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A practical and green approach toward synthesis of *N3*-substituted dihydropyrimidinones: Using Aza-Michael addition reaction catalyzed by KF/Al_2O_3

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Abstract—A simple and efficient method for the synthesis of *N3*-substituted 3,4-dihydropyrimidinones by aza-Michael addition reactions of 3,4-dihydropyrimidinones to α,β-ethylenic compounds catalyzed by KF/Al_2O_3 is described. The advantage of this method is high regioselectivity, high purity, and the use of a cheaper, milder, and efficient catalyst for the hetero-Michael addition reaction.

3,4-Dihydropyrimidinones (DHPMs), named Biginelli compounds, which were reported for the first time by Biginelli 100 years ago, have received considerable attention in the past decades due to their heterocyclic scaffold[1] and their interesting pharmacological properties,[2] such as calcium channel modulating, antihypertensive, α_{1a} adrenergic agonistic, mitotic kinesin inhibiting, and hepatitis B virus replication suppression properties. Several marine derived natural products such as Crambine, Batzelladine B (potent HIV gp-120CD4 inhibitors), and Ptilomycalin alkaloids also contain the DHPM core.[3]

Among the DHPM derivatives, most of the pharmacologically attractive DHPM derivatives are *N3*-substituted analogues.[1b,1c] It has already been pointed out that *N*3-monoalkylated Biginelli compounds cannot be obtained either by alkylation of unsubstituted derivatives, or by classical Biginelli condensation using alkylureas. In both cases, only *N1*-alkylated products are formed.[4] Generally, *N3*-substituted DHPMs were prepared in two-step reaction as described in Scheme 1. Alkylation of S-alkylated or O-alkylated Biginelli compounds **A** gives protected *N3*-substituted dihydropyrimidines **B**, which then can be deprotected in the presence of acid to obtain the desired *N*3-alkylated dihydropyrimidinones **C**. Very recently, Kappe et al. have reported *N*3-acylated 3,4-dihydropyrimidinones by acylation of 3,4-dihydropyrimidines with ethyl chloroformate and *N*,*N*-dimethylcarbamoyl chloride[5] or with anhydrides in the presence of triethylamine as base, and 4-(*N*,*N*-dimethylamino)pyridine as a catalyst.[6]

We were interested in studying the potential and efficiency of KF/Al_2O_3[7] as catalyst in the alkylation reaction of DHPMs. The application of KF/Al_2O_3 to organic synthesis[8] and Michael addition[9] chemistry has been reported by a number of authors. To our knowledge, no such study has been performed in this kind of reaction.

Preliminary experiments to examine the solvent dependence of aza-Michael reaction were performed using substrate **1a** as a model system (Table 1). Firstly, various bases, molar ratios of the reagents, and reaction times were tested using *N*,*N*-dimethylformamide (DMF) as a solvent. All comparative reactions were conducted under optimized conditions and the *N3*-substituted 3,4-dihydropyrimidine **3a** was obtained in the presence of inorganic bases. The best yield of **3a** (83%) was obtained by carrying out the reaction in DMF at room temperature overnight using equivalent amounts of DHPM **1a**,

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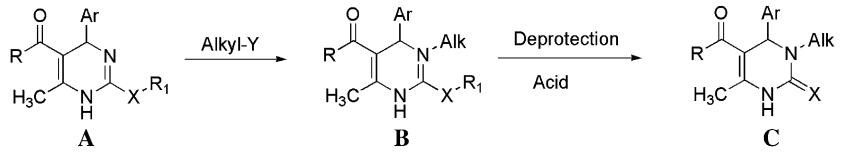
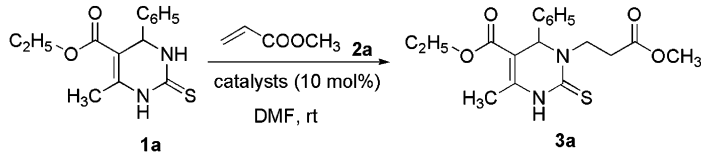


Scheme 1.

Table 1. Aza-Michael reaction of **3a** with various catalysts[a]

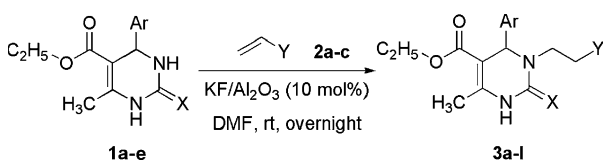


Entry	Base	Solvent	Time (h)	Yield (%)[b]
1	K_2CO_3	DMF	48	<10
2	Na_2CO_3	DMF	48	<10
3	$NaHCO_3$	DMF	48	<10
4	NaOH	DMF	24	<10
5	KOH	DMF	24	<10
6	KF/Al_2O_3	DMF	12	83
7	Et_3N	DMF	48	0[c]
8	No	DMF	48	0[c]
9	KF/Al_2O_3	DMSO	12	82
10	KF/Al_2O_3	DMF	12	83
11	KF/Al_2O_3	MeCN	12	61
12	KF/Al_2O_3	CH_2Cl_2	24	46
13	KF/Al_2O_3	THF	24	53

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), solvents (3 mL), catalysts (10 mol %), at room temperature.
[b] Isolated yields.
[c] No detected compound by ^1H NMR.

methyl acrylate **2a**, and 10 mol% of KF/Al_2O_3. No reaction was observed in the presence of Et_3N or absence of any catalysts (Table 1, entries 7 and 8). Secondly, other solvents were tested including DMSO, MeCN, CH_2Cl_2, and THF. In general, the use of DMSO, DMF, and MeCN resulted in faster reaction with higher yield, in contrast to reactions in less polar THF and DCM (Table 1).

With optimal conditions in hand, a combination of 3,4-dihydropyrimidinones **1b**–**1e** and α,β-ethylenic compounds **2b**–**c** was investigated (Scheme 2, Table 2). All reactions were conducted in DMF at room temperature in the presence of 10 mol% of KF/Al_2O_3. In each case, smooth reaction occurred to provide the desired *N3*-substituted DHPMs in high yield (69–85%), and in excellent stereoselectivity. All the products were investigated thoroughly using ^1H NMR, ^{13}C NMR, IR, Mass, and element analysis. ^1H NMR of all products show that the aza-Michael addition occurred exclusively at *N*3 position of 3,4-dihydropyrimidinones.[10,11] Kinetic experiment with ^1H NMR indicated that *N1* substitution does not take place over the course of the reaction.[12,13] The complete selectivity, we believe, is due to a difference in the electron density at *N*3 and *N*1 position. The higher basicity of the former resulted in exclusive alkylation at this position, in accordance with the literature precedence.[6] The single crystal X-ray crystallography of product **3b** also confirmed the structures of obtained products (Fig. 1).[11]



Scheme 2.

Upon completion of the reaction, the KF/Al_2O_3 catalyst was readily separated from the reaction mixture by simple filtration and could be reused without appreciable losses of its high activity and regioselectivity. For the reaction of **1a** with **2a**, over 60% yields for **3a** were obtained during the three recycling experiments (83%, 80%, and 61%).

In summary, we have documented the first aza-Michael addition of DHPMs with α,β-ethylenic compounds affording *N3*-substituted DHPMs in the presence of KF/Al_2O_3 as catalyst. The methodology described herein avoids the use of S-alkylated or O-alkylated pyrimidinethiones (Scheme 1, A) and *N3*-substituted dihydropyrimidines (Scheme 1, B) as starting materials and consequently, circumvents the unpredictable Biginelli condensation.[1b,5] Apart from the experimental simplicity, the method has advantage of increased product quality as well as higher atom economy. Moreover, this catalyst was reusable without any appreciable losses in its high activity or regioselectivity.

Table 2. Aza-Michael reactions of DHPMs with α,β-ethylenic compounds

Entry[a]	Ar	X	1	Y	2	Product	Yield (%)[b]
1	C_6H_5	S	**1a**	COOMe	**2a**	**3a**	70
3	4-ClC_6H_4	S	**1b**	COOMe	**2a**	**3b**	83
4	C_6H_5	S	**1a**	$COOC_2H_5$	**2b**	**3c**	79
5	4-ClC_6H_4	S	**1b**	$COOC_2H_5$	**2b**	**3d**	84
6	C_6H_5	S	**1a**	CN	**2c**	**3e**	74
7	4-$CH_3OC_6H_4$	S	**1c**	CN	**2c**	**3f**	77
8	4-$CH_3OC_6H_4$	O	**1d**	COOMe	**2a**	**3g**	70
9	4-ClC_6H_4	O	**1e**	COOMe	**2a**	**3h**	78
10	C_6H_5	O	**1f**	$COOC_2H_5$	**2b**	**3i**	72
11	4-ClC_6H_4	O	**1e**	$COOC_2H_5$	**2b**	**3j**	78
12	C_6H_5	O	**1f**	CN	**2c**	**3k**	69
13	4-$CH_3OC_6H_4$	O	**1d**	CN	**2c**	**3l**	85

[a] The reaction was conducted with 3,4-dihydropyrimidones (1 mmol), α,β-ethylenic compounds (1 mmol), and DMF (5 mL) in the presence of KF/Al_2O_3 (10 mol%) at room temperature for 12 h.
[b] Isolated yields.

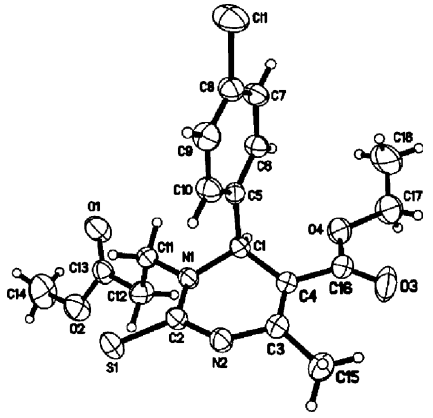


Figure 1. ORTEP diagram of compound **3b**.

Acknowledgments

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10. General experimental procedure: to a solution of α,β-ethylenic compounds (1 mmol) and 3,4-dihydropyrimidones (1 mmol) in DMF (5 ml), KF/neutral alumina (10 mol%, 15 mg) was added in one portion. After the mixture was stirred at room temperature for overnight, the catalyst was removed by simple filtration. Then the solvent was evaporated under vacuum to give the corresponding analytically pure products. Spectroscopic data for **3c**: mp 150–151 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.11 (br s, 1H), 7.33–7.25 (m, 5H), 5.27 (s, 1H), 4.33–4.26 (m, 1H), 4.17–4.05 (m, 4H), 3.70–3.63 (m, 1H), 2.94–2.86 (m, 1H), 2.59–2.52 (m, 1H), 2.14 (m, 3H), 1.25–1.19 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 175.14, 171.2, 165.17, 142.32, 141.01, 128.84, 128.39, 126.98, 102.90, 62.06, 60.76, 60.39, 53.41, 48.41, 32.03, 18.19, 14.19, 14.11; FT-IR (KBr) ν (cm^{-1}) 3298, 3082, 2992, 2938, 1704, 1644, 1245, 1215, 1197, 1098. MS: m/z = 376 (M^+). Anal. Calcd for: $C_{19}H_{24}N_2O_4S$: C, 60.62; H, 6.43; N, 7.44. Found: C, 60.69; H, 6.38; N, 7.48. **3e**: mp 154–155 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.48 (br s, 1 H), 7.32–7.24 (m, 5H), 5.53 (s, 1H), 4.31–4.24 (m, 1H), 4.17–4.07 (m, 2H), 3.71–3.64 (m, 1H), 3.11–3.01 (m, 1H), 2.44–2.32 (m, 1H), 2.27 (s, 3H), 1.25–1.16 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 175.41, 164.88, 142.30, 140.61, 129.10, 128.82, 127.04, 117.42, 103.17, 62.80, 60.58, 48.28, 17.99,

15.59, 14.15; FT-IR (KBr) v (cm^{-1}) 3208, 3058, 2992, 2944, 2260, 1701, 1653, 1266, 1239, 1200. MS: m/z = 329 (M^+). Anal. Calcd for: $C_{17}H_{19}N_3O_2S$: C, 61.98; H, 5.81; N, 12.76. Found: C, 62.05; H, 5.85; N, 12.69.

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