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One-pot two step synthesis of 5-cyano-dihydropyrimidinones using polyphosphate ester

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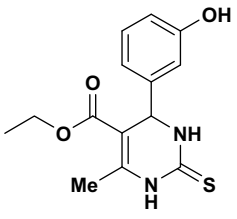
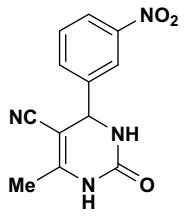
Abstract

A combination of a modified Biginelli reaction and a polyphosphate ester (PPE)-promoted dehydration reaction provides 5-cyano-dihydropyrimidinones in good to excellent overall yields.

Substituted dihydropyrimidinones (DHPMs) have been shown to serve as scaffolds for a variety of pharmacologically active molecules, including Ca^{2+} channel openers (Verapamil) plus the cytotoxic agent monastrol (**1**) and related analogs.[1,2] Efforts to identify novel cytotoxic agents, through a high throughput screen of the Bristol-Myers Squibb compound collection, led to compound **2**. This compound was later found to induce a phenotype in cells similar to the Eg5 inhibitor Monastrol.[3] The original synthesis of **2** described by Atwal et al.[4–6] involved a four step process utilizing a Knoevenagel condensation affording **2** in a 10% overall yield. To explore the SAR of this potential series of cytotoxic agents, a general and high yielding route was required. Herein, we describe the synthesis of various 5-cyano-DHPMs, in good to excellent overall yields, using a convergent, one-pot procedure.



1



2

The synthetic methodology used to generate DHPMs has been well documented and has typically involved variations of the original Biginelli reaction.[7–10] More recent reports by Kappe and Falsone[11,12] describe the synthesis of these compounds via a one-pot condensation utilizing PPE[12] to generate 5-carboxylate DHPMs, however, 5-cyano-dihydropyrimidinones **2** were not exemplified.[13]

Reports have shown that polyphosphate ester (PPE), when used in an aprotic solvent such as THF, can serve as a desiccant,[12] and simple benzamides can be dehydrated to their corresponding benzonitriles using this reagent.[14] Our plan was to investigate whether PPE could serve as a suitable reagent for forming 5-carboxamide-DHPMs. In principle, PPE should be a strong enough desiccant to dehydrate the carboxamide to give the desired nitrile, while being mild enough to use with functionally sensitive aldehydes. After extensive optimization, we found that the two steps could be carried out in a general and efficient one-pot process to afford a variety of 5-cyano-DHPMs.[15] As outlined in Table 1, addition of 0.3 equiv of PPE to a reaction mixture containing a 1:1:1.5 ratio of aldehyde/acetoacetamide/urea in THF, at 75 °C for 1 h, was optimal for the formation of 5-carboxamide-DHPMs. Subsequent treatment of that reaction mixture with an additional 2.3 equiv of PPE, followed by heating at 85 °C for 1–3 h, afforded 5-cyano-DHPMs in yields typically exceeding 70%.

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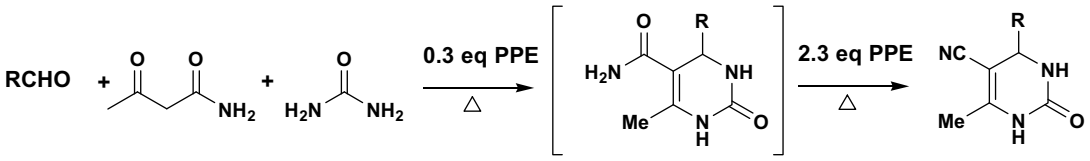
Table 1
A general two step, one-pot Biginelli reaction to generate 5-cyano-4-substituted dihydropyrimidinones



Entry	R	Yield[a,b,c] (%)
1	3-NO_2-Phenyl	94
2	3-Cl-Phenyl	78
3	3-CF_3-Phenyl	70
4	2-Thienyl	72
5	5-NO_2-2-Thienyl	91
6	4-Br-2-Thienyl	68
7	4-Ph-2-Thienyl	91
8	3-Thienyl	51
9	5-*meta*-Cl-Phenyl-2-furanyl	38
10	5-*meta*-Cl-Phenyl-2-EtO_2C-2-furanyl	27
11	6-Me-2-Pyridyl	70
12	*t*-Butyl	34
13	*n*-Butyl	97
14	Isopropyl	77
15	Methyl-benzyl ether	45
16	1-Methyl-1-pentyl	4

[a] See Ref. 14 for general procedure.
[b] Isolated yields after purification by SiO_2 gel chromatography.
[c] Characterized by ^{1}H NMR, elemental analysis, and LC/MS.

A variety of substituted aromatic, aliphatic, and heteroaromatic aldehydes, with either electron-donating or electron-withdrawing groups, provided favorable results in this reaction. For example, 5-cyano-dihydropyrimidinones generated from 3-nitro and 4-phenyl-2-thienyl benzaldehyde afforded the corresponding products in greater than 90% yield. Aliphatic aldehydes were equally amenable to these conditions with *n*-butyraldehyde providing the 5-cyano-dihydropyrimidinone in 97% yield. Quaternary substitution at the 4-position of the DHPM could also be achieved with ketones using this methodology, albeit in significantly lower yields (compounds 15 and 16).

In summary, a new method for the preparation of substituted 5-cyano-DHPMs was discovered that utilizes a multicomponent coupling reaction promoted by PPE, followed by a rapid and high yielding PPE-mediated dehydration to afford the corresponding carbonitrile. The use of PPE was well tolerated with a range of aldehydes and ketones. In addition, this methodology is cost effective and amenable to large-scale synthesis.

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13. Kappe, C. O.; Roschger, P. *J. Heterocycl. Chem.* **1989**, *26*, 55–64.
14. Dixon, L. A. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L., Ed.; Wiley: Chichester, 1995; Vol. 6, pp 4166–4169. **Caution: PPE is stable refrigerated but decomposition occurs above 150 °C.**
15. *Typical procedure for the synthesis of 5-cyano-dihydropyrimidinones*: A mixture of 3-nitrobenzaldehyde (5.0 g, 33 mmol, 1.0 equiv), acetoacetamide (3.3 g, 33 mmol, 1.0 equiv), urea (3.0 g, 50 mmol, 1.5 equiv), and polyphosphate ester (4.2 g, 10 mmol, 0.3 equiv) in THF (35 mL) was heated in a sealed tube for 45 min at 75 °C. This mixture was cooled to room temperature, additional polyphosphate ester (33 g, 76 mmol, 2.3 equiv) was added, and the heating was resumed at 85 °C for 3 h. The reaction mixture was cooled to room temperature and poured onto ice (800 g). The resulting precipitate was collected by vacuum filtration and the solid washed with water followed by a small amount of methanol and diethyl ether. The solid was then dried under vacuum to yield 6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile as a light yellow solid (8.0 g; 94%) that was used without further purification: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.70 (s, 1H), 8.21–8.23 (m, 1H), 8.16–8.17 (m, 1H), 7.98–8.00 (m, 1H), 7.80–7.81 (m, 1H), 7.74 (t, 1H, $J = 7.9$ Hz), 5.38 (s, 1H), 2.02 (s, 3H). Anal. Calcd for $C_{12}H_{10}N_4O_3$: C, 55.81; H, 3.90; N, 21.69. Found: C, 55.79; H, 3.92; N, 21.52. MS: $(M-H)^-$ 257.