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Synthesis of polysubstituted 3*H*-pyrimidin-4-ones from cyanoacetamides under Vilsmeier conditions

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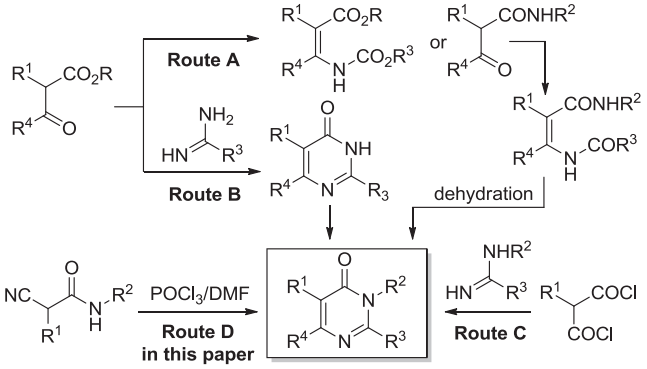
ABSTRACT

A facile and efficient approach to a variety of 6-chloro-3,5-disubstituted 3*H*-pyrimidin-4-ones **2**/**6** from the readily available cyanoacetamides **1**/**5** under Vilsmeier conditions was developed, in which the Vilsmeier reagent plays multiple roles and the possible mechanism is discussed.

1. Introduction

Functionalized 3*H*-pyrimidin-4-ones and their benzo- and heterofused analogues are pharmacophores present in many biologically active compounds.[1] Examples include angiotensin II receptor antagonists,[1a] PPAR agonists,[1b] the atypical antipsychotic drug risperidone,[1c] compounds with anticancer activity[1d] and tyrosine kinase inhibitors.[1e] In the synthesis of 3*H*-pyrimidin-4-ones, most approaches have focused on the 3-substituted 3*H*-pyrimidin-4-ones by means of dehydration of an enediamide (Scheme 1, route A),[2] the Pinner condensation of β-keto esters with non-*N*-substituted amidines (Scheme 1, route B)[3] and condensation of *N*-substituted amidines with malonyl dichlorides (Scheme 1, route C).[4] However, the methods mentioned above suffer from more or less time-consuming procedures, low yields, long reaction time, competing reactions, large excess of reactants or limited scope of substrates.[1–4] Herein, we describe a new efficient approach to a broad range of 6-chloro-3,5-disubstituted 3*H*-pyrimidin-4-ones through the reaction of the readily available cyanoacetamides under Vilsmeier conditions in which Vilsmeier reagent ($POCl_3$/DMF) plays multiple roles in the tandem process (Scheme 1, route D).



Scheme 1. Synthetic methods for pyrimidinones.

During the course of our studies on transformations from easily accessible acetoacetanilide derivatives[5,6] to relatively complex products, very recently, several new routes have been developed for the synthesis of furo/pyrano quinolines[5a,b] and quinoline derivatives.[5c,d] Also with acetoacetanilide derivatives as substrates, we achieved the synthesis of halogenated pyridine-2(1*H*)-one under Vilsmeier reaction conditions.[5e] As part of our continuing interest in the synthetic potential of substituted (functionalized) acetanilides under Vilsmeier conditions,[5e,6b,7] the reactions of a variety of cyanoacetamides **1** and **5** were examined and the significantly different results from the previous investigations[5e,6b,7] were obtained and presented in this article.

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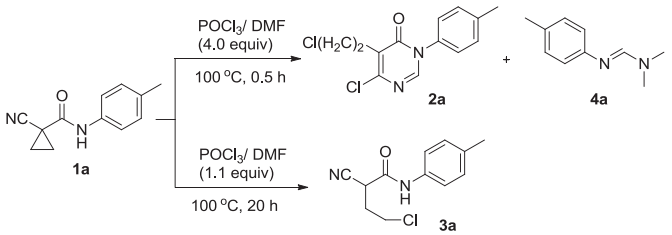
Based on the ring expansion of activated cyclopropanes,[5c–e] the substrate, 1-cyano-*N*-*p*-tolylcyclopropanecarboxamide **1a** was synthesized from easily available 2-cyano-*N*-*p*-tolylacetamide and 1,2-dibromoethane in high yield (94%) according to the known procedure[5a,8] and taken as a model substrate to optimize the reaction conditions, including reaction temperature and the feed ratio of **1a** and Vilsmeier reagent. It was found that, upon treatment of **1a** (2.0 mmol) with $POCl_3$ (1.1 equiv) in DMF (1 mL) at 100 °C for 20 h, 4-chloro-2-cyano-*N*-*p*-tolylbutanamide **3a** was obtained in 95% yield (Scheme 2). Compound **3a** could be further converted into 6-chloro-5-(2-chloroethyl)-3-*p*-tolylpyrimidin-4(3*H*)-one **2a** in 40% yield when 4 equiv of $POCl_3$ were used at 100 °C for 0.5 h. After repeated experiments, the optimal conditions for the formation of 3*H*-pyrimidin-4-one **2a** were obtained. Therefore, treatment of **1a** with 4 equiv of $POCl_3$ in DMF at 100 °C for 0.5 h led to **2a** in 66% of yield together with 25% yield of *N*,*N*-dimethyl-*N*′-*p*-tolylformimidamide **4a** (Scheme 2). The structure of **2a** was further confirmed by the X-ray single crystal analysis[9] (Fig. 1).



Scheme 2. The reactions of **1a** under different conditions.

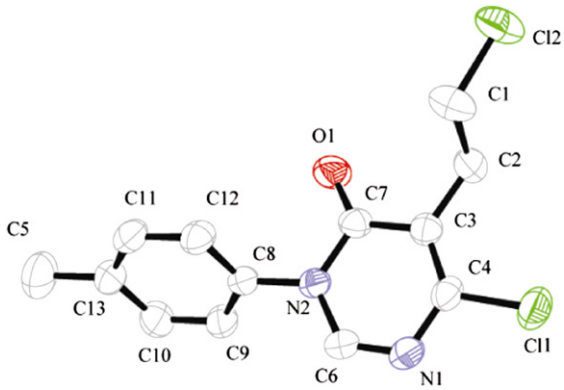
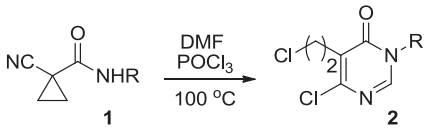


Fig. 1. ORTEP drawing of **2a**.

Having established the optimal conditions for the synthesis of 3*H*-pyrimidin-4-one **2a**, the scope with respect to the amide motif was then examined. Under the optimized conditions (Scheme 2), it was observed that the selected precursors, 1-cyano-*N*-substituent-cyclopropanecarboxamides **1b**–**e**, bearing either electron-donating or electron-withdrawing group(s) on the aryl ring, efficiently gave the corresponding dichloro products **2b**–**e** in good yields (Table 1, entries 2–5). In addition, the above cyclization reaction was proven effective for *N*-Bz substituted substrates. Under the optimized conditions, product **2f** was produced in 61% yield from the reaction of 1-cyano-*N*-alkylcyclopropanecarboxamide **1f** with $POCl_3$/DMF (Table 1, entry 6). However, a complicated mixture was afforded by the reaction of *N*-unsubstituted 1-cyanocyclopropanecarboxamide under the identical conditions.

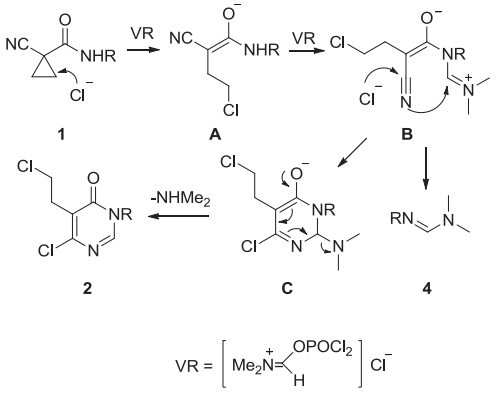
On the basis of the above results and our previously reports,[5e,6b,7] a plausible mechanism for the formation of 6-chloro-5-(2-chloroethyl)-3-substituted pyrimidin-4(3*H*)-ones **2a**–**f** is presented and depicted in Scheme 3. The transformation commences from the ring opening of **1** mediated by Vilsmeier reagent, to generate intermediate **A**.[10] Subsequent Vilsmeier–Haack reactions at the amide moiety of **A** yields the iminium intermediate **B**. Then the nucleophilic nitrogen of nitrile grouping attacks on the iminium intermediate **B**[7d,11] and followed cyano carbon captures the chlorine ion to give the ring closing intermediate **C**. Finally, pyrimidin-4(3*H*)-ones **2** is produced by the elimination of a dimethylamine.[5e,6b,7d,e] On the other hand, the cleavage of the C–N bond of the amide moiety of iminium intermediate **B** lead to byproducts **4** (Scheme 3 and 2).[10,12]

Table 1
Synthesis of 3*H*-pyrimidin-4-ones **2a**–**f**[a]



Entry	Substrate		Time (h)	Product	Yield[b] (%)
	1	R			
1	**1a**	4-MeC_6H_4	0.5	**2a**	66
2	**1b**	C_6H_5	3.0	**2b**	53
3	**1c**	4-ClC_6H_4	1.0	**2c**	57
4	**1d**	4-$COOEtC_6H_4$	1.7	**2d**	54
5	**1e**	3-MeC_6H_4	0.5	**2e**	50
6	**1f**	$CH_2C_6H_5$	1.2	**2f**	50

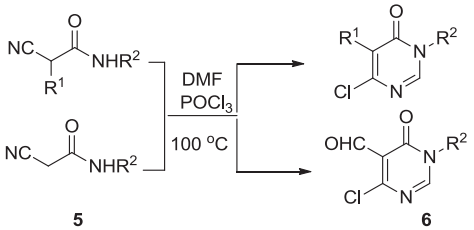
[a] Reagents and conditions: 1 (2.0 mmol), $POCl_3$(8.0 mmol)/DMF, 100 °C.
[b] Isolated yields.



Scheme 3. The proposed mechanism for the formation of **2**.

According to the proposed mechanism (Scheme 3), it is clear that the Vilsmeier reagent plays multiple roles in the reaction process and thus helps the introduction of two chloro substituents on the 6-position of the pyrimidine ring and the side chain, respectively. Encouraged by these results and the transformation **3a** to **2a** (Scheme 2), the versatility of this facile approach to 3*H*-pyrimidin-4-ones was further evaluated by performing the reactions of cyanoacetamides with a variety of substitutes at α-position instead of a cyclopropane subunit under Vilsmeier conditions. All the typical reactions, for example, **5a**–**d**,[8] proceeded smoothly to give the corresponding substituted 3*H*-pyrimidin-4-ones **6a**–**d** in good yields (Table 2, entries 1–4) under the optimized conditions. The reactive allyl functional group (Table 2, entries 3 and 4) was found intact under the reaction conditions. Much to our delight, cyanoacetamides **5e**–**h** (unsubstituted at the α-position) could efficiently produce the annulation products **6e**–**h**, with a CHO group at the 5-position of 3*H*-pyrimidin-4-one ring (Table 2, entries 5–8).[13] It should be noted that, the above method of making 3*H*-pyrimidin-4-ones is complementary to other methods (A, B and C in Scheme 1) and produces 3*H*-pyrimidin-4-ones with substituents (X or CHO) that might permit further elaboration of the structure.

Table 2
Synthesis of 3*H*-pyrimidin-4-ones **6a**–**h**[a]



Entry	Substrate			Time (h)	Product	Yield[b] (%)
	1	R^1	R^2			
1	**5a**	Me	4-MeC_6H_4	4.0	**6a**	74
2	**5b**	Bz	4-MeC_6H_4	1.2	**6b**	58
3	**5c**	Allyl	4-MeC_6H_4	3.0	**6c**	53
4	**5d**	Allyl	4-ClC_6H_4	1.2	**6d**	64
5	**5e**	H	4-$OMeC_6H_4$	0.5	**6e**	70
6	**5f**	H	4-MeC_6H_4	1.7	**6f**	71
7	**5g**	H	4-ClC_6H_4	1.0	**6g**	56
8	**5h**	H	3-MeC_6H_4	0.5	**6h**	48

[a] Reagents and conditions: **5** (2.0 mmol), $POCl_3$/DMF (8.0 mmol), 100 °C.
[b] Isolated yields.

2. Conclusions

In summary, a facile and efficient route to polysubstituted (functionalized) 3*H*-pyrimidin-4-ones **2** and **6** has been developed by the reactions of readily available cyanoacetamides **1** and **5** under Vilsmeier conditions. The reaction has many advantages, such as simple operation, good yields, short reaction time and a broad range of substrates and the potential of the products. Further research is in progress.

3. Experimental section

3.1. General procedure for the preparation of 2 and 6 (2a as example)

A mixture of phosphoryl trichloride (0.74 mL, 8 mmol) and DMF (1.0 mL) was well stirred for 5 min at room temperature, then added 1-cyano-*N*-*p*-tolylcyclopropanecarboxamide (**1a**) (400 mg, 2 mmol), the reaction system was stirred for 0.5 h (monitored by TLC) at 100 °C before it was slowly poured into ice-water (15 mL). Neutralized with saturated $NaHCO_3$ until pH>7, filtrated and dried in vacuum to afford crude compound. Then the residue was purified by a short flash silica gel column chromatography to give compound **2a** (372 mg, 69%) as white crystals (eluent: diethyl ether/petroleum ether 3/10).

*3.1.1. Selected data for **2a**.* White solid; mp: 133–135 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.42 (s, 3H), 3.18 (t, J=6.5 Hz, 2H), 3.78 (t, J=6.5 Hz, 2H), 7.23 (d, J=7.0 Hz, 2H), 7.33 (d, J=7.0 Hz, 2H), 8.01 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.23, 30.97, 41.05, 122.47, 126.20, 130.34, 133.51, 140.13, 148.16, 156.16, 160.31; MS: calcd m/z 282.0, found 283.0 $[(M+1)]^+$; IR (KBr, neat): ν 1669, 1585, 1536, 1512, 1395, 1323, 1247, 1128, 1083, 1020, 922, 824 cm^{-1}. Anal. Calcd for $C_{13}H_{12}Cl_2N_2O$: C, 55.14; H, 4.27; N, 9.89. Found: C, 55.52; H, 4.43; N, 10.08.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.07.006.

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8. For details of the preparation of **1**, see the Supplementary data; see also: White, D. A. *Synth. Commun.* **1977**, *7*, 559–568.
9. CCDC-714403 (**2a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

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