Iodotrimethylsilane-Accelerated One-Pot Synthesis of 5-Unsubstituted 3,4-Dihydropyrimidin-2(1*H*)-ones: A Novel Procedure for the *Biginelli*-Like Cyclocondensation Reaction at Room Temperature[1])

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A novel *Biginelli*-like cyclocondensation reaction is efficiently catalyzed by iodotrimethylsilane (Me_3SiI) in MeCN. The reaction proceeds at room temperature by a three-component one-pot condensation of ketones with aldehydes and urea to afford 5-unsubstituted 3,4-dihydropyrimidin-2(1*H*)-ones in good yields (*Scheme 1* and *Table*).

Introduction. – The *Biginelli* reaction [1], first described more than a century ago, consists in a three-component, one-pot condensation of β-keto esters with aldehydes and ureas under strongly acidic conditions to afford 3,4-dihydropyrimidinones. Recently, the interest in the synthesis of these derivatives has increased tremendously because they exhibit promising activities as calcium-channel modulators, antihypertensive agents, α-1a receptor antagonists, and neuropeptide Y (NPY) antagonists [2], as an anticancer drug capable of inhibiting Kinesinmotor protein [3], and as an anti-HIV agent in some marine natural products containing the dihydropyrimidinone structure [4]. Thus, *Biginelli*'s reaction for the synthesis of dihydropyrimidinone has received renewed interest, and several improved procedures have recently been reported [5], although some of these methods involve strong *Lewis* acids such as $BF_3 \cdot OEt_2$, protic acids such as HCl, or AcOH, and additives. Generally these reagents require long reaction times and reflux temperatures. In this regard, we recently reported a rapid, high-yielding protocol for the synthesis of dihydropyrimidinones using iodotrimethylsilane [6] at room temperature. Eventhough several reagents are available for the synthesis of *Biginelli*'s compounds, the reports on the synthesis of novel *Biginelli*-like structures is very limited [7][8]. The reported methods result in low yields ($< 0.5\%$) with multiple by-products, either proceed in a multistep fashion *via* the saponification of an ester group at C(5) followed by thermal decarboxylation [9] or require harsh reaction conditions. More recently, $FeCl_3 \cdot 7H_2O$ [10] has been employed for this transformation but the reaction requires long reaction times and reflux conditions.

As an extension to the *Biginelli* reaction [6], we herein disclose a novel, highly efficient *Biginelli*-like cyclocondensation reaction for the preparation of 5-unsubstituted 3,4-disubstituted pyrimidinones in the presence of iodotrimethylsilane (Me_3SiI) in

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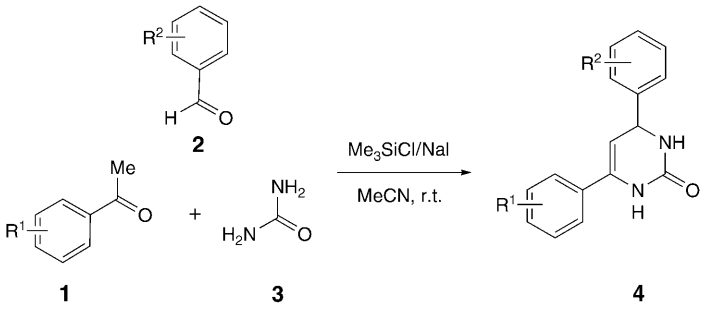
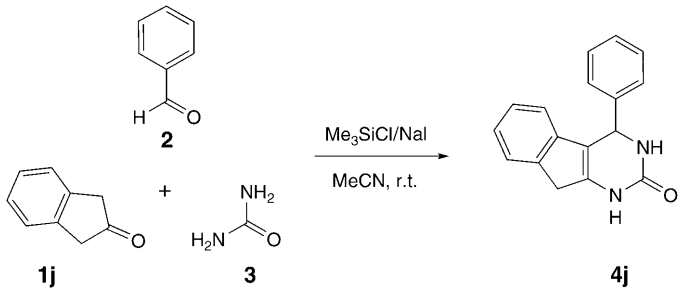
MeCN at room temperature (*Scheme 1*). To the best of our knowledge, there are no earlier reports on one-pot syntheses of *Biginelli*-like structures at room temperature.

Scheme 1



Results and Discussions. – First, we studied the reaction of acetophenone (**1**), benzaldehyde (**2**), and urea (**3**) in the presence of Me_3SiI generated *in situ* from Me_3SiCl and NaI in MeCN. The reaction was found to be very fast, and complete conversion was observed in 1 h at room temperature to afford 5-unsubstituted 3,4-dihydro-4,6-diphenylpyrimidin-2(1*H*)-one (**4a**) in 87% yield (*Table*, *Entry 1*). Encouraged by these results, several substituted acetophenones **1** were examined under similar conditions (*Table*, *Entries 2–7*). To explore the generality of the present protocol, cyclic ketones such as α-tetralone (=3,4-dihydronaphthalen-1(2*H*)-one), indan-2-one (=1,3-dihydro-2*H*-indan-2-one), and chromanone (=2,3-dihydro-1-benzopyran-4-one) were also treated with aldehydes **2** and urea (**3**) to produce novel fused pyrimidinones in good yields (see, *e.g.*, *Table*, *Entries 8–12*; *Scheme 2*). Electron-rich as well as electron-deficient aldehydes proved to be excellent substrates for the cyclocondensation reaction. In all cases, the three component one-pot reaction proceeded smoothly and rapidly to afford the corresponding 5-unsubstituted 3,4-dihydropyrimidin-2(1*H*)-one derivatives in excellent yields.

Scheme 2

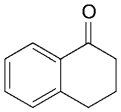
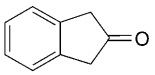
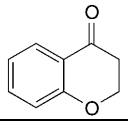


In conclusion, we have developed a simple and general method for the synthesis of 5-unsubstituted 3,4-disubstituted pyrimidin-2(1*H*)-ones using Me_3SiI as an efficient *Lewis* acid catalyst. The method offers several advantages including short reaction

Table. *Iodotrimethylsilane-Mediated Three-Component* Biginelli-*Like Cyclocondensation Reaction*[a])

Entry	Ketone **1**	Aldehyde **2**	Time [min]	Product **4**	
				yield [%][b])	m.p. [°]
1	PhC(=O)Me	PhCHO	45	87 (**4a**)	218–219
2	4-Me–C_6H_4–C(=O)Me	PhCHO	50	84 (**4b**)	174–175
3	4-Cl–C_6H_4–C(=O)Me	PhCHO	60	81 (**4c**)	223–224
4	4-MeO–C_6H_4–C(=O)Me	PhCHO	55	85 (**4d**)	152–153
5	4-Me–C_6H_4–C(=O)Me	4-NO_2–C_6H_4–CHO	55	80 (**4e**)	214–215
6	4-MeO–C_6H_4–C(=O)Me	4-NO_2–C_6H_4–CHO	60	82 (**4f**)	232–233
7	4-OH–C_6H_4–C(=O)Me	PhCHO	60	82 (**4g**)	204–206
8	α-tetralone[c])	PhCHO	50	88 (**4h**)	260–262
9	α-tetralone[c])	4-F–C_6H_4–CHO	55	86 (**4i**)	220–222
10	indan-2-one[d])	PhCHO	50	75 (**4j**)	gummy material
11	indan-2-one[d])	4-F–C_6H_4–CHO	50	77 (**4k**)	gummy material
12	chromanone[e])	PhCHO	50	88 (**4l**)	272–274

[a]) Reaction run at room temperature. [b]) Yields of isolated products.

[c])  [d])  [e]) 

times, high yields, and simple product-isolation procedures, which makes it a useful addition to existing methods.

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Experimental Part

*One-pot Synthesis of 5-Unsubstituted 3,4-Dihydropyrimidin-2(1*H*)-ones. Procedure A*: Me_3SiCl (8 mmol) was added to a stirred mixture of acetophenone (**1**; 10 mmol), benzaldehyde (**2**, R^2 = H; 10 mmol), urea (**3**; 15 mmol), and NaI (8 mmol) in MeCN (5 ml) at r.t. After the reaction was complete (TLC monitoring), the mixture was poured into crushed ice, and the separated solid product was filtered and recrystallized from EtOH to afford pure, **4a** in 87% yield.

Similarly, compounds **4b**–**i** and **4l** were prepared.

Procedure B: Me_3SiCl (8 mmol) was added to a stirred mixture of indan-2-one (= 1,3-dihydro-2*H*-inden-2-one; **1j**; 10 mmol), benzaldehyde (**2**, R^2 = H) or 4-fluorobenzaldehyde (**2**, R^2 = 4-F; 10 mmol), urea (**3**; 15 mmol), and NaI (8 mmol) in MeCN (5 ml) at r.t. After the reaction was complete (TLC monitoring), the mixture was poured into crushed ice, extracted with AcOEt, washed with sodium thiosulfate soln., dried (Na_2SO_4), and evaporated and the residue purified by column chromatography (hexane/AcOEt): **4j** or **4k** as gummy materials.

*Data of 1,3,4,9-Tetrahydro-2*H*-indeno[1,2-*d*]pyrimidin-2-one* (**4j**): Gummy material. IR (KBr): 3228, 3231, 2940, 1667, 1455, 1254, 772. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.39 (*AB*(‘*q*’), *J* = 22.0, 2 H); 5.50 (*s*, 1 H); 6.19 (br. *s*, NH); 6.50 (*d*, *J* = 7.3, 1 H); 6.88 (*t*, *J* = 8.1, 1 H); 6.96 (*t*, *J* = 7.3, 1 H); 7.15–7.32 (*m*, 4 H); 7.39 (*d*, *J* = 7.3, 2 H); 9.56 (br. *s*, NH). ^{13}C-NMR (75 MHz, $CDCl_3$): 35.23; 56.86; 111.55; 117.51; 122.80; 123.41; 126.54; 127.44; 128.36; 128.88; 137.94; 139.91; 141.84; 141.94; 154.06. FAB-MS: 263 (*M* + H).

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