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Expedient Synthesis of 5-Unsubstituted 3,4-Dihydropyrimidin-2(1*H*)-ones.

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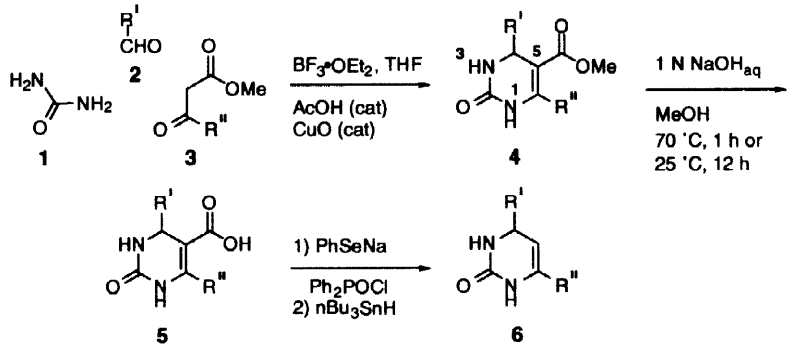
Abstract: A new procedure for the synthesis of 5-unsubstituted 3,4-dihydropyrimidin-2(1*H*)-ones is described. Two plausible mechanisms for the key chemical transformation are advanced.

Keywords: Pyrimidinones; Decarboxylation; Biginelli reaction.

The 3,4-dihydropyrimidin-2(1*H*)-one ring system is contained within a number of pharmacologically active agents, for example, calcium channel blockers.[1] This heterocycle can be assembled via the classical Biginelli condensation reaction employing urea (**1**), an aldehyde (**2**), and an acetoacetate derivative (**3**).[2] Recent engineering to improve reaction conditions now make 3,4-dihydropyrimidinones **4** available in excellent yields (Scheme 1).[3]

Our own interest in 3,4-dihydropyrimidinones stemmed from our need to procure less accessible 5-unsubstituted analogs such as **6**. However, literature methods for the syntheses of these compounds result in low yields (<0.5%), require multistep transformations,[4] or necessitate the use of harsh reaction conditions.[5] To bypass these difficulties, we envisioned a process beginning with the hydrolysis of the readily obtained esters **4** to give the corresponding acids **5**, followed by formation of acyl selenides and subsequent radical induced decarbonylation.[6] In the event, hydrolysis of ester **4h** to carboxylic acid **5h** proceeded without incident. Unfortunately, the formation of the acyl selenide and the attempted decarbonylation reaction led to uncharacterizable complex mixtures.

Scheme 1.



In a previous report, an account was given wherein 5-pyrimidinone carboxylic acids analogous to **5** were decarboxylated by heating a neat melt to the sublimation/melting point temperature (220 °C) of the corresponding

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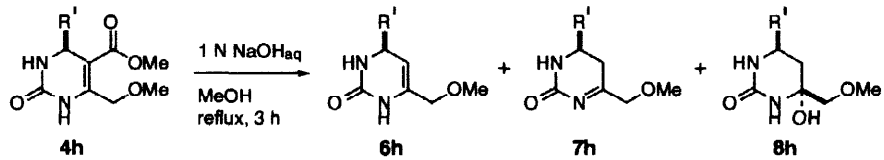
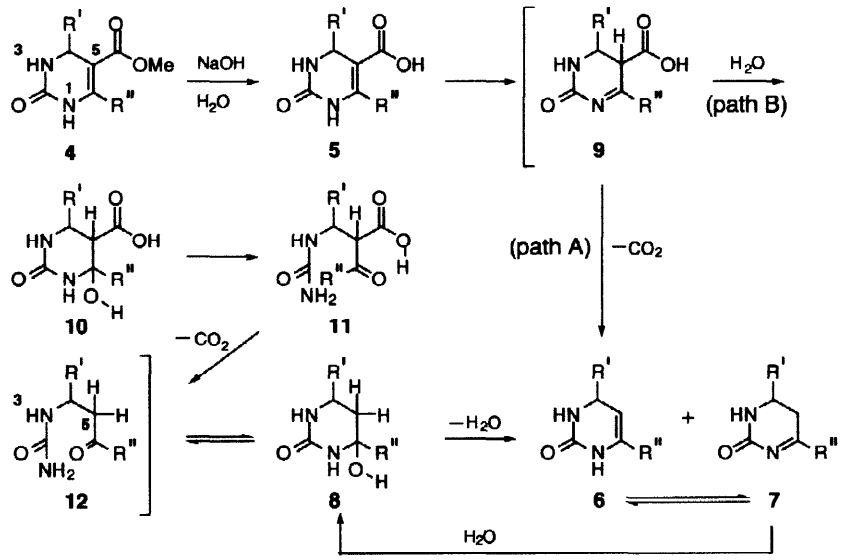
acid.[5] To determine if this methodology would be applicable to our substrates, a thermogravimetric analysis (TGA) of carboxylic acid **5g** was carried out. The TGA of **5g** showed a weight loss of 15.4% at 240 °C, indicative of decarboxylation (calculated 14.8%), and complete degradation by 300 °C. This rapid decomposition of **6g** above 240 °C raised concern about the generality of this thermal decarboxylation as it related to our target structures. However, during the exploratory and optimization phase of this work, we observed that decarboxylation of acid **5h** could be induced at significantly lower temperatures in alkaline solutions. It is this discovery which forms the basis of our new synthetic procedure. Thus, after ester **4h** was refluxed in methanol with 1.0 N aqueous sodium hydroxide, products **6h**, **7h**, and **8h** were isolated (Scheme 2). The overall yields of **6** and **7** could be augmented by recycling **8** (i.e. resubjecting **8** to the hydrolysis conditions or heating **8** in 3N hydrochloric acid solution).

Scheme 2.



We rationalize the overall transformation to proceed via two potentially competing mechanistic pathways (A & B) as outlined in Scheme 3. Intermediate **9** is common to both pathways and according to route A suffers decarboxylation to provide **6** directly. Base catalyzed isomerization of **6** provides **7** which after hydration affords **8**.

Scheme 3.

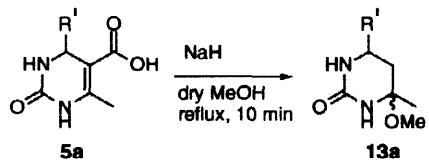


Alternatively, the addition of water to the imine **9** generates the tetrahedral intermediate **10** (path B), which after collapse produces the β-keto carboxylic acid **11**. This intermediate is then primed to undergo decarboxylation in the usual manner to produce the γ-keto urea, **12**. Intramolecular condensation of ketone **12** affords product **8** which subsequently leads to compounds **6** and **7**.

Both proposed mechanistic pathways are consistent with the outcome of the following experiments: (1) treatment of ester **4f** with $NaOD/D_2O$ in refluxing CD_3OD produced 5-deutero-**6f**, 5,5-dideutero-**7f**, and the 5,5-dideutero-**8f**. (2) When the N-1 position of **5e** bears a methyl group, no reaction was observed with sodium hydroxide in refluxing methanol. The latter experiment suggests that the isomerization of **5** to **9** is a prerequisite for decarboxylation. (3) Treatment of ester **4a** with 1.0 N aqueous sodium hydroxide in refluxing methanol for 1 h produced exclusively the corresponding carboxylic acid **5a**. When **5a** was redissolved in methanol and subjected to identical reaction conditions, **6a** was the sole isolated product (51% overall from **4a**) indicating that the reaction proceeds through the intermediacy of carboxylic acid **5**. In a control experiment, no reaction was observed when a methanolic solution of carboxylic acid **5g** was refluxed for 16 h. (4) Refluxing compound **8f** in methanol with 1.0 N aqueous sodium hydroxide produced a 1:1 mixture of products **6f** and **7f** in 30% yield, as well as unreacted starting material **8f**.

We tentatively favor reaction path A based on the observation that carboxylic acid **5a** produced **13a** in >60% yield when treated with three equivalents of sodium hydride in refluxing methanol; unreacted starting material **5a** was the only other isolable product (Scheme 4). These reaction conditions preclude the formation of intermediate **11**.

Scheme 4.



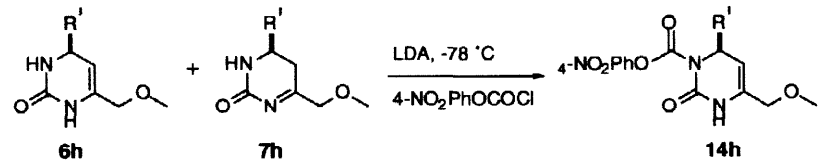
5a **13a**

Importantly, when **5a** was reacted with sodium hydride under similar conditions in the absence of a proton source (dioxane) no reaction was observed. In spite of this result, we cannot exclude for the present that reaction path B may be operative under aqueous conditions.

In Table 1 are collated some additional examples which speak to the scope of the synthetic procedure. In general, reactions were conducted with five equivalents of aqueous sodium hydroxide in refluxing dioxane or methanol until the reaction was judged to be complete (2-12 hours). The use of lithium, sodium, or potassium hydroxide produced similar results. In one instance, the substitution of solid sodium hydroxide for 1.0 N aqueous sodium hydroxide in methanol led to a higher product yield (cf **4h**, Table 1).[7] Occasionally, inseparable mixtures with varying ratios of **6** and **7** were obtained.[8]

The use of mixtures of **6** and **7** in synthesis produces products derived primarily from regioisomer **6**. For example, treatment of a 1:1 mixture of **6h** and **7h** with LDA followed by the addition of 4-nitrophenyl chloroformate resulted predominantly in acylation product **14h** (78% yield).

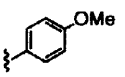
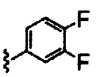
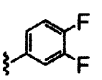
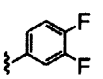
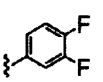
Scheme 5.



6h **7h** **14h**

In conclusion, our new procedure for the synthesis of 5-unsubstituted 3,4-dihydropyrimidin-2(1*H*)-ones represents a significant improvement over existing methods documented in the literature and makes this ring system accessible for inclusion into pharmacologically important agents.

Table 1.

Entry	R'	Conditions[a]	R''	% Yield 6/7	% Yield 8
a	(±) 	A (MeOH)	Me	51 (**6a**) <5% of **7a**	5
b	(±) 	A (MeOH)	tBu	85	
c	(±) 	A (MeOH)	CF_3		64
d	(±) 	A (MeOH)	Me	39 (2.8:1)	40
e	(±) 	A (MeOH) A (dioxane)	Me	43 (1.6:1) 36 (1.6:1)	46 41
f	(±) 	A	CH_2OMe	42 (1.6:1)	27
g	(-) 	A	CH_2OMe	50	
h	(+) 	A B	CH_2OMe	54 71	12
i	(±) 	A	CH_2OMe	31	

[a] Refluxing dioxane or MeOH; A = 1.0 N aqueous NaOH; B = solid NaOH.

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7. No attempt was made to rigorously exclude moisture.
8. It is advisable that reaction products **6** and **7** not be stored at room temperature for a prolonged period of time. In some instances, decomposition has been observed.