EurJOC
European Journal of Organic Chemistry

A Journal of
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Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201700737

Link to VoR: http://dx.doi.org/10.1002/ejoc.201700737

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Efficient Synthesis of 4- and 5-Substituted 2-Aminopyrimidines by Coupling of β-Chlorovinyl Aldehydes and Guanidines

Anna S. Komendantova,[a] Alexander V. Komkov,[a] Yulia A. Volkova,*[a] and Igor V. Zavarzin[a]

Abstract: A general, practical and simple synthesis of functionalized 2-aminopyrimidines starting from β-chlorovinyl aldehydes and amidines is reported. In the presence of potassium carbonate, various ketones have been efficiently incorporated into the pyrimidine derivatives by two-step sequence involving the Vilsmeier-Haack reaction followed by the condensation with guanidines. The protocol is distinguished by operational simplicity, inexpensive reagents and functional group tolerance. In many cases, pure solid products can be obtained in high to excellent yields without using column chromatography. The synthetic value of the method was demonstrated by the efficient synthesis of steroidal pyrimidines and a precursor of the antitumor agents Imatinib and Mocetinostat.

Introduction

The pyrimidine family represents one of the most prominent classes of therapeutically active agents and, consequently, it has been the focus of many drug discovery efforts.[1] Thus, a number of biologically active compounds[2] and FDA-approved commercial drugs, *e.g.* the antitumor agents Imatinib and Dabrafenib,[3] antibacterial agent Sulfamerazine,[4] the drug Rosuvastatin that reduces levels of "bad" cholesterol,[5] and the antianxielytic agent Buspirone,[6] have the 2-aminopyrimidine structural motif (Figure 1). This pyrimidine moiety emerges also in a wide range of naturally occurring compounds, especially in DNA and RNA.[1c,e] Moreover, recent discoveries in materials sciences have proved that 2-aminopyrimidines are useful supramolecular synthons for the construction of molecular capsules and in crystal engineering.[7]

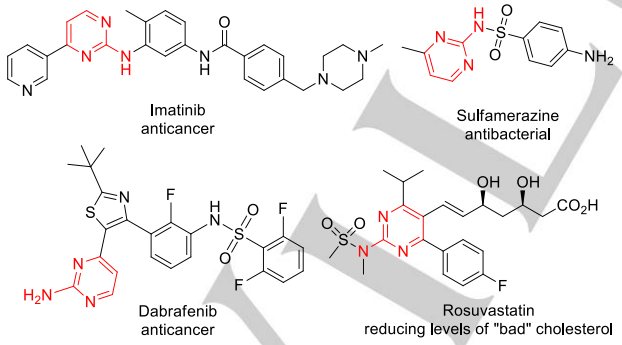
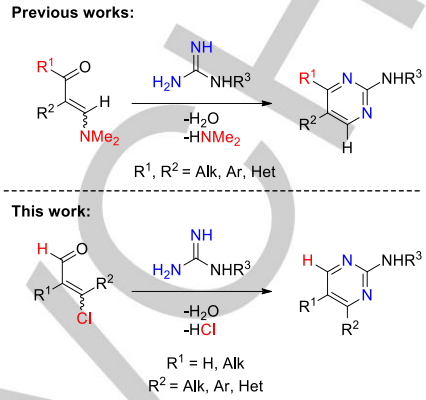


Figure 1. 2-Aminopyrimidine-based FDA-approved drug molecules.



Scheme 1. Synthesis of 2-aminopyrmidines *via* the condensation of α,β-unsaturated carbonyl compounds and guanidine.

The importance of the 2-aminopyrimidine scaffold has encouraged the development of various methods for its synthesis.[8] Among recently reported elegant cycloaddition reactions of 1,2,3-triazines with amidines,[9] [2+2+2] annulation of 2-lithio-1,8-bis(dimethylamino)naphthalene with cyanides,[10] three-component condensation of ketones, arylacetylenes and guanidine[11] can be mentioned. However, the most direct methods for the construction of 2-aminopyrimidines rely on the condensation of guanidines with activated α,β-unsaturated ketones,[12] primarily β-enamino ketones (Scheme 1). This approach, which was first proposed in the 1960-1970s,[13] to date have become widely applied in medicinal chemistry due to a great diversity of obtainable products.[2b,14] Unfortunately, this method often suffers from drawbacks, such as harsh reaction conditions, moderate yields and high labor content/cost of preparing starting materials (prolonged reflux in xylene or using Bredereck's reagent).[14a,2d]

In an effort to find a more efficient synthetic approach towards 2-aminopyrimidines, we focus our attention on the poorly studied condensation of chlorovinyl aldehydes with guanidine[15] able to circumvent these limitations (Scheme 1). Chlorovinyl aldehydes are readily available from enolizable ketones by the Vilsmeier-Haack reaction using cheap $POCl_3$-DMF reagent.[16] They are stable for storage in solution and do not require any special conditions for preparation. Chlorovinyl aldehydes proved to be highly reactive ambident electrophiles that easily undergo a variety of cyclization reactions,[17] especially with compounds having bis-nucleophilic properties.[18] Inspired by these previous studies and in continuation of our research on the synthesis of N-heterocycles,[19] we elaborated a conceptually simple, practical and general methodology for the synthesis of 4,5-substituted pyrimidines based on the condensation of β-chlorovinyl aldehydes with amidines under mild conditions.

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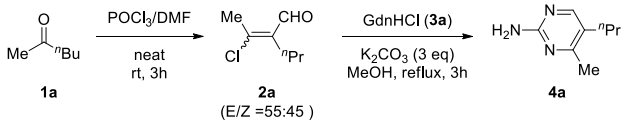
Supporting information for this article is given via a link at the end of the document.

Results and Discussion

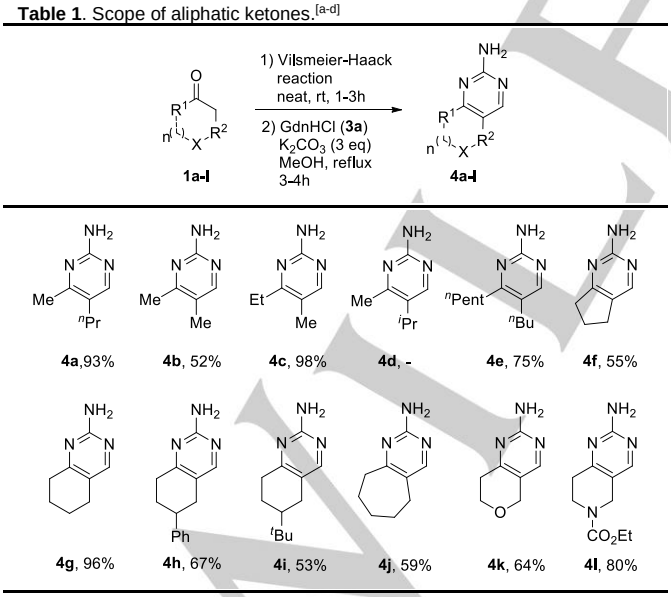
We started our research on the model reaction of chlorovinyl aldehyde **2a** derived from 2-hexanone (**1a**) with guanidine hydrochloride (GdnHCl, **3a**) in the presence of a base to optimize various reaction parameters. Complete data concerning the optimization of the base (K_2CO_3, Et_3N, ^{t}BuOK), temperature (rt→100°C), solvent (MeOH, CH_3CN, t-BuOH, H_2O, DMF, $CHCl_3$) and additives are presented in the Supporting Information. The principle results were that pyrimidine **4a** was generated as the major product only in MeOH in the presence of K_2CO_3 (Scheme 2). The product yield strongly decreased to ≤5% as the solvent or base were changed and as the temperature was reduced. The best results were obtained by performing the reaction using a **2a**/**3a** ratio of 1:1.5 in refluxing methanol with 3 equiv. of potassium carbonate for 3 h to afford compound **4a** in 93% yield (Table 1).



Scheme 2. Initial trial experiment.

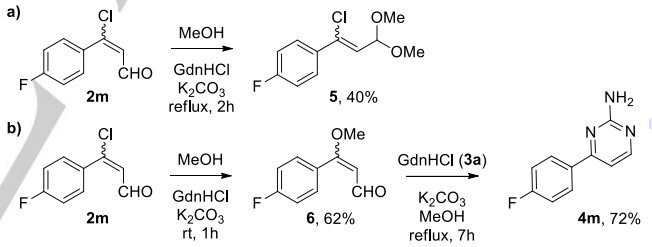
With the optimal reaction conditions in hand, we examined various ketones **1** as well as different amidines **3** with the aim of synthesizing a variety of 2-amino-4,5-substituted pyrimidines (Tables 1-3). We found that this two-step procedure is a quite general approach since the reactions of both symmetrical and asymmetrical linear aliphatic ketones smoothly proceeded to give diverse pyrimidines **4a-d** in good to excellent yields (52-98%, Table 1). The only exeption was sterically hindered 4-methylpentan-2-one; traces amounts of corresponding product **4d** were detected. Cyclic aliphatic ketones, such as cycloheptanone, -hexanone and -pentanone, produced the corresponding pyrimidines **4f-j** in slightly lower yields (53-85%), which can be attributed to side decomposition processes. In addition, 4-tetrahydropyranone **1i**, as well as 4-piperidone **1l**, was tolerated under these mild reaction conditions. Substituted 7,8-dihydropyrano[4,3-d]pyrimidine-2-amine **4k** and 2-amino-7,8-dihydropyrido[4,3-d]pyrimidine **4l** were synthesized in 64% and 80% yields, respectively. All products **4a-l** were obtained as pure materials by simple extraction with dichloromethane.

Table 1. Scope of aliphatic ketones.[a-d]



[a] Reaction conditions: *step 1*, ketone **1** (1.0 equiv), $POCl_3$ (1.4-3.0 equiv) and DMF (1.6-3.7 equiv) at rt for 1-3 h; *step 2*, chlorovinyl aldehyde **2** (0.40 mmol), GdnHCl **3a** (1.5 equiv) and K_2CO_3 (3.0 equiv) in methanol (10 mL) under reflux for 3-4 h. [b] Isolated yield. [c] Yield calculated with respect to intermediate chlorovinyl aldehyde purity. [d] The yields of β-chlorovinyl aldehydes lie in the range of 31-85% (see *Supporting information*).

It was shown that the transformations can also be performed with acetophenones using the modified protocol (Table 2). The optimal temperature requirements for the condensation of GdnHCl with chlorovinyl aldehydes derived from acetophenones are the storage for 1 h at rt followed by 7-9 h reflux. The direct reflux of model substrate **2m** in MeOH in the presence of K_2CO_3 and a Gdn salt resulted in formation of undesirable acetal **5** as the major product in 40% yield (Scheme 3, line a). On the contrary, the storage of chlorovinyl aldehyde **2m** in the presence of K_2CO_3 and GdnHCl in MeOH at rt gave rise to 3-methoxy-acrylaldehyde **6**, the product of Ad_N of the methoxide anion at the chlorovinyl center (Scheme 3, line b). Subsequently, compound **6** smoothly underwent condensation with guanidine upon heating to form the target **4m** in good yield.

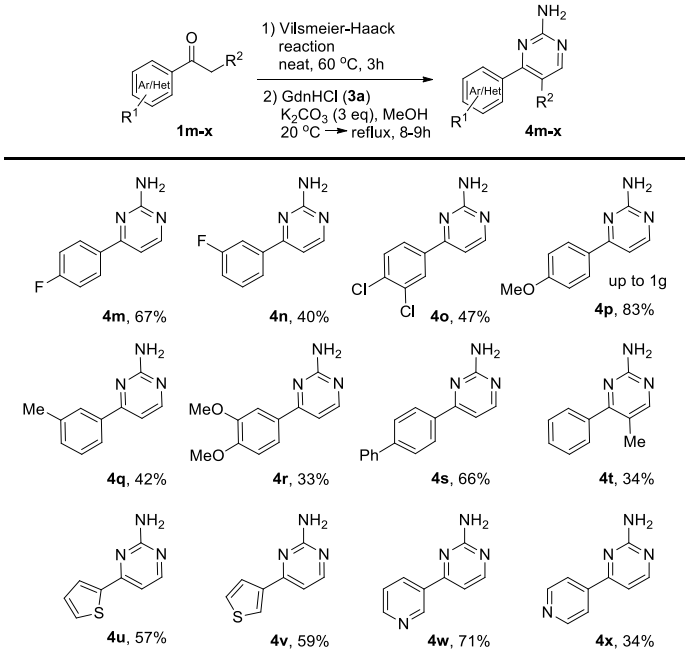


Scheme 3. Influence of the temperature on reaction mode.

The extension of this protocol to diverse acetophenones resulted in the formation of a series of 4-aryl-2-aminopyrimidines **4m-s** bearing both electron-withdrawing groups (4-F, 3-F, 3,4-Cl_2, 4-NO_2, 3-NO_2) and electron-donating groups (3-Me, 4-Ph, 4-OMe, 2,4-$(OMe)_2$) at the aryl moiety. Products were isolated by column chromatography in moderate to good yields. In addition to acetophenones, propiophenone was also employed to form 5-methyl-4-phenylpyrimidine-2-amine (**4t**) in reasonable yield. To explore the efficiency of this method, a gram-scale experiment was conducted; up to 1g of product **4p** was obtained without loss in the yield.

Pyridinecarboxaldehydes, as well as a thiophene-carboxaldehydes, were tolerated under these reaction conditions and the corresponding polyheterocyclic products **4u-x** were synthesized in 34-71% yields. In particular, 4-(pyridin-3-yl)pyrimidine-2-amine **4w**, which is a synthetic precursor of the antitumor agents Imatinib and Mocetinostat,[20] was isolated in 71% yield.

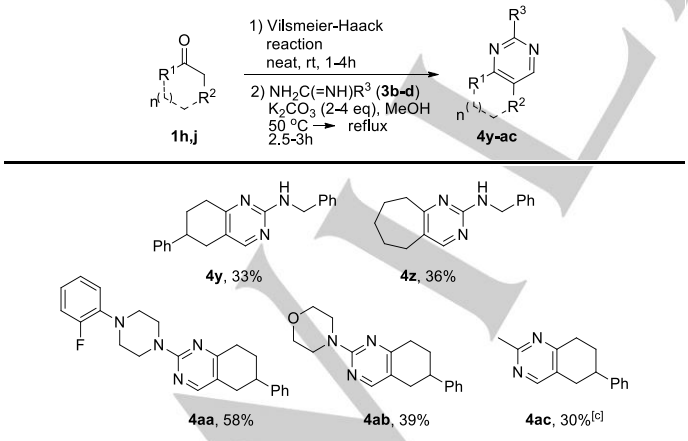
Table 2. Scope of aromatic ketones.[a-c]



[a] Reaction conditions: *step 1*, ketone **1** (1.0 equiv), $POCl_3$ (1.2-4.7 equiv) and DMF (1.5-7.9 equiv) at 60 °C for 3 h; *step 2*, chlorovinyl aldehyde **2** (0.40 mmol), GdnHCl **3a** (3.0 equiv) and K_2CO_3 (3.0 equiv) in methanol (10 mL) at rt for 1h and under reflux for 8-9 h. [b] Isolated yield. [c] The yields of β-chlorovinyl aldehydes lie in the range of 33-98% (see *Supporting information*).

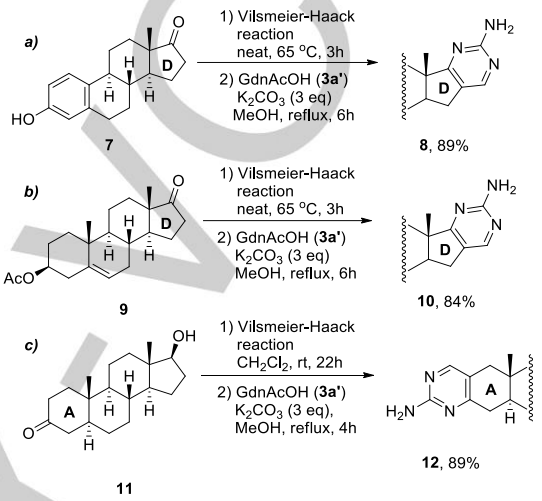
Diverse guanidines **3b-d** bearing the benzyl group, morpholine and piperazine residues were well tolerated under the reaction conditions to give the pyrimidines **4y-ab** in moderate to good yields (Table 3). In addition to guanidines, acetamidine can also be employed to form the corresponding **4ac** in 30% yield.

Table 3. Scope of amidine.[a-c]



[a] Reaction conditions: *step 1*, ketone **1** (1.0 equiv), $POCl_3$ (2.0-3.0 equiv) and DMF (1.6-3.7 equiv) at rt for 3 h; *step 2*, chlorovinyl aldehyde **2** (1.0 equiv), amidine (1.0-2.0 equiv) and K_2CO_3 (2.0-4.0 equiv) in methanol at 50 °C for 30 min and under reflux for 2.5-3.0 h. [b] Isolated yield [c] *step 2*: chlorovinyl aldehyde **2h** (1.0 equiv), acetamidine hydrochloride (2.0 equiv) and K_2CO_3 (4.0 equiv) in DMF at 80 °C for 4 h.

Having explored the scope of the method with relatively simple molecules, we extended this method to complex natural products. We examined steroids, one of the largest and most diverse class of natural products.[21] Heterosteroids bearing annulated azaheterocycles are known to exhibit a wide range of biological activities, *e.g.*, antiproliferative,[22] anti-inflammatory[23] and antimicrobial.[24] We first examined estrone **7** and 3β-hydroxyandrost-5-en-17-one **9** under standard conditions (Scheme 4, lines a,b).



Scheme 4. Synthesis of steroidal aminopyrimidines.

We found that both compounds **7** and **9** were readily transformed into the corresponding steroidal D-ring annulated aminopyrimidines **8** and **10** (89% and 84% yields, respectively) upon subsequent treatment with the Vilsmeier-Haack reagent and guanidine acetate (**3a'**) in the presence of potassium carbonate. Steroidal A-ring annulated aminopyrimidine **12** was synthesized in a similar way from dihydrotestosterone **11** in high yield (Scheme 4, line c). As a good method for scaling up production of **8**, **10**, and **12**, this strategy allows for easy purification by washing with water in the last step to give analytical pure compounds.

Conclusions

In summary, we elaborated the effective and general synthesis of 2-aminopyrimidines from ketones by the two-step procedure. The approach involves the following simple reactions: (1) the Vilsmeier-Haack reaction of enolizable ketones giving β-chlorovinyl aldehydes and (2) the condensation of the former with amidines to form highly substituted pyrimidines in moderate to excellent isolated yields (30-98%). The mild reaction conditions, operational simplicity, low cost of reagents and good functional group tolerance are undeniable advantages of the developed method. Almost half of the synthesized 2-aminopyrimidines have not been previously described and, in some cases, pure products were obtained without using column chromatography in good to excellent yields. Notably, the

reaction can be carried out on gram scale in almost the same yields. The wide availability of reagents implies that an extensive range of substituents can be selectively incorporated into the pyrimidine ring. Taking into account that the starting materials are readily available and in view of potential applications of the products, this method is highly promising in organic synthesis and medicinal chemistry.

Acknowledgements

This work was financially supported by the Russian Foundation for Basic Research and the Moscow City Government in the framework of the research project No. 15-34-70030 “mol_a_mos”.

Keywords: pyrimidine, • β-chlorovinyl aldehyde • ambident electrophile • heterosteroids

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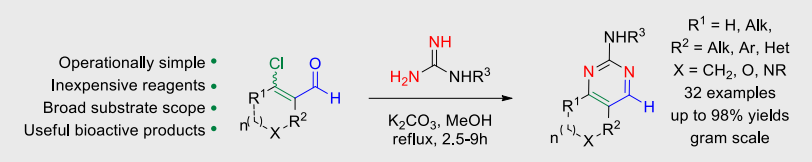

A condensation of ambident elecrophilic β-chlorovinyl aldehydes with guanidines was developed for the synthesis of library of 4- and 5-substituted 2-aminopyrimidines derivatives under mild conditions by employing potassium carbonate in methanol.

Synthetic method

Anna S. Komendantova, Alexander V. Komkov, Yulia A. Volkova, Igor V. Zavarzin*

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Efficient Synthesis of 4- and 5-Substituted 2-Aminopyrimidines by Coupling of *β*-Chlorovinyl Aldehydes and Guanidines