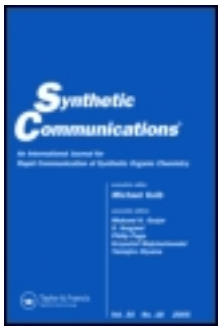

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of 5-cinnamoyl-3,4-dihydropyrimidine-2(1 H)-ones

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Accepted author version posted online: 10 Feb 2014.Published online: 10 Feb 2014.

To cite this article: Synthetic Communications (2014): Synthesis of 5-cinnamoyl-3,4-dihydropyrimidine-2(1 H)-ones, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

To link to this article: http://dx.doi.org/10.1080/00397911.2013.869341

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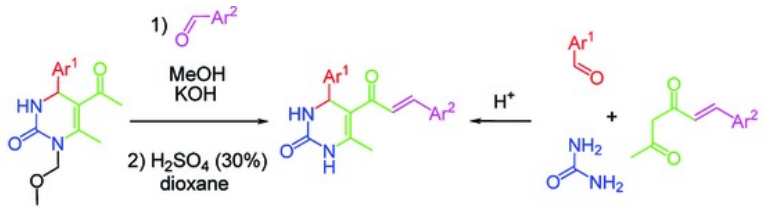
Abstract

Two different approaches to the synthesis of 1-unsubstituted 5-cinnamoyl-3,4-dihydropyrimidine-2(1*H*)-ones have been developed. The first includes N(1)-protection of the starting 5-acetyl-3,4-dihydropyrimidine-2(1*H*)-one, further Claisen-Schmidt reaction and cleavage of the protecting group. The second approach consists of one-pot condensation of urea, aldehyde and cinnamoylacetone as dicarbonyl component. The ability of 5-cinnamoylderivatives synthesis starting from 5-acetyl-1,3-dialkyl-3,4-dihydropyrimidine-2(1*H*)-ones is also shown.



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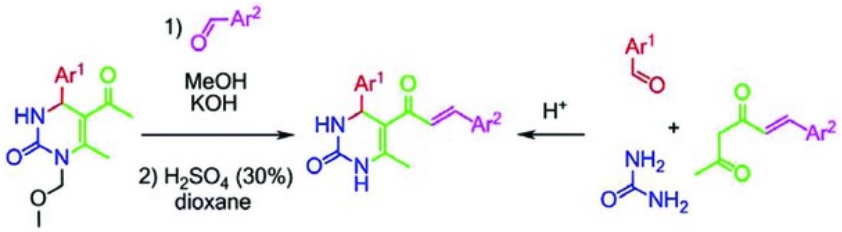

KEYWORDS: 3,4-dihydropyrimidin-2(1*H*)-ones; Biginelli reaction; one-pot condensation; protecting group; methoxymethylation.

INTRODUCTION

The use of 1,4-dihydropyridine calcium channel modulators for the treatment of cardiovascular diseases is well known.[1] Nifedipine, amlodipine and their analogs are widely introduced in medicinal practice.[2]

The derivatives of 3,4-dihydropyrimidin-2(1*H*)-one (DHPM) are the isosteres and 3-*aza*-analogs of nifedipine and the range of biological activities of DHPMs is also very high.[3] DHPMs are often synthesized by Biginelli reaction, which includes the ternary condensation of urea, aldehyde and dicarbonyl compound (or its equivalent).[4] Noteworthy, that these compounds may be readily functionalized by N(3)-position,[5] and the latter compounds are the analogs of non-symmetrical 1,4-dihydropyridines. Usually,

the introduction of needed group in position 5 is usually performed by use of different dicarbonyl compounds or their synthetic equivalents in the starting Biginelli condensation.[4c,5b,5d,6]

Recently we have shown, that the activity of 5-acetyl-DHPMs towards different reagents strongly depends on the presence of alkyl substituent in the position 1.[6c,7] For example, the reaction of 1-unsubstituted 5-acetyl- DHPMs with 4-bromobenzaldehyde occurs in the very hard conditions, while 1-alkylsubstituted 5-acetyl-DHPMs smoothly give targeted 5-cinnamoylderivatives in high yields.[6c]

Thus, the significance of the common strategy, which should allow to obtain target 1-unsubstituted 5-functionalized DHPMs as by modification of substituent in the position 5 as by use of functionalized 1,3-dicarbonyl compounds is obvious. In the present work we try to use this strategy for the synthesis of 5-functionalized DHPMs by the example of their cinnamoylderivatives.

RESULTS AND DISCUSSION

The first approach to 5-cinnamoyl-DHPMs synthesis should include the introduction of protecting group (PG) in the DHPM molecule (with the aim to increase the activity of 5-acetyl group and solubility), further functionalization of 5-acetyl group and cleavage of PG (Scheme 1). In this case the substituent in the position 5 of preformed DHPM ring is under functionalization.

Methoxymethyl (MOM) PG was chosen. Being stable in the basic conditions, further it should allow to carry out Claisen-Schmidt condensation, but it could be easily removed in acidic conditions. Benzyl protecting group was undesirable in our case because of the instability of cinnamoyl fragment to hydrogenolysis.[8] Of course, in the case of another 5-functionalized derivatives, Bn-group may also be used.[9]

We have investigated the alkylation of compound **1** by MOM-Cl under action of NaH in DMF, 1,4-dioxane and THF. The best result was achieved in NaH/1,4-dioxane system with the use of 1.1 equiv. excess of MOM-Cl (see experimental). In every case, both 1-MOM- and 1,3-di-MOM-derivatives were obtained (compounds **2** and **3**, correspondingly), but they were efficiently separated by flash-column chromatography using Al_2O_3 and CH_2Cl_2-EtOAc as eluents. Interestingly, that the action of the excess of MOM-Cl and NaH in DMF on the starting compound **1** lead to the obtaining of oil **4**, being the MOM-ether of compound **3** enol form (Scheme 2).

The structure of compound **4** was established by NOE-experiment. Under irradiation of 6-methyl group signals (2.09 ppm) the signals of two MeO-groups (3.22 ppm and 3.26 ppm, respectively) gave the enhancement, as well as signals of N(1)CH_2-protons (4.96 ppm and 5.14 ppm) and the signal of the only proton of CH_2=C-group near 3.93 ppm (Scheme 3).

4-Bromobenzaldehyde was used as model aldehyde in further reactions because of the relatively low solubility of the reaction products and, thus, the ability of purification, as well as ability of the identification of bromoderivatives by means of MS techniques.

Actually, compound **2** readily reacted with 4-bromobenzaldehyde in MeOH/KOH solution, giving the yellow precipitate of 5-cinnamoylderivative **5**. The latter was smoothly deprotected by action of 30% aqueous H_2SO_4 in 1,4-dioxane, furnishing target yellow crystals of compound **6a** (Scheme 4).

Comparing with ^{1}H NMR-spectrum of the compound **2**, ^{1}H NMR-spectrum of the compound **5** has the only signal of Me-group. Instead of it, the amount of the aromatic protons increases from 5 (compound **2**) to 11 (compound **5**), the signals of CH=CH-protons appear in the area of aromatic protons. On the one hand, deprotected compound **6a** has no MOM-group signals in ^{1}H NMR-spectrum and the signal of N(1)H (9.26 ppm) appears. On the other hand, MS-spectrum of compound **6a** contains an intensive signal of the molecular ion with m/z 397, that evidences the success of the chosen procedure.

Noteworthy, that aggregative states of the compounds **1** (mp 242–4°C), **2** (mp 114–6°C), **3** (oil at r. t.), **4** (oil at r. t.), **5** (mp 159–161°C), **6a** (mp 228–231°C) are significant and, obviously, are determined by the ability of mentioned compounds to the formation of intermolecular hydrogen bonds.

The second general approach of 5-cinnamoylDHPMs synthesis is based on previously formed functionality (3-phenyl-2-propenoyl moiety in cinnamoylacetone), which should be introduced in the target molecule by effective one-pot Biginelli reaction.

We synthesized cinnamoylacetone **7** by action of cinnamoyl chloride on acetoacetic ester and further ketone disintegration of cinnamoylacetoacetic ester in water under 140°C (3 atm) accordingly to known procedure.[10] As expected, compound **7** readily reacted with urea and different benzaldehydes in acidic media, giving target products **6b-d** (Scheme 5).

Interestingly, that in the case of benzaldehyde (compound **6b**, R = H) standard conditions for Biginelli reaction were used (EtOH/HCl), while synthesis of compound **6c** with donor substituent in aromatic ring ($R = NMe_2$) required conc. HCl as reaction media and glacial acetic acid was needed for compound **6d** with acceptor ($R = NO_2$) synthesis. These results are in good agreement with data, obtained by us earlier for the synthesis of 5-acetyl-4-arylDHPMs starting from benzaldehydes with substituent of different polarity.[11]

At the same time, in the present work we carried out the reaction of 4-bromobenzaldehyde and 4-ethylDHPM **8**, because 4-alkyl-3,4-dihydropyrimidin-2(1*H*)-ones possess a number of advantages (greater solubility, smaller molecular weight etc.), comparing with their 4-aryl analogues.[12] In fact, compound **8** easily produced 5-cinnamoyl derivative **9** in the reaction with 4-bromobenzaldehyde in mild conditions

(Scheme 6), thus, it was shown, that 5-acetyl-1,4-dialkylDHPMs actually could form 5-cinnamoylderivatives, like compounds type **2** could.

The structure of compound **8** was confirmed by both ^{1}H NMR spectrum (existence of vinyl protons signals and absence of 6-Me-group signal) and MS-spectrum (peak of molecular ion with m/z 363).

Finally, the contrary synthesis of 5-(4-bromocinnamoyl)-1-ethyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one **10**,[6c] described earlier, was performed by ethylation of compound **6a** (Scheme 7).

All the spectroscopic data of compound **10** were identical to previously reported.[6c]

CONCLUSION

In summary, by the example of 5-cinnamoylderivatives synthesis we have shown, that 5-functionalized DHPMs may be synthesized by two principal approaches: 1) by protecting of position 1, 5-functionalization and removal of the protecting group; 2) starting from pre-formed functionality in dicarbonyl component and its interaction in one-pot Biginelli reaction with urea and aldehyde.

Additionally, the ability of 5-acetyl-1,3-dialkyl-3,4-dihydropyrimidine-2-(1*H*)-ones to form corresponding 5-cinnamoylderivatives was also shown.

EXPERIMENTAL

Aldehydes, urea, 1,3-pentanedione, alkylhalides, solvents and inorganic reagents were commercially available. NaH was used as 60% suspension in mineral oil. Cinnamoylacetone was synthesized according to ref.[10] DMF and 1,4-dioxane were distilled and stored under molecular sieves (4 Å). Reactions with air- and/or moisture-sensitive compounds were performed under argon. Melting points were determined using a Kofler hot-stage apparatus. Column chromatography was performed using Al_2O_3 (60–100 μm) and silica with CH_2Cl_2, EtOAc and EtOAc/CH_2Cl_2 mixtures as eluents. The purity of the compounds, monitoring of the reaction course and fraction selection in preparative column chromatography were performed by TLC on MERCK ALUGRAM Xtra SIL G/UV 254 and KAVALIER Silufol UV-254 plates, using EtOAc–CH_2Cl_2 mixtures as eluents). ^{1}H NMR spectra were recorded at 200 MHz using a Varian Mercury VX-200 spectrometer with $Si(CH_3)_4$ as internal standard, chemical shifts are performed in ppm, coupling constants are given in Hz. ^{13}C NMR-spectra were recorded in DMSO-d_6 at 100 MHz using Bruker Avance 400 spectrometer with $Si(CH_3)_4$ as internal standard. Mass spectra (EI, 70 eV) were obtained using a Varian 1200L instrument using a direct probe exposure (DEP) method. IR spectra were recorded on KBr pellets using a Specord IR-75 spectrometer. Elemental analyses (C, H, N) were obtained using EuroEA-3000 instrument.

Selected Procedures

5-Acetyl-6-methyl-1-methoxymethyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (2)

The solution of **1** (8 g, 0.035 mol) in 1,4-dioxane (60 ml) was added to the flask with NaH (60% suspension in mineral oil, 1.53 g, 0.038 mol) with the use of syringe. The reaction mixture was stirred for 1 h at 60°C. After cooling to the room temperature, MOM-Cl (3.08 g, 0.038 mol) was added dropwise. Then the mixture was stirred for 1 h at room temperature and 30 min at 60°C. After filtration through the thin (3-5 mm) layer of Al_2O_3, the obtained solution was evaporated to dryness. The residual solid was purified by flash column chromatography (Al_2O_3, 250 mL of EtOAc) and then crystallized from the mixture of benzene/hexane (1:1) to give compound **2**. White solid; yield: 3.17 g (33%); mp 114–116°C. IR (KBr): 1682, 1659, 1598, 1457, 3216 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ_H = 8.17 (d, *J* = 3.4 Hz, 1H, NH), 7.2–7.4 (m, 5H, Ph), 5.23 (d, *J* = 3.4 Hz, 1H, H-4), 5.12 (d, *J* = 11.0 Hz, 1H, CH_2), 5.02 (d, *J* = 11.0 Hz, 1H, CH_2), 3.13 (s, 3H, OCH_3), 2.43 (s, 3H, CH_3), 2.11 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 16.23, 31.12, 53.66, 56.03, 73.47, 114.39, 127.21, 128.35, 129.36, 143.72, 147.75, 153.18, 197.23. MS (EI, 70 eV): *m*/*z* (%) = 274 ($M^{+\cdot}$, 15), 259 (55), 229 (70), 167 (75), 45 (100). Anal. Calcd. for $C_{15}H_{18}N_2O_3$ (274.32): C, 65.68; H, 6.61; N, 10.21. Found: C, 65.63; H, 6.56; N, 10.20.

5-Acetyl-6-methyl-1-methoxymethyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (2) and 5-acetyl-1,3-dimethoxymethyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (3)

A solution of **1** (5 g, 0.022 mol) in DMF (30 mL) was added to the flask with NaH (60% suspension in mineral oil, 1.15 g, 0.029 mol) with the use of syringe. The obtained

mixture was stirred for 1 h at 0-5ºC. Then MOM-Cl (1.93 g, 0.024 mol) was added dropwise to the reaction mixture. After additional stirring for 1.5 h at room temperature, the solution was poured into 350 mL of water and the product was extracted 3 times with 50 mL of EtOAc, The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The residual solid was purified by column chromatography (EtOAc/CH_2Cl_2 (1:1, 100 mL), EtOAc (150 mL)) to give compound **2 (**0.65 g, 11%) as a white solid and **3**.

5-Acetyl-1,3-*bis*(methoxymethyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (3).

Yellow viscous oil; yield: 0.9 g (13%). IR (KBr): 1682, 1662, 1614, 1456 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ_H = 7.2–7.4 (m, 5H, Ph), 5.46 (s, 1H, H-4), 5.19 (d, *J* = 11.0 Hz, 1H, CH_2), 5.06 (d, *J* = 11.0 Hz, 1H, CH_2), 5.05 (d, *J* = 11.0 Hz, 1H, CH_2), 4.47 (d, *J* = 11.0 Hz, 1H, N(3)CH_2), 3.18 (s, 3H, OCH_3), 3.12 (s, 3H, OCH_3), 2.42 (s, 3H, CH_3), 2.21 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 16.43, 31.43, 55.88, 56.39, 57.28, 74.68, 78.09, 116.25, 127.43, 128.65, 129.39, 141.37, 146.91, 153.47, 196.80. MS (EI, 70 eV): *m*/*z* (%) = 318 (M+·, 22), 303 (20), 285 (82), 241 (100), 198 (11), 45 (75). Anal. Calcd for $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.97; N, 8.80. Found: C, 64.10; H, 6.90; N, 8.80.

5-[3-(4-Bromophenyl)-2-propenoyl]-1-methoxymethyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (5)

A mixture of **2** (1.1 g, 4.01 mmol), 4-bromobenzaldehyde (0.81 g, 4.41 mmol) and KOH (saturated solution in MeOH, 1.1 mL) in MeOH (7 mL) was stirred at ambient temperature for 3.5 h. The product precipitated over night. After filtration and washing 3 times with MeOH (3 mL) the product was crystallized from EtOH to give compound **5**.

Bright orange solid; yield: 0.80 g (45%); mp 159–161°C. IR (KBr) 1688, 1657, 1613, 1485 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ_H = 8.15 (d, *J* = 3.1 Hz, 1H, NH), 7.53–7.67 (m, 4H, Ar), 7.16–7.36 (7H, m, CH=CH, Ph), 5.4 (d, *J* = 3.1 Hz, 1H, H-4), 5.15 (d, *J* = 10.8 Hz, 1H, CH_2), 5.04 (d, *J* = 10.8 Hz, 1H, CH_2) 3.17 (s, 3H, OCH_3), 2.35 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 16.95, 53.92, 56.04, 73.46, 115.26, 124.29, 127.06, 127.79, 128.23, 129.24, 131.08, 132.51, 134.60, 141.08, 144.15, 145.73, 153.26, 190.53. MS (EI, 70 eV): *m*/*z* (%) = 440 ($M^{+\cdot}$, 90), 409 (16), 379 (33), 129 (98), 102 (80). Anal. Calcd for $C_{22}H_{21}BrN_2O_3$: C, 59.87; H, 4.80; Br, 18.11; N, 6.35. Found: C, 59.81; H, 4.70; Br, 18.11; N, 6.33.

5-[3-(4-Bromophenyl)-2-propenoyl]-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (6a)

To a stirred solution of **5** (1 g, 2.26 mmol) in dioxane (10 mL) the 30% aqueous solution of H_2SO_4 (30 ml) was added dropwise. The monitoring of MOM-group cleavage was performed by TLC using mixture of EtOAc/CH_2Cl_2 (1:1) as eluent. The formed precipitate was filtered off and washed 3 times with the mixture of dioxane/water (1:1, 3 mL) and 3 times with water (3 mL) giving compound **6a**. Yellow solid; yield: 0.80 g (89%); mp 228–231°C. IR (KBr) 1709, 1659, 1614, 1485, 3245 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ_H = 9.26 (s, 1H, NH), 7.89 (s, 1H, NH), 7.51–7.66 (m, 4H, Ar), 7.15–7.36 (m, 7H, CH=CH, Ph), 5.47 (d, *J* = 3.1 Hz, 1H, H-4), 2.27 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 19.62, 54.61, 110.69, 123.85, 127.07, 127.63, 128.00, 129.17, 130.84, 132.46, 134.92, 139.59, 145.26, 148.55, 152.74, 187.90. MS (EI, 70 eV): *m*/*z* (%) = 398 ($M^{+\cdot}$, 100), 334 (8), 274 (76), 185 (28), 153 (13), 128 (20). Anal. Calcd for

$C_{20}H_{17}BrN_2O_2$: C, 60.47; H, 4.31; Br, 20.11; N, 7.05. Found: C, 60.40; H, 4.27; Br, 20.15; N, 7.01.

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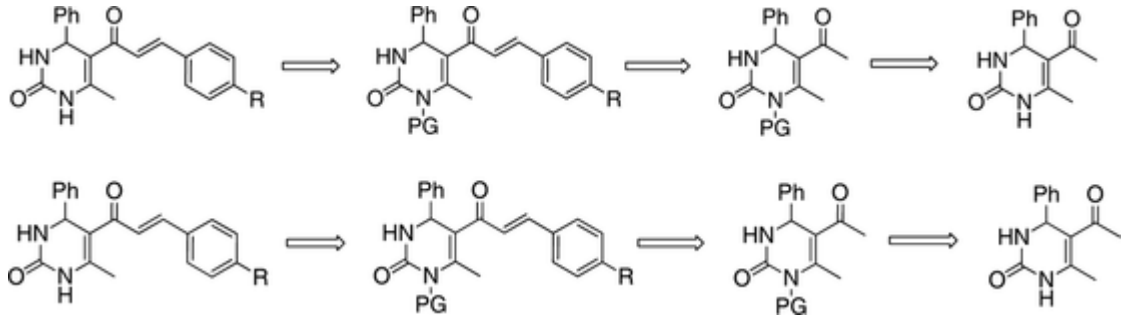
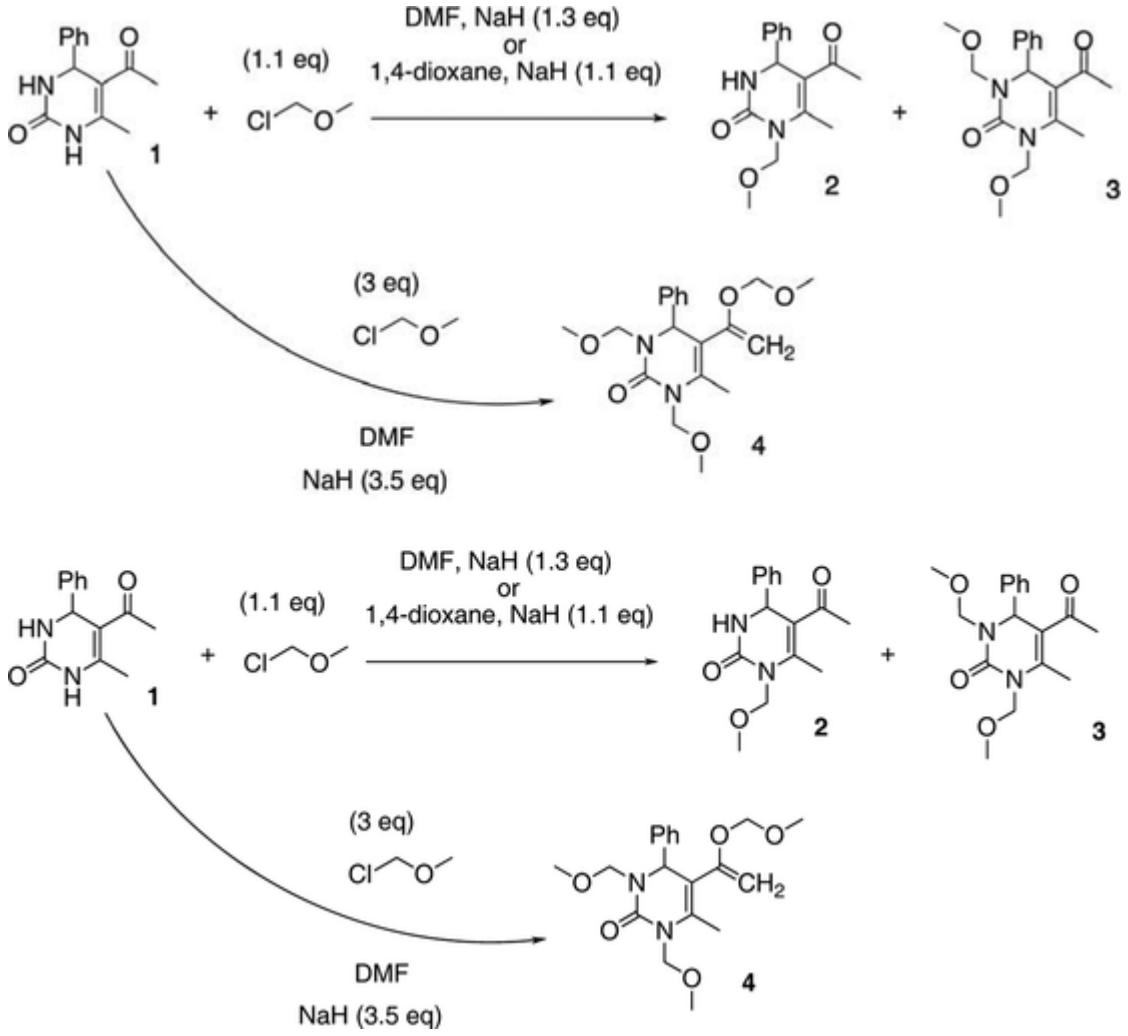
Scheme 1. Retrosynthetic plan of the synthesis of target 5-cinnamoyl-3,4-dihydropyrimidin-2(1*H*)-ones by first approach.

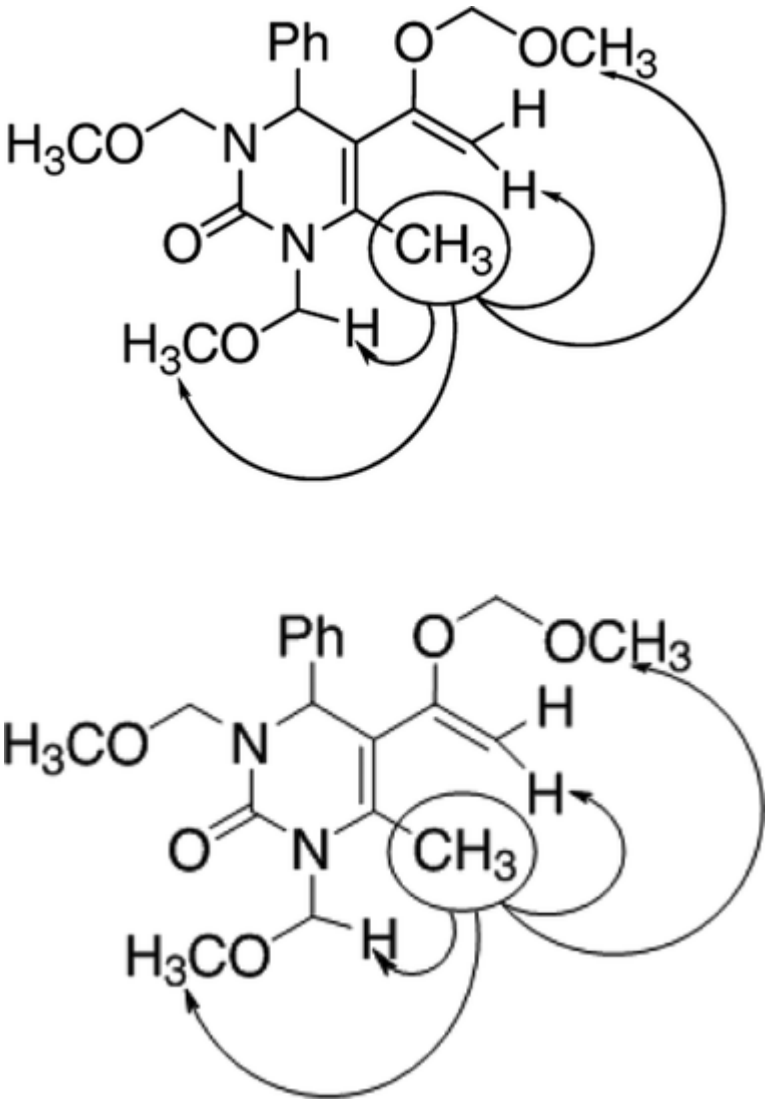


Scheme 2. Alkylation of 5-acetyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one **1.**

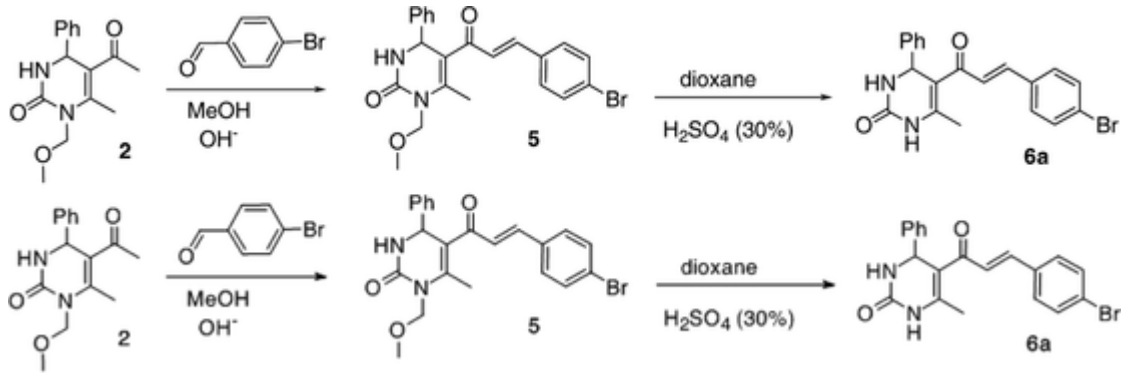
Scheme was changed!



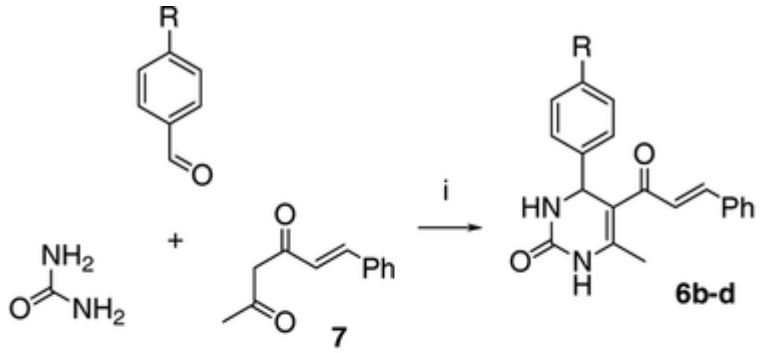
Scheme 3. NOE-experiment for compound **4**.



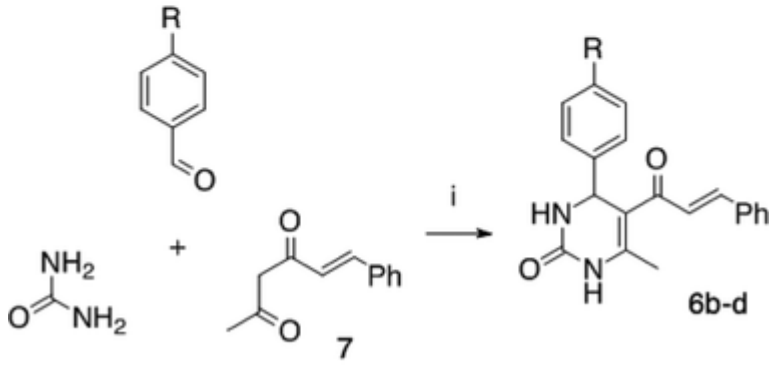
Scheme 4. Synthesis of cinnamoyl derivative **6a** by first approach.



Scheme 5. Synthesis of compounds **6b-d** by second approach.

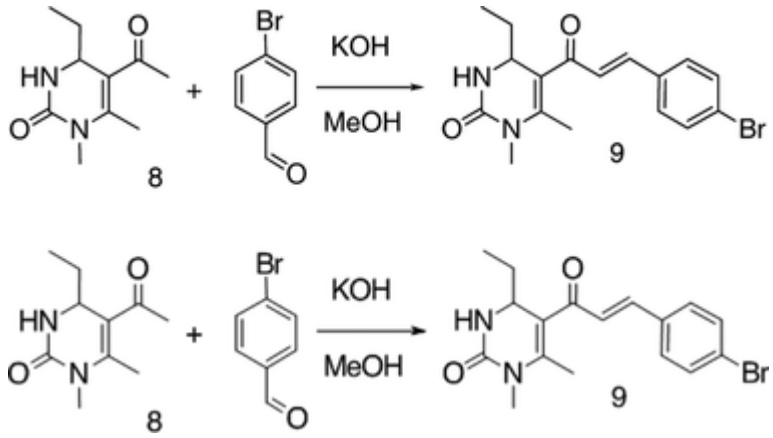


R = H (b), NMe_2 (c), NO_2 (d)
i: EtOH/HCl (b), conc. HCl (c), HOAc (d)



R = H (b), NMe_2 (c), NO_2 (d)
i: EtOH/HCl (b), conc. HCl (c), HOAc (d)

Scheme 6. Synthesis of 5-acetyl-5-cinnamoyl-4-ethyl-3,4-dihydropyrimidin-2(1*H*)-one **8**.



Scheme 7. Contrary synthesis of known compound **9** by ethylation of compound **6a.**