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Metalation of Biginelli Compounds. A General Unprecedented Route to C-6 Functionalized 4-Aryl-3,4-dihydropyrimidinones

Kamaljit Singh,* Sukhdeep Singh, and Aman Mahajan

Department of Applied Chemical Sciences & Technology, Guru Nanak Dev University, Amritsar - 143 005, India

Kamaljit19in@yahoo.co.in

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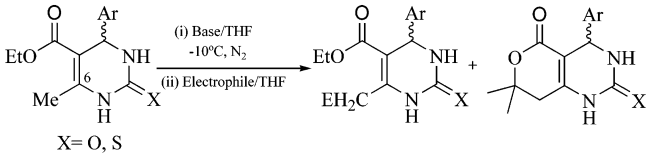
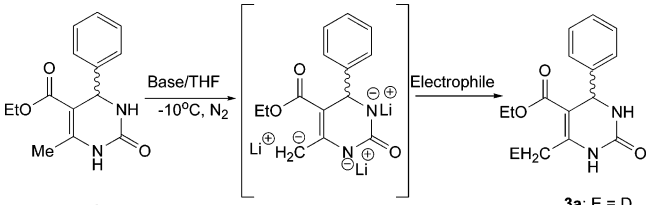


4-Aryl-6-methyl-3,4-dihydro-2(1*H*)-pyrimidinone esters (DHPMs) readily undergo metalation at the C-6 methyl (vinylogous ester) position on treatment with lithium diisopropylamide at −10 °C. The resulting anion intermediates can be treated with electrophilic reagents to afford functionalized DHPMs that have been chemically elaborated mainly at the C-6 position. Di- and trianion formation is also possible at both the vinylogous methyl and NH positions when reactions are performed with excess equivalents of the base.

A careful examination of the current literature has revealed that elaboration of C-6 of 4-aryl-6-methyl-3,4-dihydro-2(1*H*)-pyrimidinone esters (Biginelli DHPMs)[1] through reactions of the lithio salts with electrophiles are unprecedented. Strategies for the synthesis of the DHPM nucleus have varied from one-step to multistep approach, but the methods[1,2] for the peripheral elaboration are scarce[2e,f] or of limited synthetic scope. The privileged DHPMs have emerged as the integral backbone of several calcium channel blockers, antihypertensive agents, α-1a-antagonists, and marine alkaloids. Most notable among these are the batzelladine alkaloids, which are found to be potent HIVgp-120-CD4 inhibitors.[3] The scaffold decoration[2h] of DHPMs is highly important for creating structural diversity to produce "druglike" molecules for biological screening. In analogy with the 1,4-dihydropyridines (NADH analogues),[4] the elaborated DHPMs are considered to be conformationally flexible, and the consequent effects on the calcium channel modulatory activities are well-documented.[5] To the best of our knowledge, the only report for the functionalization of the C-6 methyl group is through bromination (invariably plagued by *gem*-dibromination) and subsequent reaction with some nucleophiles.[2e,f] In view of the potential usefulness of the C-6 elaborated DHPMs,[6] we have undertaken this investigation, and in this note, we report the first rational synthesis of C-6 elaborated DHPMs.

TABLE 1. Deuterium Incorporation and Condition Optimization for Metalation of Dihydropyrimidinone 1a



entry	electrophile (temp)	base (equiv)	product	isolated yield (%)
1	d_4-methanol (r.t.)	LDA (3.1)	**3a**	70
2	EtBr (0 °C)	n-BuLi (2.1)	**3b**	55
3	EtBr (0 °C)	n-BuLi (3.1)	**3b**	50
4	EtBr (0 °C)	n-BuLi (4.1)	**3b**	55
5	EtBr (0 °C)	n-BuLi (5.1)	**3b**	56
6	EtBr (0 °C)	LDA (3.1)	**3b**	60
7	EtBr (0 °C)	LDA (4.1)	**3b**	71

We initially examined the metalation of the simple 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydro-2(1*H*)-pyrimidinone **1a** with LDA (−10 °C) and subsequent quenching at ambient temperature with d_4-methanol to determine optimal conditions for vinylogous C-6 methylmetalation. Deuterium distribution (%-d_1 incorporation and location) in the resultant product was determined by the high field ^{1}H and ^{13}C analyses and was found to be exclusively at the C-6 methyl (vinylogous ester) (100%-d_1) as indicated by the exclusive formation of **3a** (entry 1, Table 1). No deuterium incorporation was observed at any other position in the molecule, which indicates the exclusive metalation of the least acidic and consequently the most nucleophilic C-6 position. The other two potential nitrogen centered metalation/substitution sites if deuterated were exchanged under the aqueous workup conditions of the method. Moreover, no addition product resulting from nucleophilic attack at the ester group of **1a** was observed. Use of 1.1 equiv of LDA gave no deuterium incorporation in the molecule.[7]

Treatment of **1a** with 2.1 equiv of freshly prepared *n*-BuLi (2.3 N in hexanes) in THF at −10 °C followed by stirring at room temperature (r.t.) for 3 h yielded the pale

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(7) Use of *n*-BuLi was found not to yield satisfactory results.

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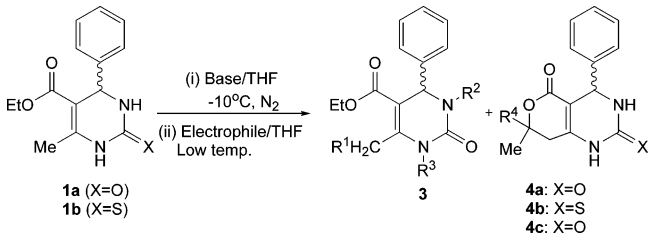
TABLE 2. Reactions of 5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydro-2(1*H*)-pyrimidinone 1 Anions with Electrophiles: Formation of 3 and 4



entry	electrophile (temp)	base (equiv)	product (3/4)[a]	R^1	R^2	R^3	R^4	isolated yield (%)
1	MeI (0 °C and r.t.)	LDA (4.1)	**3c**	H	Me	Me	–	26
		LDA (3.1)						20
		LDA (4.1)	**3d**	Me	Me	H	–	30
		LDA (3.1)						10
		LDA (4.1)	**3e**	Me	H	H	–	22
		LDA (3.1)						30
		LDA (4.1)	**3f**	H	Me	H	–	5
2	$PhCH_2Cl$ (r.t.)	LDA (3.1)	**3g**	CH_2Ph	H	H	–	50
3	4-Me-$C_6H_4SO_2Cl$ (−78 °C)	LDA (4.1)	**3h**	Cl	H	H	–	55
		LDA (3.1)						37
4	Me_2CO (r.t.)	LDA (3.1)	**3i**	$C(OH)Me_2$	H	H	–	38
			4a	–	H	H	Me	35
		LDA (4.1)	**4b**	–	H	H	Me	62
5	$MeCOCH_2Ph$ (0 °C)	LDA (4.1)	**4c**	–	H	H	CH_2Ph	72
6	4-$NO_2C_6H_4CHO$ (−78 °C)	LDA (4.1)	**3j**	4-$NO_2C_6H_4CH(OH)$	H	H	–	58
		LDA (3.1)						8
7	2,4-di-(OMe)C_6H_3CHO (0 °C)	LDA (4.1)	**3k**	2,4-di(OMe)$C_6H_3CH(OH)$	H	H	–	60
8	$(n\text{-}Pr)_2S_2$ (0 °C)	LDA (3.1)	**3l**	n-PrS	H	H	–	35
			3m	$n\text{-}(PrS)_2$	H	H	–	30
9	Ph_2S_2 (0 °C)	LDA (3.1)	**3n**	$(PhS)_2$	H	H	–	35
10	n-EtCOCl (−5 °C)	LDA (4.1)	**3o**	H	n-EtCO	H	–	60
11	HCOOEt	LDA (4.1)	**3p**	H	CHO	H	–	40
12	Me_3SiCl (0 °C)	LDA (4.1)	**3q**	Me_3Si	H	H	–	75

[a] The formation of any ethyl 2-alkoxy/alkylthio-6-methyl-4-aryl-1,4-dihydropyrimidine-5-carboxylate was not detected.[13]

yellow colored anion **2**.[8] After 3 h at r.t., ethyl bromide (3.0 equiv) was added to the metalation solution cooled at 0 °C, and the reaction was allowed to warm to room temperature and quenched with saturated aqueous NH_4-Cl to obtain the C-6 alkylated product **3b**. Increasing the amount of the base (Table 1) did not increase the yield in any significant way unless LDA (4.1 equiv)[9] was employed when the blood red anion of **1a** yielded **3b** (entry 7, Table 1, 71% yield), after quenching with ethyl bromide. Except for the isolation of DHPM **1a** (<10% yield, recycled), no evidence of the formation of N- or O-alkylated DHPMs was noticed in these reactions.

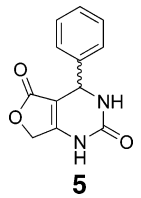
We subsequently studied the reaction of metalated **1** with different types of electrophiles (Table 2). Use of rather reactive methyl iodide gave a complex mixture of all possible products comprising **3c**−**f**, out of which the C-6 substituted DHPM **3e** was obtained in 30% yield. Benzyl chloride furnished **3g** (entry 2) in 50% yield. *p*-Toluenesulfonyl chloride furnished the halogenated derivative **3h** (entry 3)[10] in 55% yield. Lithiation of **1a** with 3.1 equiv of LDA at low temperature followed by treatment with acetone gave a mixture (1:1, approximately) of DHPM **3i** (entry 4, 38%) and lactone **4a** (35%) when the reaction was carried out in the usual manner. Independent treatment of **3i** with *p*-toluenesulfonic acid in refluxing toluene furnished **4a** (80%). However, in the reaction of the anion of **1b** with acetone, employing 3.1 or 4.1 equiv of LDA, exclusive formation of **4b** (62%) was observed. Likewise, the reaction of the lithio salt of **1a** with phenyl acetone furnished the lactone **4c** as a diastereomeric mixture in 72% yield.[11]

Reactions of aldehydes (entries 6 and 7, Table 2) were executed using 4.1 equiv of LDA for anion generation, and the corresponding C-6 elaborated products **3j** and **3k** were obtained in 58 and 60% yields, respectively, as diastereomeric mixtures (7:3 ratio, approximately). The use of di-*n*-propyldisulfide as electrophile for quenching the anion of **1a** furnished C-6-mercaptopropyl derivative **3l** (entry 8, 35%) along with the bis-substituted thioacetal **3m** (30%); the latter was presumably formed through the deprotonation of more acidic proton adjacent to the

(8) Although a number of lithio intermediates can be envisioned, metalated **1** in this note is depicted as the C-6 and N-localized anion for simplicity and clarity.

(9) The anion generation time was also reduced from 3 to 1.5 h.

(10) Upon solvent-free heating (210 °C), **3h** yielded 4-phenyl-4,7-dihydro-1*H*-3*H*-furo[3,4-*d*]pyrimidine-2,5-dione **5**,[2g] in 80% yield.



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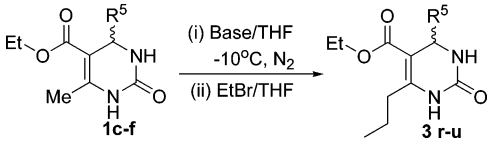
(11) Isolated in 7:3 ratio. The ^1H NMR of the crude mixture was complex. However, in the ^1H NMR spectra of the isolated diastereomers, the chemical shifts showed considerable separation (see Supporting Information).

TABLE 3. C-6 Elaborated DHPMs from the Metalation of 1c−f



entry	DHPM 1	R^5	product	isolated yield (%)
1	**1c**	4-OMe-C_6H_4	**3r**	65
2	**1d**	3,4,5-tri(OMe)C_6H_2	**3s**	78
3	**1e**	H	**3t**	72
4	**1f**	Et	**3u**	67

mercaptopropyl substituent followed by reaction with di-*n*-propyldisulfide. However, in the reaction of diphenyldisulfide, C-6 di-substituted DHPM **3n** (entry 9, 35%) was formed exclusively.

The hard electrophile *n*-propionyl chloride furnished only N-3 substituted product **3o** (entry 10, Table 2) in 60% yield. Likewise, reaction of ethyl formate with the anion of **1a** furnishes N-3 formylated product **3p** (entry 11), exclusively. The formation of N-3 acylated DHPMs, otherwise tedious to synthesize,[12a] is prized for their special biological effects.[12b] Trimethylsilyl chloride quenched the anion of **1a** to furnish the C-6 elaborated DHPM **3q** (entry 12, 75%) exclusively.

To further explore the scope of this methodology, we performed metalation reactions of various C-4 aryl as well as alkyl substituted Biginelli substrates with LDA (4.1 equiv), using ethyl bromide as electrophile (0 °C) using the standardized procedure. The corresponding C-6 elaborated products were obtained in a synthetically useful manner (Table 3).

In summary, DHPM derivatives readily undergo vinylogous metalation at the C-6 position with alkyllithium bases. The resulting anion intermediates can be treated with a variety of electrophilic reagents to afford important C-6 elaborated DHPMs in modest to good yields.[14] This methodology permits a variety of electrophilic functionalities to be introduced at the C-6 methyl position of variously C-4 substituted DHPMs.

Experimental Section

Typical Procedure for C-6 Alkylation of 5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydro-2(1*H*)-pyrimidinone 1a. To a suspension of DHPM **1a** (1.3 g, 5 mmol) in 10 mL of dry THF under a blanket of dry N_2, LDA (4 equiv in 37 mL of dry THF) was added dropwise through a cannula at −10 °C. After the addition, the reaction mixture was warmed to room temperature and stirred for an additional 3 h until blood red colored carbanion was generated. To this carbanion, the appropriate electrophile (3.0 equiv), dissolved in 10 mL of dry THF, was added dropwise. Upon addition of the electrophile (Table 2), the red color was quenched in most of the cases, indicating the consumption of the carbanion. Stirring was continued for additional time (Table 2) to complete the reaction, after which a saturated aqueous solution of NH_4Cl was introduced. The reaction was treated with brine and extracted with ethyl acetate (3 × 25 mL). The extracts were dried over anhydrous Na_2SO_4, and the mixture was concentrated under reduced pressure. The products were isolated using flash chromatography using silica gel-G (60−120 mesh) and mixtures of ethyl acetate/hexane as eluent. For preparing samples for microanalytical analysis, crystallization was done using a combination of dry DCM and hexane or methanol and petroleum ether (entries 3−7; Table 2). The characteristic data of the selected compounds are presented below.

Entry 7, Table 1. 5-Ethoxycarbonyl-6-propyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (3b): Creamy white solid; R_f: 0.5 (30% *v*/*v* ethyl acetate/hexane); yield 71%; mp 162−165 °C (DCM); IR (KBr): ν_{max} 3245, 1705, 1665 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.95 (t, 3H, *J* 7.2 Hz), 1.15 (t, 3H, *J* 6.9 Hz), 1.62 (m, 2H), 2.66 (m, 2H), 4.06 (q, 2H, *J* 7.0 Hz), 5.37 (d, 1H, *J* 3 Hz), 6.43 (br, 1H, NH, exchanged with D_2O), 7.25 (m, 5H), 8.68 (br, 1H, NH, exchanged with D_2O); ^{13}C NMR ($CDCl_3$): δ 13.7, 14.0, 21.6, 26.8, 33.3, 55.3, 59.8, 100.8, 126.4, 127.7, 128.5, 143.8, 150.6, 153.8, 165.3; Anal. Required for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72; Found: C, 66.88; H, 6.53; N, 9.65; MS: *m/z* 288 (M^+).

Entry 4, Table 2.5-Ethoxycarbonyl-6-(2-hydroxy-2-methyl-propyl)-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (3i): White solid; R_f: 0.4 (65% ethyl acetate/hexane); yield: 38%; mp 160−162 °C (methanol); IR (KBr): ν_{max} 3480, 3260, 1695, 1635 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.14 (t, 3H, *J* 7.2 Hz), 1.33 (s, 3H,), 1.35 (s, 3H), 2.72 (s, 1H), 3.08 (ABq, 2H, *J* 79.8 Hz, *J* 14.4 Hz), 4.05 (q, 2H, *J* 7.2 Hz), 5.42 (d, 1H, *J* 2.7 Hz), 5.51 (br, 1H, NH, exchanged with D_2O), 7.32 (m, 5H), 8.06 (br, 1H, NH, exchanged with D_2O); ^{13}C NMR ($CDCl_3$): δ 14.0, 29.6, 30.1, 41.3, 56.0, 60.1, 71.8, 73.6, 103.0, 126.6, 127.9, 128.7, 143.7, 147.9, 152.4, 165.9, and 175.8; Anal. Required for $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.97; N, 8.80; Found: C, 64.12; H, 6.58; N, 8.55; MS: *m/z* 318 (M^+).

Entry 4, Table 2. 7,7-Dimethyl-4-phenyl-3,4,7,8-tetrahydro-1*H*-pyrano[4,3-d]pyrimidine-2,5-dione (4a): White solid; R_f: 0.6 (70% ethyl acetate/hexane); yield: 35%; mp 240 °C (methanol); IR (KBr): ν_{max} 3274, 1710, 1664 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 1.22 (s, 3H), 1.37 (s, 3H), 2.47 (ABq, 2H, *J* 64.2 Hz, *J* 17.7 Hz), 5.29 (d, 1H *J* 3.6 Hz) 6.96 (br, 1H, NH, exchanged with D_2O), 7.21 (m, 5H), 9.47 (br, 1H, NH, exchanged with D_2O); ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 25.9, 28.0, 35.6, 53.4, 97.4, 126.0, 127.2, 128.0, 128.1, 143.0, 145.9, 152.0, and 163.5. Anal. Required for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29; Found: C, 65.82; H, 5.90; N, 9.93; MS: *m/z* 272 (M^+).

Entry 5, Table 2. 7-Benzyl-7-methyl-4-phenyl-3,4,7,8-tetrahydro-1*H*-pyrano[4,3-d]pyrimidine-2,5-dione (4c, Major Diastereomer): White solid; R_f: 0.5 (80% ethyl acetate/hexane); yield: 60%; mp 232 °C (ethanol); IR (KBr): ν_{max} 3404, 1693, 1674 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 1.26 (s, 3H), 2.54 (ABq, 2H, *J* 74.7 Hz, *J* 17.4 Hz), 2.98 (m, 2H), 5.19 (d, 1H, *J* 1.8 Hz), 7.25 (m, 10H), 7.61 (br, 1H, NH, exchanged with D_2O), 9.52 (br, 1H, NH, exchanged with D_2O); ^{13}C NMR ($CDCl_3$ + DMSO-d_6): 23.4, 29.3, 32.2, 45.2, 52.2, 78.2, 95.7, 125.0, 125.3, 125.9, 126.6, 126.8, 129.1, 134.2, 145.6, 150.2, and 162.0; Anal. Required for $C_{21}H_{20}N_2O_3$: C, 72.40; H, 5.79; N, 8.04; Found: C, 72.84; H, 5.28; N, 7.83. MS: *m/z* 349 (M^+).

Entry 6, Table 2. 5-Ethoxycarbonyl-6-[2-hydroxy-2-(4-nitro-phenyl)ethyl]-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (3j, Major Diastereomer): Dark yellow crystalline solid; R_f: 0.4 (70% ethyl acetate/hexane); yield: 58%; mp 202 °C (ethanol); IR (KBr): ν_{max} 3577, 3371, 3220, 1697, 1685 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 1.12 (t, 3H, *J* 7.07 Hz), 3.17 (ABX system, 2H, *J* 13.5 Hz, *J* 9.2 Hz, *J* 2.8 Hz), 4.03 (q, 2H, *J* 7.1 Hz), 5.14 (dd, 1H, *J* 9.2 Hz, *J* 2.8 Hz), 5.25 (m, 1H, OH, exchanged with D_2O), 5.35 (d, 1H, *J* 2.4 Hz), 6.40 (br, 1H, NH, exchanged with D_2O), 7.31 (m, 5H), 7.67 (d, 2H, *J* 8.5 Hz), 8.17 (d, 2H, *J* 8.53 Hz), 8.94 (br, 1H, NH, exchanged with D_2O); ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 13.7, 55.1, 59.8, 72.0, 101.3, 123.1, 126.1, 126.2, 126.4, 127.4, 128.3, 143.8, 146.6, 148.1, 152.0, 152.2,

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(13) Eynde, J. J. V.; Audiart, N.; Canonne, V.; Michel, S.; Haverbeke, Y. V.; Kappe, C. O. *Heterocycles* **1997**, *45*, 1967.

(14) The structures of all compounds were supported by 300 MHz ^1H and 75 MHz ^{13}C NMR and mass spectra. All compounds gave a single spot on TLC analysis and correct micro analytical data (see Supporting Information).

165.7; Anal. Required for $C_{21}H_{21}N_3O_6$: C, 61.31; H, 5.14; N, 10.21; Found: C, 62.02; H, 5.51; N, 9.99; MS: *m/z* 411 (M^+).

Entry 8, Table 2. 5-Ethoxycarbonyl-6-propylmercaptomethyl 4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (3l): Creamy white solid; R_f: 0.6 (40% ethyl acetate/hexane); yield: 35%; mp 100−103 °C (DCM); IR (KBr): ν_{max} 3220, 1701, 1639 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.93 (t, 3H, *J* 7.2 Hz), 1.16 (t, 3H, *J* 7.5 Hz), 1.57 (m, 2H), 2.45 (t, 2H, *J* 7.2 Hz), 3.97 (ABq, 2H, *J* 43.4 Hz, *j* 15.4 Hz), 4.07 (q, 2H, *J* 7.0 Hz), 5.42 (d, 1H, *J* 2.4 Hz), 5.72 (br, 1H, NH, exchanged with D_2O), 7.29 (m, 5H), 7.70 (br, 1H, NH, exchanged with D_2O); ^{13}C NMR ($CDCl_3$): δ 13.3, 14.0, 22.6, 30.7, 33.9, 55.9, 60.3, 103.0, 126.5, 128.0, 128.7, 143.3, 145.5, 152.5, and 165.1; Anal. Required for $C_{17}H_{22}N_2O_3S$: C, 61.05; H, 6.63; N, 8.38; Found: C, 59.68; H, 6.17; N, 8.12; MS: *m/z* 334 (M^+).

Entry 12, Table 2. 5-Ethoxycarbonyl-6-trimethylsilanylmethyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (3q): Pale yellow solid; R_f: 0.5 (30% ethyl acetate/hexane); yield: 75%; mp 185 °C (DCM); IR (KBr): ν_{max} 3238, 1699, 1635 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.10 (s, 9H), 1.19 (t, 3H, *J* 7.2 Hz), 2.49 (ABq, 2H, *J* 56.1 Hz, *J* 12.5 Hz), 4.08 (q, 2H, *J* 7.0 Hz), 5.43 (br, 1H, NH, exchanged with D_2O), 5.44 (d, 1H, *J* 2.8 Hz), 6.68 (br, 1H, NH, exchanged with D_2O), 7.34 (m, 5H); ^{13}C NMR ($CDCl_3$): δ −1.1, 14.1, 23.6, 55.4, 59.6, 98.4, 126.5, 126.5, 127.6, 127.8, 128.5, 128.6, 144.2, 150.5, 153.5, and 165.9; Anal. Required for $C_{17}H_{24}N_2O_3Si$: C, 61.41; H, 7.28; N, 8.43; Found: C, 61.12; H, 7.35; N, 8.16; MS: *m/z* 333 (M^+).

Entry 3, Table 3. 5-Ethoxycarbonyl-6-propyl-1,2,3,4-tetrahydropyrimidin-2(1*H*)-one (3t): White crystalline solid; R_f: 0.45 (45% *v*/*v* ethyl acetate/hexane); yield 67%; mp 162−164 °C (DCM); IR (KBr): ν_{max} 3253, 3126, 1704, 1654 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.98 (t, 3H, *J* 7.5 Hz), 1.25 (t, 3H, *J* 7.2 Hz), 1.61 (m, 2H), 2.63 (m, 2H), 4.15 (s, 2H), 4.16 (q, 2H, *J* 7.2 Hz), 5.42 (br, 1H, NH, exchanged with D_2O), 7.33 (br, 1H, NH, exchanged with D_2O); ^{13}C NMR ($CDCl_3$): δ 13.7, 14.2, 21.3, 33.4, 59.9, 96.2, 151.0, 154.2, and 165.4; Anal. Required for $C_{10}H_{16}N_2O_3$: C, 56.59; H, 7.60; N, 13.20 Found: C, 56.36; H, 8.0; N, 13.60; MS: *m/z* 212 (M^+).

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Supporting Information Available: Characterization data and $^1H/^{13}C$ spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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