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Carbon–carbon bond construction at the 2-position of polysubstituted pyrimidinones

Dawei Zhang,* Kelvin Sham, Guo-Qiang Cao, Randall Hungate and Celia Dominguez

Department of Small Molecule Drug Discovery, AMGEN Inc., One AMGEN Center Drive, Thousand Oaks, CA 91320, USA

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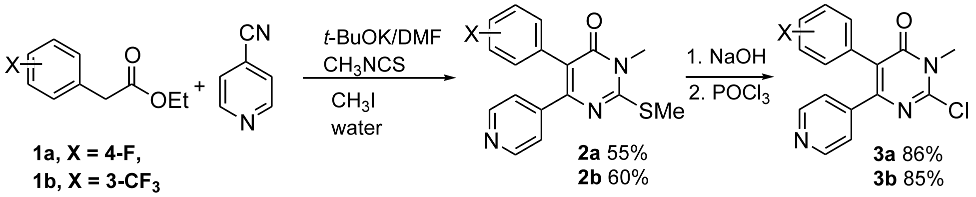
Abstract—A novel synthetic method to introduce a carbon–carbon bond at the 2-position of pyrimidinones via nucleophilic addition of Grignard reagents to 2-cyano pyrimidinones at ambient conditions is disclosed. This unique approach leads to the preparation of such biologically important molecules as polysubstituted pyrimidinones in good to excellent yields. © 2002 Elsevier Science Ltd. All rights reserved.

During the course of a recent investigation, we became interested in the introduction of a carbon–carbon bond at the 2-position of substituted pyrimidinones. It has been previously reported in the literature that the carbon–carbon bond can be built into 2-pyrimidines, a similar heteroaromatic system to our targeted pyrimidinones, by palladium catalyzed Stille,[1] Suzuki[2–4] or Heck[5,6] reaction derived from 2-chloropyrimidines. Therefore, we first examined the cross-coupling reaction of 2-chloropyrimidinones under these reported coupling conditions for pyrimidines. As a readily available starting material, 2-chloropyrimidinones have been prepared in our lab[7] in good overall yield and sub-kilogram scale outlined in Scheme 1.

2-Chloropyrimidinone **3b** was cross-coupled successfully with piperidine triflate[8] **4** to give compound **5** in moderate to good yields under the reported coupling conditions for 2-chloropyrimidines (Scheme 2).[9] The double bond in the piperidine ring was reduced followed by removal of the Boc group to give compound **6**.

Alternatively, a carbon–carbon bond was introduced via palladium and CuI co-catalyzed reaction of 2-chloropyrimidinone **3a** with an alkyne to afford compound **7** in moderate yield (Scheme 3). The triple bond was cleanly reduced under normal hydrogenation conditions.

The limitation of the transition metal catalyzed reaction discussed above is the difficulty of directly displacing the chloride of the 2-chloropyrimidinones with an alkyl group. Efforts to introduce the alkyl group under relatively mild conditions were explored. Initially, nucleophiles such as methyl magnesium bromide, phenethyl magnesium chloride, phenyl magnesium bromide, methyl lithium, and phenyl lithium at or below room temperature failed to react with compound **2** or **3** to generate the desired corresponding carbon analogs. As in the case of chloropyrimidines, compounds **2** and **3** react readily with 'soft' nucleophiles such as amines,[7] but their reactivity towards organo lithium reagents or Grignard reagents is somewhat sluggish. The chloride of starting material **3** was gradually hydrolyzed to hydroxyl group under elevated temperature and prolonged reaction time. However, once the chloropyrimidinones **3** were converted to the cyanopyrimidinones **8** (Scheme 4), as reported for the synthesis of 2-cyanopyrimidine,[10] compounds **9**–**13** were prepared cleanly in



Scheme 1. Preparation of 2-chloropyrimidinones.

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* Corresponding author. Tel: (805) 447-4743; fax: (805) 480-1337; e-mail: daweiz@amgen.com

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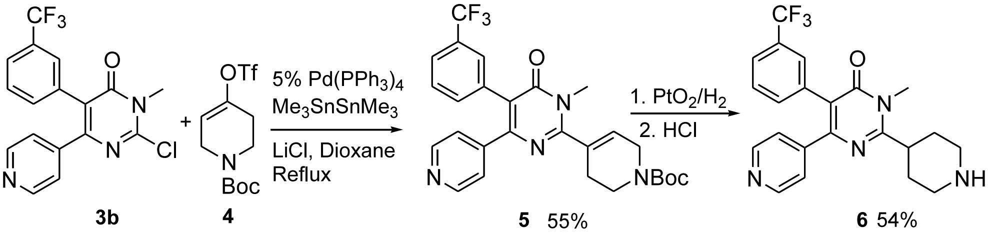
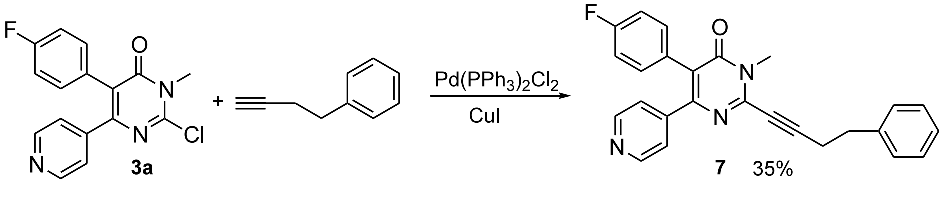


Scheme 2. Cross-coupling reaction employing 2-chloropyrimidinone.



Scheme 3. Construction of a carbon–carbon bond between 2-chloropyrimidinone and an alkyne.

good to excellent yields by reaction of Grignard reagents with compounds **8** at 0°C for 30 min. (Scheme 4 and Table 1). No ketones were formed via direct attack of Grignard reagents on the cyano group itself. This result is in contrast to previously reported results in the literature that Grignard reagents only add to the cyano carbon of cyanopyridines[11] or cyanopyrimidines.[12]

Yields of compounds **9**–**13** are reported in Table 1.

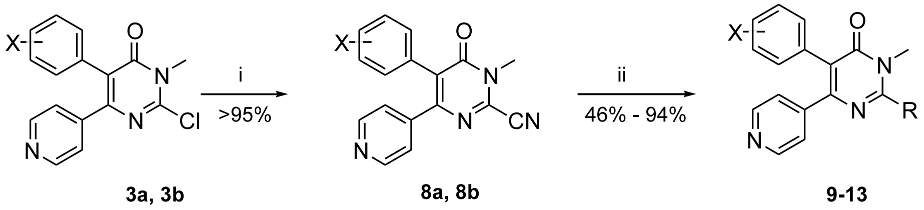
In summary, a novel synthetic method for the preparation of polysubstituted pyrimidinones has been reported. In contrast to the low reactivity of 2-thiolmethylpyrimidinones **2** or 2-chloropyrimidinones **3** toward Grignard reagents or organo lithium reagents, 2-cyanopyrimidinones **8** undergo facile reaction with various Grignard reagents to directly afford 2-carbon substituted pyrimidinones **9**–**13** in good isolated yields. The biological evaluation of these compounds as well as the application of this methodology to different substrates is currently underway.

Preparation of compound **5**: To an oven-dried 50 mL round bottom flask under nitrogen were added triflate **4** (466 mg, 1.40 mmol, 1.00 equiv.), chloride **3b** (514 mg, 1.40 mmol, 1.00 equiv.), tetrakis(triphenylphosphine)palladium (0) (81 mg, 0.07 mmol, 0.05 equiv.), and anhydrous lithium chloride (180 mg, 4.20 mmol, 3.00 equiv.). Hexamethylditin (460 mg, 1.40 mmol, 1.00 equiv.) was next added followed by anhydrous dioxane (10 mL) and the mixture was heated to reflux for 18 h under nitrogen. The cooled mixture was then poured into saturated aqueous potassium fluoride solution and vigorously stirred for 2 h. The two-phase mixture was filtered and the organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated in vacuum. Purification by flash column chromatography (1–3% MeOH–$CHCl_3$) afforded **5** (394 mg, 55%) as an off-white foam: ^1H NMR ($CDCl_3$, 400 MHz) δ 8.44 (d, $J=5.60$ Hz, 2H), 7.43 (m, 2H), 7.32 (m, 2H), 7.08 (d, $J=5.69$ Hz, 2H), 6.11 (brs, 1H), 4.11 (m, 2H), 3.68 (m, 2H), 3.58 (s, 3H), 2.54 (m, 2H), 1.45 (s, 9H). MS (ES+): 513.3 $(M+H)^+$; (ES−): 511.5 $(M-H)^-$.

Preparation of compound **13**: To a solution of compound **8b** (149 mg, 0.42 mmol, 1.00 equiv.) in THF (15

Table 1.

Compound	X	R	Yield (isolated) (%)
9	4-F	-Me	94
10	4-F	$-CH_2CH_2Ph$	72
11	4-F	$-CH_2CN$	46
12	$3-CF_3$	-Ph	58
13	$3-CF_3$	$-CH_2CH_2Ph$	78



Scheme 4. Reaction of Grignard reagents with 2-cyanopyrimidinones. *Reagents and conditions*: (i) NaCN (1.00 equiv.), triethylenediamine (2.00 equiv.), NMP/water (20/1), rt, 1 h; (ii) RMgX, THF, 0°C, 30 min for compounds **9**, **10**, **12**, and **13**; *n*-BuLi/CH_3CN, THF, 0°C, 30 min for compound **11**.

mL) at 0°C was added phenethyl magnesium bromide (1.0 M in THF, 0.63 mL, 0.63 mmol, 1.50 equiv.). After 30 min, the reaction was quenched with water (15 mL), and extracted with EtOAc (3×50 mL). The organic layer was washed again with water (3×15 mL), dried over $MgSO_4$, filtered and concentrated into yellow oil. Purification by preparative TLC plate (1:1; hexane:EtOAc) afforded compound **13** as a light yellow solid (142 mg, 78%): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.50 (d, $J=6.0$ Hz, 2H), 7.55 (d, $J=8.0$ Hz, 1H), 7.49 (s, 1H), 7.43–7.26 (m, 7 H), 7.15 (d, $J_=6.0$ Hz, 2H), 3.63 (s, 3H), 3.25–3.14 (m, 4H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 162.24, 160.17, 155.46, 149.68, 145.43, 140.12, 134.16, 131.20, 130.88, 130.56, 130.23, 128.81, 128.76, 128.46, 127.69, 126.67, 125.23, 124.80, 123.89, 122.52, 121.75, 119.81, 32.25, 30.96, 29.72 ppm; MS (ES+): 436 $(M+H)^+$; (ES−): 434 $(M-H)^-$. Anal. ($C_{25}H_{20}F_3N_3O\cdot 0.5H_2O$) C, H, N.

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