hz, 1H), 7.92 (dd, J=8.80, 1.64 Hz, 1H), 7.83 (d, J=7.7 Hz, 1H), 7.64 (t, J=7.90 Hz, H), 7.57–7.53 (m, 1H), 7.11–7.08 (m, 1H), 6.08 (dd, J=12.84, 3.28 Hz, 1H), 3.05 (dd, J=16.80, 12.56 Hz, 1H), 2.94 (dd, J=16.80, 3.40 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9, 161.1, 148.8, 141.2, 136.6, 132.1, 130.1, 127.3, 123.7, 122.3, 121.4, 121.0, 118.3, 78.4, 44.7. MS m/z (relative intensity) 269 (M^+, 78), 147 (73), 119 (100), 92 (80), 63 (22).

*4.4.7. 2,3-Dihydro-2-(4-methoxyphenyl)-4H-1-benzopyran-4-one (**7a**).* Pale yellow solid; mp: 87–88 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (dd, J=8.44, 1.64 Hz, 1H), 7.48–7.50 (m, 1H), 7.41 (d, J=6.88 Hz, 2H), 7.03–7.07 (m, 2H), 6.96 (d, J=6.88 Hz, 2H), 5.43 (dd, J=13.32, 2.80 Hz, 1H), 3.83 (s, 3H), 3.10 (dd, J=16.84, 13.32 Hz, 1H), 2.85 (dd, J=16.84, 2.80 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.13, 161.57, 159.91, 136.07, 130.72, 127.67, 126.96, 121.45, 120.86, 118.07, 114.14, 79.27, 55.28, 44.38. MS m/z (relative intensity) 254 (M^+, 63), 139 (13), 134 (100), 121 (28), 119 (23), 91 (16), 77 (5), 57 (8).

*4.4.8. 2,3-Dihydro-2-(4-methylphenyl)-4H-1-benzopyran-4-one (**8a**).* Colorless solid; mp: 81–83 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (dd, J=8.08, 1.76 Hz, 1H), 7.49 (m, 1H), 7.37 (d, J=7.81 Hz, 2H), 7.23 (d, J=7.81 Hz, 1H), 7.02–7.06 (m, 2H), 5.43 (dd, J=13.32,

2.80 Hz, 1H), 3.08 (dd, *J*=16.84, 13.32 Hz, 1H), 2.86 (dd, *J*=16.84, 2.80 Hz, 1H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.06, 161.58, 138.63, 136.08, 135.71, 129.43, 126.97, 126.14, 121.47, 120.89, 118.09, 79.46, 44.49, 21.14. MS *m*/*z* (relative intensity) 238 (M^+, 29), 181 (19), 141 (33), 139 (100), 118 (27).

4.4.9. 2,3-Dihydro-2-(4-chlorophenyl)-4H-1-benzopyran-4-one (***9a***). Colorless solid; mp: 93–95 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (dd, *J*=8.32, 1.68 Hz, 1H), 7.47–7.51 (m, 1H), 7.37–7.42 (m, 4H), 7.02–7.06 (m, 2H), 5.44 (dd, *J*=13.08, 2.88 Hz, 1H), 2.99 (dd, *J*=16.84, 13.08 Hz, 1H), 2.85 (dd, *J*=16.84, 2.88 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.40, 161.23, 137.22, 136.22, 134.50, 128.97, 127.45, 127.02, 121.74, 120.84, 118.02, 78.74, 44.50. MS *m*/*z* (relative intensity) 258 (M^+, 59), 147 (32), 138 (32), 120 (100), 103 (16), 92 (45), 77 (9), 64 (12).

4.4.10. 2,3-Dihydro-2-(4-nitrophenyl)-4H-1-benzopyran-4-one (***10a***). Yellow solid; mp: 156–157 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.32 (d, *J*=8.7 Hz, 2H), 7.95 (dd, *J*=8.4, 1.64 Hz, 1H), 7.70 (d, *J*=8.7 Hz, 2H), 7.58–7.54 (m, 1H), 7.13–7.09 (m, 2H), 5.61 (dd, *J*=12.4, 3.76 Hz, 1H), 3.04 (dd, *J*=16.84, 12.32 Hz, 1H), 2.95 (dd, *J*=16.84, 3.76 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8, 161.1, 148.2, 146.0, 136.7, 127.4, 127.0, 124.3, 122.4, 121.1, 118.3, 78.5, 44.8. MS *m*/*z* (relative intensity) 269 (M^+, 100), 252 (8), 222 (4), 147 (24), 120 (44), 92 (19), 64 (4).

4.4.11. 2-(Naphthalen-2-yl)chroman-4-one (***11a***). Colorless solid; mp: 122–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96–7.86 (m, 5H), 7.59–7.52 (m, 4H), 7.09 (m, 2H), 7.11–7.09 (m, 2H), 5.67 (d, *J*=12.8 Hz, 1H), 3.04 (m, 1H), 2.95 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.0, 161.7, 140.5, 136.4, 130.1, 127.3, 121.8, 121.2, 118.5, 118.3, 114.3, 112.1, 55.5, 44.9. MS *m*/*z* (relative intensity) 274 (M^+, 90), 154 (100), 153 (45), 128 (24), 92 (18), 77 (5).

4.4.12. 2-(Thiophen-2-yl)chroman-4-one (***12a***). Colorless solid, mp 88–89 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.94 (dd, *J*=8.2, 1.6 Hz, 1H), 7.53–7.49 (m, 1H), 7.37 (dd, *J*=5.04, 1.00 Hz, 1H), 7.14 (d, *J*=3.40 Hz, 1H), 7.08–7.02 (m, 3H), 5.73 (dd, *J*=11.92, 3.28 Hz, 1H), 3.19 (dd, *J*=16.84, 11.72 Hz, 1H), 3.06 (dd, *J*=16.84, 3.28 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4, 161.1, 141.6, 136.5, 127.2, 127.1, 126.6, 126.1, 122.0, 121.1, 118.4, 75.3, 44.5. MS *m*/*z* (relative intensity) 230 (M^+, 100), 219 (19), 146 (9), 120 (19), 110 (55), 92 (21), 66 (11).

4.4.13. 2,2′-(1,4-Phenylene)dichroman-4-one (***13a***). Colorless solid mp: 211–213 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.95 (m, 2H), 7.57 (s, 4H), 7.52–7.50 (m, 2H), 7.09–7.05 (m, 4H), 5.52 (dd, *J*=13.2, 2.8 Hz, 2H), 3.08 (dd, *J*=16.8, 13.2 Hz, 2H), 2.81 (dd, *J*=16.8, 2.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 161.6, 139.6, 136.5, 127.3, 126.8, 121.9, 121.1, 118.3, 79.4, 44.8; MS *m*/*z* (relative intensity) 370 (M^+, 100), 326 (34) 249 (50), 147 (57), 130 (75), 92 (78).

4.4.14. 6-Chloro-2-phenylchroman-4-one (***14a***). Pale yellow solid; mp: 96–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J*=2.64 Hz, 1H), 7.24–7.34 (m, 6H), 6.86 (d, *J*=8.80 Hz, 1H), 5.32 (dd, *J*=13.20, 2.84 Hz, 1H), 2.92 (dd, *J*=16.96, 13.20 Hz, 1H), 2.75 (dd, *J*=16.96, 2.84 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.75, 159.92, 138.22, 135.98, 128.92, 128.88, 127.16, 126.36, 126.11, 121.68, 119.85, 79.78, 44.23; MS *m*/*z* (relative intensity) 260 (M^+, 30), 258 (100), 181 (34), 156 (25), 154 (82), 126 (19), 104 (43), 84 (45), 57 (22).

4.4.15. 6-Methoxy-2-phenylchroman-4-one (***15a***). Pale yellow solid; mp: 89–91 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.49 (m, 5H), 7.35 (d, *J*=3.16 Hz, 1H), 7.12 (dd, *J*=9.04, 3.16 Hz, 1H), 6.98 (d, *J*=9.04 Hz, 1H), 5.43 (dd, *J*=13.36, 2.84 Hz, 1H), 3.18 (s, 3H), 3.06 (dd, *J*=16.96, 13.36 Hz, 1H), 2.87 (dd, *J*=16.96, 2.84 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.85, 156.19, 154.16, 138.79, 128.75, 128.65, 126.07, 125.29, 120.70, 119.36, 107.31, 79.62, 55.72, 44.49. MS *m*/*z* (relative intensity) 254 (M^+, 60), 150 (90), 122 (8), 111 (13), 97 (19), 84 (100), 71 (24), 55 (30).

4.4.16. 6-Chloro-2-(4-nitrophenyl)chroman-4-one (***16a***). Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.32 (d, *J*=8.7 Hz, 2H), 7.90 (d, *J*=2.6 Hz, 1H), 7.67 (d, *J*=8.7 Hz, 2H), 7.50 (dd, *J*=8.8, 2.7 Hz, 1H), 7.65 (d, *J*=8.8 Hz, 1H), 5.63 (dd, *J*=11.8, 4.3 Hz, 1H), 3.04 (dd, *J*=16.9, 11.9 Hz, 1H), 2.95 (dd, *J*=16.9, 4.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.7, 159.5, 148.3, 145.5, 136.5, 128.1, 127.0, 126.7, 124.4, 121.9, 120.0, 78.7, 44.5. MS *m*/*z* (relative intensity) 303 (M^+, 82), 286 (11), 181 (56), 154 (100), 126 (65), 77 (20), 63 (47).

4.4.17. 2-Phenyl-2H-benzo[h]chromen-4(3H)-one (***17a***). Colorless solid; mp: 115–117 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.52 (d, *J*=8.6 Hz, 2H), 7.97 (d, *J*=9.0 Hz, 1H), 7.78 (d, *J*=8.0 Hz, 1H), 7.68 (t, *J*=7.7 Hz, 2H), 7.55–7.40 (m, 6H), 7.20 (d, *J*=9.0 Hz, 1H), 5.61 (dd, *J*=13.7, 2.7 Hz, 1H), 3.04 (dd, *J*=16.4, 13.8 Hz, 1H), 2.95 (dd, *J*=16.5, 2.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.1, 163.9, 138.7, 137.7, 131.7, 129.8, 129.5, 129.0, 128.9, 128.6, 126.4, 126.1, 125.1, 119.0, 112.8, 79.0, 45.9. MS *m*/*z* (relative intensity) 273 (M^+, 100), 246 (7), 196 (16), 170 (85), 142 (35), 114 (45), 103 (8).

4.4.18. 2-(4-Chlorophenyl)-2H-benzo[h]chromen-4(3H)-one (***18a***). Colorless solid; mp: 136–138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.49 (d, *J*=8.6 Hz, 2H), 7.97 (d, *J*=9.0 Hz, 1H), 7.78 (d, *J*=8.0 Hz, 1H), 7.68 (t, *J*=7.7 Hz, 2H), 7.48–7.42 (m, 5H), 7.18 (d, *J*=9.0 Hz, 1H), 5.60 (dd, *J*=13.6, 2.9 Hz, 1H), 3.18 (dd, *J*=16.4, 13.6 Hz, 1H), 2.96 (dd, *J*=16.5, 3.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.8, 163.7, 137.9, 137.2, 134.8, 131.7, 131.6, 130.0, 129.5, 129.3, 129.1, 128.6, 127.7, 126.1, 125.3, 118.9, 112.8, 79.0, 45.8. MS *m*/*z* (relative intensity): 310 (M+2, 22), 308 (M^+, 45), 197 (8), 170 (100), 142 (25), 114 (40), 103 (14).

4.4.19. 2-(2,6-Diphenyl-1,2,5,6-tetrahydropyrimidin-4-yl)phenol (***i***). Yellow solid; mp: 144–146 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57–7.55 (m, 2H), 7.50–7.48 (m, 3H), 7.42–7.38 (m, 4H), 7.36–7.32 (m, 3H), 6.95 (dd, *J*=8.3, 1.0 Hz, 1H), 6.85–6.81 (m, 1H), 4.27 (dd, *J*=10.8, 4.2 Hz, 1H), 3.17 (ddd, *J*=17.6, 4.2, 2.8 Hz, 1H), 2.74 (ddd, *J*=17.5, 10.8, 3.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 162.3, 142.7, 141.8, 132.7, 129.1, 128.8, 128.5, 128.1, 127.3, 127.1, 126.6, 119.3, 118.4, 118.0, 75.2, 55.4, 34.6, 21.4, 21.3. MS *m*/*z* (relative intensity) 329 (M+1, 100), 328 (M^+, 62), 224 (65), 194 (88). HRMS calcd for chemical formula: $C_{22}H_{21}N_2O$ (M^++H) 329.1654 found 329.1663.

4.4.20. 2-(2,6-Dip-tolyl-1,2,5,6-tetrahydropyrimidin-4-yl)phenol (***ii***). Yellow solid; mp: 161–163 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, *J*=8.0 Hz, 1H), 7.43 (d, *J*=8.0 Hz, 2H), 7.36–7.32 (m, 2H), 7.22–7.20 (m, 4H), 6.94 (d, *J*=7.8 Hz, 1H), 6.85–6.81 (m, 1H), 4.27 (dd, *J*=10.8, 4.2 Hz, 1H), 3.16 (ddd, *J*=17.6, 4.2, 2.8 Hz, 1H), 2.74 (ddd, *J*=17.5, 10.8, 3.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 162.4, 142.4, 141.4, 139.9, 138.9, 138.1, 137.8, 132.6, 129.7, 129.5, 127.1, 126.9, 126.4, 119.4, 118.4, 118.0, 75.2, 55.4, 34.6, 21.4, 21.3. MS *m*/*z* (relative intensity) 357 (M+1, 89), 356 (M^+, 58), 307 (29), 222 (100), 120 (35). HRMS calcd for chemical formula: $C_{24}H_{25}N_2O$ (M^++H) 357.1967 found 357.1959.

4.4.21. 2-(2,6-Dip-tolyl-1,2,5,6-tetrahydropyrimidin-4-yl)phenol (***ii′***). Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (dd, *J*=8.0, 1.3 Hz, 1H), 7.43 (d, *J*=8.0 Hz, 2H), 7.37–7.30 (m, 1H), 7.30–7.27 (m, 2H), 7.22–7.18 (m, 4H), 7.02 (dd, *J*=8.2, 1.0 Hz, 1H), 6.88–6.81 (m, 1H), 5.97 (s, 1H), 4.08 (dd, *J*=9.2, 4.9 Hz, 1H), 3.16 (dd, *J*=17.8, 4.9 Hz, 1H), 2.74 (ddd, *J*=17.8, 9.2, 1.96 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 162.4, 142.4, 141.3, 139.6, 138.4, 138.1, 137.9, 132.6, 129.7, 129.5, 127.1, 126.9, 126.4, 119.4, 118.4, 118.0, 70.2, 55.4, 34.6, 21.4, 21.3.

4.4.22. 2-(2,6-Bis(4-fluorophenyl)-1,2,5,6-tetrahydro pyrimidin-4-yl) phenol (***iii***). Yellow solid; mp: 164–166 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52–7.46 (m, 3H), 7.44–7.40 (m, 2H), 7.33–7.29 (m, 1H),

7.10–7.04 (m, 4H), 6.94 (dd, *J*=4.8, 8.2 Hz, 1H), 4.25 (dd, *J*=4.0, 10.9 Hz, 1H), 3.17 (ddd, *J*=2.5, 3.3, 17.5 Hz, 1H), 2.73 (ddd, *J*=3.2, 10.9, 17.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 163.9 (d, J_{C-F}=245 Hz), 163.62 (d, J_{C-F}=245 Hz), 161.9, 138.2 (d, J_{C-F}=3 Hz), 137.4 (d, J_{C-F}=3 Hz), 132.7, 128.7 (d, J_{C-F}=8 Hz), 128.0 (d, J_{C-F}=8 Hz), 118.9, 118.1 (d, J_{C-F}=130 Hz), 115.9, 115.7, 115.5, 74.6, 54.9, 34.4. MS (EI) *m*/*z* (%) 365 (M+1, 75), 364 (M^+, 50), 230 (72), 154 (100), 136 (62), 122 (20). HRMS calcd for chemical formula: $C_{22}H_{19}N_2OF_2$ (M^+) 365.1465 found 365.1466.

*4.4.23. 2-(2,6-Bis(4-fluorophenyl)-1,2,5,6-tetrahydro pyrimidin-4-yl) phenol (**iii'**).* Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, *J*=8.0 Hz, 1H), 7.54–7.49 (m, 2H), 7.39–7.31 (m, 3H), 7.15–7.01 (m, 4H), 6.87 (t, *J*=7.8 Hz, 1H), 4.05 (dd, *J*=4.9, 9.2 Hz, 1H), 3.18 (dd, *J*=4.9, 17.8 Hz, 1H), 2.80 (ddd, *J*=1.3, 9.2, 17.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 163.8 (d, J_{C-F}=245 Hz), 163.7 (d, J_{C-F}=245 Hz), 162.3, 138.0 (d, J_{C-F}=3 Hz), 137.1 (d, J_{C-F}=3 Hz), 132.9, 129.1 (d, J_{C-F}=8 Hz), 128.3 (d, J_{C-F}=8 Hz), 126.9, 119.2, 118.3 (d, J_{C-F}=130 Hz), 115.9, 115.7, 115.6, 115.4, 70.8, 48.1, 32.3.

*4.4.24. 2-(2,6-Bis(4-methoxyphenyl)-1,2,5,6-tetrahydropyrimidin-4-yl)phenol (**iv**).* Yellow solid mp: 168–170 °C (decomposed), ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J*=8.2 Hz, 1H), 6.25 (s, 1H), 6.19–6.14 (m, 2H), 6.11 (s, 2H), 6.09 (s, 2H), 4.79 (m, 1H), 4.07–4.01 (m, 1H), 3.7 (s, 21H), 3.08–3.01 (m, 1H), 2.82 (d, *J*=15.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.6, 169.6, 163.8, 161.4, 160.6, 159.0, 128.2, 111.8, 110.8, 109.5, 104.6, 102.6, 91.4, 91.0, 65.9, 56.0, 55.9, 55.8, 55.7, 55.6, 55.5, 55.3, 46.6, 28.4. MS *m*/*z* (relative intensity) 412 (M+Na+H, 20), 411 (M+Na, 95) 389 (M+H, 100), 254 (60); HRMS calcd for chemical formula: $C_{24}H_{24}N_2O_3$ (M+H) 389.1865 found 389.1866.

*4.4.25. 4-Chloro-2-(2,6-diphenyl-1,2,5,6-tetrahydro pyrimidin-4-yl) phenol (**v**).* Yellow solid; mp: 157–159 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.53 (d, *J*=6.9 Hz, 2H), 7.45–7.31 (m, 9H), 7.25–7.23 (m, 1H), 7.32–7.29 (d, *J*=8.8 Hz, 1H), 4.09 (dd, *J*=10.8, 4.0 Hz, 1H), 3.16 (ddd, *J*=17.5, 3.3, 2.9 Hz, 1H), 2.74 (ddd, *J*=17.5, 10.8, 3.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 160.9, 142.4, 141.4, 132.5, 129.2, 128.9, 128.6, 128.3, 127.1, 126.8, 126.6, 122.8, 120.1, 119.8, 75.5, 55.6, 34.6. MS *m*/*z* (relative intensity) 363 (M+1, 55), 362 (M^+, 42), 307 (33), 260 (19), 258 (47), 194 (100), 136 (57), 106 (23).

*4.4.26. 2-(2,6-Diphenyl-1,2,5,6-tetrahydropyrimidin-4-yl)-4-methoxyphenol (**vi**).* Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J*=7.0 Hz, 2H), 7.44 (d, *J*=5.5 Hz, 1H), 7.41–7.30 (m, 8H), 6.43 (d, *J*=2.4 Hz, 1H), 6.38 (dd, *J*=8.8, 1.1 Hz, 1H), 4.30 (dd, *J*=10.9, 4.0 Hz, 1H), 3.82 (s, 3H), 3.15 (ddd, *J*=17.4, 4.0, 2.5 Hz, 1H), 2.81 (ddd, *J*=17.4, 10.9, 3.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 165.6, 163.5, 142.7, 141.8, 128.9, 128.7, 128.1, 127.1, 126.6, 112.8, 106.0, 101.9, 74.9, 55.7, 48.6, 32.3; MS *m*/*z* (relative intensity) 359 (M+1, 62), 358 (M^+, 37), 254 (65), 194 (100); HRMS calcd for chemical formula: $C_{23}H_{23}N_2O_2$ (M^+) 359.1760 found 359.1761.

*4.4.27. 2-(2,6-Diphenyl-1,2,5,6-tetrahydropyrimidin-4-yl)-4-methoxyphenol (**vi'**).* Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J*=7.4 Hz, 2H), 7.46 (d, *J*=6.0 Hz, 1H), 7.45–7.34 (m, 7H), 7.32–7.29 (m, 2H), 6.50 (d, *J*=2.4 Hz, 1H), 6.42 (dd, *J*=8.8, 2.5 Hz, 1H), 4.09 (dd, *J*=9.3, 4.8 Hz, 1H), 3.84 (s, 3H), 3.16 (dd, *J*=17.7, 4.8 Hz, 1H), 2.81 (ddd, *J*=17.7, 9.4, 1.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 165.6, 163.5, 142.7, 141.4, 129.1, 128.5, 128.2, 127.3, 126.6, 112.8, 106.0, 101.9, 70.9, 55.5, 48.6, 32.3.

*4.4.28. 2-(2,6-Bis(2,4,6-trimethoxyphenyl)-1,2,5,6-tetrahydropyrimidin-4-yl)phenol (**vii**).* Yellow solid mp: 126–128 °C (decomposed), δ 7.42 (dd, *J*=7.9, 1.4 Hz, 1H), 7.25–7.21 (m, 1H), 6.85 (dd, *J*=8.3, 1.0 Hz, 1H), 6.74–6.70 (m, 1H), 6.20 (d, *J*=11.9 Hz, 1H), 6.13 (s, 2H), 6.11 (s, 2H), 4.84–4.77 (m, 1H), 3.98–3.95 (m, 1H), 3.83 (s, 12H), 3.76 (s, 6H), 3.07–3.01 (m, 1H), 2.84–2.78 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): 170.6, 169.6, 163.8, 161.4, 160.6, 159.0, 128.2, 111.8, 110.8, 109.5, 104.6, 102.6, 91.4, 91.0, 65.9, 56.0, 55.9, 55.8, 55.7, 55.6, 55.5, 55.3, 55.2, 46.6, 28.4. MS *m*/*z* (relative intensity) 515 (M+Na, 26), 510 (M+2, 25) 509 (M+H, 100), 314 (15), 196 (32); HRMS calcd for chemical formula: $C_{28}H_{32}N_2O_7$ (M+H) 509.2288 found 539.2279.

*4.4.29. 2-(2,6-Bis(2,4,6-trimethoxyphenyl)-1,2,5,6-tetrahydropyrimidin-4-yl)-4-methoxyphenol (**viii**).* Yellow solid mp: 168–170 °C (decomposed), δ 7.25 (d, *J*=8.2 Hz, 1H), 6.25 (s, 1H), 6.19–6.14 (m, 2H), 6.11 (s, 2H), 6.09 (s, 2H), 4.79 (m, 1H), 4.07–4.01 (m, 1H), 3.7 (s, 21H), 3.08–3.01 (m, 1H), 2.82 (d, *J*=15.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.6, 169.6, 163.8, 161.4, 160.6, 159.0, 128.2, 111.8, 110.8, 109.5, 104.6, 102.6, 91.4, 91.0, 65.9, 56.0, 55.9, 55.8, 55.7, 55.6, 55.5, 55.3, 46.6, 28.4. MS *m*/*z* (relative intensity) 561 (M+Na, 20), 540 (M+2, 32) 539 (M+H, 100), 344 (17), 196 (22); HRMS calcd for chemical formula: $C_{28}H_{32}N_2O_7$ (M+H) 539.2393 found 539.2341.

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References and notes

1. (a) Blicke, F. F. *Org. React.* **1942**, *1*, 303–341; (b) Kleinnmann, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, NY, 1991; Vol. 2, Chapter 4.1; (c) Martin, S. F. *Acc. Chem. Res.* **2002**, *35*, 895–904; (d) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102–112.
2. Kabayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069–1094.
3. (a) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044–1070; (b) Hudlicky, T. *Chem. Rev.* **1996**, *96*, 3–30.
4. (a) Misra, M.; Pandey, S. K.; Pandey, V. P.; Pandey, J.; Tripathi, R.; Tripathi, R. P. *Bioorg. Med. Chem.* **2009**, *17*, 625–633; (b) Khan, A. T.; Parvin, T.; Choudhury, L. H. *J. Org. Chem.* **2008**, *73*, 8398–8402; (c) Clarke, P. A.; Zaytzev, A. V.; Whitwood, A. C. *Tetrahedron Lett.* **2007**, *48*, 5209–5212.
5. (a) Zhang, Z.-W.; Lu, G.; Chen, M.-M.; Lin, N.; Li, Y.-B.; Hayashi, T.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2010**, *21*, 1715–1721; (b) Aydin, J.; Kumar, K. S.; Eriksson, L.; Szabo, K. J. *Adv. Synth. Catal.* **2007**, *349*, 2585–2594; (c) Benito-Garagorri, D.; Bocokic, V.; Kirchner, K. *Tetrahedron Lett.* **2006**, *47*, 8641–8644; (d) Lin, Y.-R.; Zhou, X.-T.; Dai, L.-X.; Sun, J. *J. Org. Chem.* **1997**, *62*, 1799–1803.
6. Kobayashi, S.; Furuta, T. T.; Sugita, K.; Okitsu, O.; Oyamada, H. *Tetrahedron Lett.* **1999**, *40*, 1341–1344.
7. Siener, T.; Müller, U.; Jansen, M.; Holzgrabe, U. *Pharmazie* **1998**, *53*, 442–445.
8. (a) Ohta, Y.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2009**, *11*, 1979–1982; (b) Suzuki, Y.; Ohta, Y.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2009**, *74*, 4246–4251; (c) Dotsenko, V. V.; Krivokolysko, S. G.; Rusanov, E. B.; Litvinov, V. P. *Russ. Chem. Bull.* **2007**, *56*, 1437–1440; (d) Roth, H. J.; Troschütz, R. *Arch. Pharm.* **1977**, *310*, 48–55.
9. (a) Zhou, Z.; Zhao, P.; Huang, W.; Yang, G. *Adv. Synth. Catal.* **2006**, *348*, 63–67; (b) Paredes, A.; Alzuru, M.; Mendez, J.; Rodriguez-Ortega, M. *Biol. Pharm. Bull.* **2003**, *26*, 108–109; (c) Nussbaumer, P.; Lehr, P.; Billich, A. *J. Med. Chem.* **2002**, *45*, 4310–4320; (d) Khattab, A. M.; Grace, M. H.; El-Khrisy, E. A. *Pharmazie* **2001**, *56*, 661–662; (e) van Acker, F. A. A.; Hageman, J. A.; Haenen, G. R. M. M.; van der Vijgh, W. J. F.; Bast, A.; Menge, W. M. P. B. *J. Med. Chem.* **2000**, *43*, 3752–3760; (f) Horie, T.; Tominaga, H.; Kawamura, Y.; Hada, T.; Ueda, N.; Amano, Y.; Yamamoto, S. *J. Med. Chem.* **1991**, *34*, 2169–2176.
10. (a) Maiti, A.; Cuendet, M.; Croy, V. L.; Endringer, D. C.; Pezzuto, J. M.; Cushman, M. *J. Med. Chem.* **2007**, *50*, 2799–2806; (b) Roelens, F.; Heldring, N.; Dhooge, W.; Bengtsson, M.; Comhaire, F.; Gustafsson, J.-Å; Treuter, E.; Keukeleire, D. D. *J. Med. Chem.* **2006**, *49*, 7357–7365; (c) Ferrali, M.; Donati, D.; Bambagioni, S.; Fontani, M.; Giorgi, G.; Pietrangelo, A. *Bioorg. Med. Chem.* **2001**, *9*, 3041–3047; (d) Lipinski, C. A.; Aldinger, C. E.; Beyer, T. A.; Bordner, J.; Burdi, D. F.; Bussolotti, D. L.; Inskeep, P. B.; Siegel, T. W. *J. Med. Chem.* **1992**, *35*, 2169–2177; (e) Ankhiwala, M. D. *J. Indian Chem. Soc.* **1990**, *67*, pp 913–915; (f) Pouget, C.; Fagnere, C.; Basly, J.-P.; Habrioux, G.; Chulia, A.-J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1059–1061; (g) Hsieh, H. K.; Lee, T. H.; Wang, J. P.; Wang, J. J.; Lin, C. N. *Pharm. Res.* **1998**, *15*, 39–46.
11. Li, W.-D. Z.; Ma, B.-C. *Org. Lett.* **2005**, *7*, 271–274.
12. (a) Monserrat, J.-P.; Chabot, G. G.; Hamon, L.; Quentin, L.; Scherman, D.; Jaouen, G.; Hillard, E. A. *Chem. Commun.* **2010**, 5145–5147; (b) Kumar, D.; Patel, G.; Mishra, B. G.; Varma, R. S. *Tetrahedron Lett.* **2008**, *49*, 6974–6976; (c) Kagawa, H.; Shigematsu, A.; Ohta, S.; Harigaya, Y. *Chem. Pharm. Bull.* **2005**, *53*, 547–554;

(d) Chaturvedi, R.; Patil, P. N.; Mulchandani, N. B. *Indian J. Chem.* **1992**, *31B*, 340–341; (e) Brennan, C. M.; Hunt, I.; Jarvis, T. C.; Johnson, C. D.; McDonnell, P. D. *Can. J. Chem.* **1990**, *68*, 1780–1785; (f) Nabaei-Bidhendi, G.; Bannerjee, N. R. *J. Indian Chem. Soc.* **1990**, *67*, 43–45; (g) Dhar, D. N. *The Chemistry of Chalcone and Related Compounds*; Cambridge University: London, 1973.

13. (a) Akcok, I.; Çağır, A. *Bioorg. Chem.* **2010**, *38*, 139–143; (b) Chandrasekhar, S.; Vijeender, K.; Reddy, K. V. *Tetrahedron Lett.* **2005**, *46*, 6991–6993; (c) Bagade, M. B.; Thool, A. W.; Lokhande, P. D.; Ghiya, B. *J. Indian J. Chem.* **1991**, *30B*, 973–975; (d) Reichel, L.; Weber, F. G. *Pharmazie* **1975**, *30*, 195–196; (e) Keane, D. D.; Marathe, K. G.; O'Sullivan, W. I.; Philbin, E. M.; Simons, R. M.; Teague, P. C. *J. Org. Chem.* **1970**, *35*, 2286–2290; (f) Dutta, C. P.; Roy, L. P. K. *Indian J. Chem.* **1975**, *13*, 425–426.
14. (a) Maki, Y.; Shimada, K.; Sako, M.; Hirota, K. *Tetrahedron* **1988**, *44*, 3187–3194; (b) Pandey, G.; Krishna, A.; Kumaraswamy, G. *Tetrahedron Lett.* **1987**, *28*, pp 4515–4516; (c) Hoshino, Y.; Takeno, N. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2903–2904; (d) Sanicanin, Z.; Tabakovic, I. *Tetrahedron Lett.* **1986**, *27*, 407–408; (e) Matsushima, R.; Kageyama, H. *J. Chem. Soc., Perkin Trans. 2* **1985**, 743–748; (f) Stermitz, F. R.; Adamovics, J. A.; Geigert, J. *Tetrahedron* **1975**, *31*, 1593–1595; (g) Harris, T. M.; Carney, R. L. *J. Am. Chem. Soc.* **1967**, *89*, 6734–6741.
15. (a) Sing, O. V. *Org. Prep. Proced. Int.* **1993**, *25*, 693–695; (b) Izumi, T.; Hino, T.; Kasahara, A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1265–1267; (c) Jyotsna, D.; Rao, A. V. S. *Indian J. Chem.* **1987**, *26B*, 877–878; (d) Bhatia, V. K.; Krishnamurthy, H. G.; Madhav, R.; Seshadri, T. R. *Tetrahedron Lett.* **1968**, *9*, 3859–3862.
16. (a) Joglekar, S. J.; Samant, S. D. *Tetrahedron Lett.* **1988**, *29*, 241–244; (b) Subramanian, R. S.; Balasubramanian, K. K. *J. Chem. Soc., Chem. Commun.* **1990**, 1469–1470; (c) Wang, L.; Liu, X.; Dong, Z.; Fu, X.; Feng, X. *Angew. Chem., Int. Ed.* **2008**, *47*, 8670–8673; (d) Kumar, A.; Sharma, S.; Tripathi, V. D.; Srivastava, S. *Tetrahedron* **2010**, *66*, 9445–9449; (e) Dubrovskiy, A. V.; Larock, R. C. *Org. Lett.* **2010**, *12*, 3117–3119; (f) Chen, P.-Y.; Wang, T.-P.; Chiang, M. Y.; Huang, K.-S.; Tzeng, C.-C.; Chen, Y.-L.; Wang, E.-C. *Tetrahedron* **2011**, *67*, 4155–4416.
17. (a) Togo, H.; Iida, S. *Synlett* **2006**, 2159–2175; (b) Jereb, M.; Vrazic, D.; Zupan, M. *Tetrahedron* **2011**, *67*, 1355–1387.
18. (a) Chu, C.-M.; Huang, W.-J.; Liu, J.-J.; Yao, C.-F. *Tetrahedron Lett.* **2007**, *48*, 6881–6885; (b) Lin, C.; Fang, H.; Tu, Z.; Liu, J.-T.; Yao, C.-F. *J. Org. Chem.* **2006**, *71*, 6588–6591; (c) Ko, S.; Lin, C.; Tu, Z.; Wang, Y.-F.; Wang, C.-C.; Yao, C.-F. *Tetrahedron Lett.* **2006**, *47*, 487–492; (d) Gao, S.; Tzeng, T.; Sastry, M. N. V.; Chu, C.-M.; Liu, J.-T.; Lin, C.; Yao, C.-F. *Tetrahedron Lett.* **2006**, *47*, 1889–1893; (e) Chu, C.-M.; Gao, S.; Sastry, M. N. V.; Yao, C.-F. *Tetrahedron Lett.* **2005**, *46*, 4971–4974; (f) Ko, S.; Sastry, M. N. V.; Lin, C.; Yao, C.-F. *Tetrahedron Lett.* **2005**, *46*, 5771–5774; (g) Shivaji, V. M.; Sastry, M. N. V.; Wang, C.-C.; Yao, C.-F. *Tetrahedron Lett.* **2005**, *46*, 6345–6348; (h) Lin, C.; Hsu, J.; Sastry, M. N. V.; Fang, H.; Tu, Z.; Liu, J.-T.; Yao, C.-F. *Tetrahedron* **2005**, *61*, 11751–11757.
19. (a) Xia, J.; Qiu, R.; Yin, S.; Zhang, X.; Luo, S.; Au, C.-T.; Xia, K.; Wong, W.-Y. *J. Organomet. Chem.* **2010**, *695*, 1487–1492; (b) Sharghi, H.; Jokar, M. *Can. J. Chem.* **2010**, *88*, 14–26; (c) Kidwai, M.; Mishra, N. K.; Bansal, V.; Kumar, A.; Mozumdar, S. *Tetrahedron Lett.* **2009**, *50*, 1355–1358; (d) Jafari, A. A.; Moradgholi, F.; Tamaddon, F. *Eur. J. Org. Chem.* **2009**, 1249–1255; (e) Li, H.; Zeng, H.-y.; Shao, H.-w. *Tetrahedron Lett.* **2009**, *50*, 6858–6860; (f) Sawant, D. P.; Justus, J.; Balasubramanian, V. V.; Ariga, K.; Srinivasu, P.; Halligudi, S. B.; Vinu, A.; Velmathi, S. *Chem.—Eur. J.* **2008**, *14*, 3200–3212; (g) Khan, A. T.; Parvin, T.; Choudhury, L. H. *Eur. J. Org. Chem.* **2008**, 834–839; (h) Wu, P.; Wan, Y.; Cai, J. *Aust. J. Chem.* **2008**, *61*, 359–363; (i) Wu, H.; Shen, Y.; Fan, L.-y.; Wan, Y.; Zhang, P.; Chen, C.-f.; Wang, W.-x. *Tetrahedron* **2007**, *63*, 2404–2408; (j) Bigdeli, M. A.; Nemati, F.; Mahdavinia, G. H. *Tetrahedron Lett.* **2007**, *48*, 6801–6804; (k) Wang, R.; Li, B.-g.; Huang, T.-k.; Shi, L.; Lu, X.-x. *Tetrahedron Lett.* **2007**, *48*, 2071–2073; (l) Eftekhari-Sis, B.; Abdollahifar, A.; Hashemi, M. M.; Zirak, M. *Eur. J. Org. Chem.* **2006**, 5152–5157; (m) Ollevier, T.; Nadeau, E.; Guay-Bégin, A.-A. *Tetrahedron Lett.* **2006**, *47*, 8351–8354; (n) Kataki, D.; Phukan, P. *Indian J. Chem., Sect. B* **2006**, *45B*, 1759–1761; (o) Xu, L.-W.; Xia, C.-G.; Li, L. *J. Org. Chem.* **2004**, *69*, 8482–8484; (p) Iimura, S.; Nobutou, D.; Manabe, K.; Kobayashi, S. *Chem. Commun.* **2003**, 1644–1645; (q) Manabe, K.; Mori, Y.; Kobayashi, S. *Tetrahedron* **2001**, *57*, 2537–2544; (r) Manabe, K.; Kobayashi, S. *Org. Lett.* **1999**, *1*, 1965–1967.
20. Takajo, T.; Kambe, S.; Sato, K. *Synthesis* **1977**, 647–649.
21. Muravyova, E. A.; Desenko, S. M.; Musatov, V. I.; Knyazeva, I. V.; Shishkina, S. V.; Shishkin, O. V.; Chebanov, V. A. *J. Comb. Chem.* **2007**, *9*, 797–803.
22. (a) Sakhno, Y. I.; Desenko, S. M.; Shishkina, S. V.; Shishkin, O. V.; Sysoye, D. O.; Groth, U.; Kappe, C. O.; Chebanov, V. A. *Tetrahedron* **2008**, *64*, 11041–11049; (b) Zefirov, N. S.; Palyulin, V. A.; Dashevskaya, E. E. *J. Phys. Org. Chem.* **1990**, *3*, 147–158.
23. CCDC numbers of compounds (**i**) and (**ii'**) are 828379 and 828380, respectively. These data can be obtained free of charge from Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/datarequest/cif.
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