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Tetrahedron
Tetrahedron 63 (2007) 7845–7849

Synthesis of pyrimidine-5-carbaldehydes from α-formylaroylketene dithioacetals

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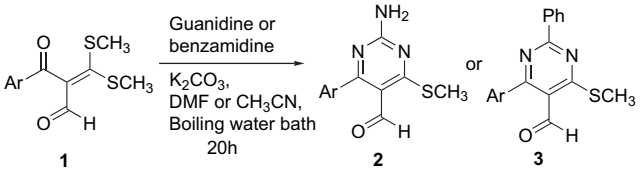
Received 2 March 2007; revised 10 May 2007; accepted 24 May 2007
Available online 2 June 2007

Abstract—A facile one pot synthetic path for the preparation of pyrimidine-5-carbaldehydes from α-formylaroylketene dithioacetals is described. Amidines were allowed to react with α-formylaroylketene dithioacetals in DMF or acetonitrile to afford the pyrimidine-5-carbaldehydes. The starting compounds reported earlier were synthesized from α-oxoketene dithioacetals in excellent amount.

1. Introduction

Pyrimidines are extremely important compounds with a wide array of synthetic and industrial applications. Not only they are an integral part of the genetic materials, viz. DNA and RNA as nucleotides and nucleosides but also play critical roles especially in pharmaceutical fields.[1] Some pyrimidine derivatives also give stable and good quality nanomaterials having many important electrical and optical properties.[2] Though there are thousands of pyrimidine derivatives synthesized and used in different fields, little attention has been given to the synthesis of pyrimidine-5-carbaldehydes, which can be converted to derivatives useful for the treatment of Alzheimer's disease.[3] Soai et al. found that the 5-pyrimidyl alkanols formed by the action of the pyrimidine-5-carbaldehydes and diisopropyl zinc are efficient asymmetric autocatalysts.[4] Moreover, 4,6-diaryl pyrimidine-5-carbaldehydes have been used to prepare double picket fence porphyrins, which are used as models for hemoproteins and as second generation oxidation catalysts by Dehaen et al.[5] A literature survey indicated that there are few methods for the synthesis of pyrimidinecarbaldehydes, especially for 5-pyrimidinecarbaldehydes. The usual method for the synthesis of pyrimidine-5-carbaldehydes is the formylation of hydroxypyrimidines or by the functional group interconversion of substituents already present in the pyrimidine ring.[6]

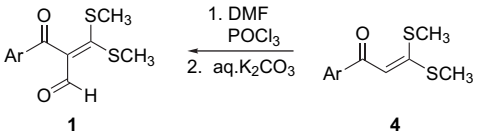
The increasing importance of pyrimidines and their derivatives as intermediates for the synthesis of biologically and industrially useful compounds prompted us to utilize 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes **1** previously reported from our laboratory,[7] to synthesize pyrimidine-5-carbaldehydes **2** and **3** using amidines (Scheme 1). We envisioned that the presence of a highly reactive formyl group on the pyrimidine may make the compound valuable precursors for the synthesis of highly functionalized and annulated heterocyclic compounds.



Scheme 1. Synthesis of pyrimidine-5-carbaldehydes.

2. Results and discussion

2-Aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes **1** were prepared as reported from our laboratory by the reaction of aroylketene dithioacetals **4** with the Vilsmeier–Haack reagent (Scheme 2).[7]



Scheme 2. Synthesis of 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes.

Keywords: Pyrimidine-5-carbaldehydes; α-Formylaroylketene dithioacetals; α-Oxoketene dithioacetals; Amidines.
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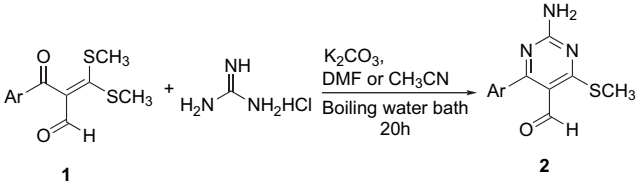
0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.05.098

Among the numerous synthetic routes to the formation of substituted pyrimidines, the reactions of 1,3-dicarbonyl compounds and ketene dithioacetals with substituted amidines are well known and have been much used.[8] It thus seemed to be of interest to examine the reactions of guanidine and benzamidine, two common amidines, with 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes **1** to synthesize pyrimidines.

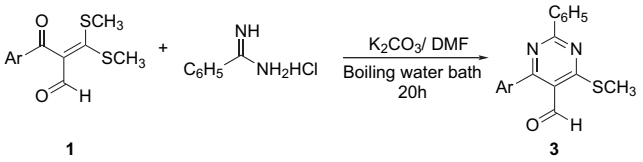
Generally the reaction of ketene dithioacetals and amidines are carried out in the presence of strong bases such as sodium alkoxide or sodium hydride. Junjappa and co-workers developed a general method for the synthesis of 6-alkoxypyrimidines by reacting guanidine with oxoketene dithioacetal in the presence of the corresponding alcohol/alkoxide medium.[9] In the presence of strong bases, we had encountered the problem of deformylation of 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes **1**.[10] Therefore, bases like K_2CO_3 were the best choice for cyclization of the above reaction. Yu and Cai had obtained the highest yield of pyrimidines from ketene dithioacetals in the presence of acetonitrile among different solvents.[11] We tried the reaction in DMF and acetonitrile and found a drastic increase of the yield in the latter one to about 70–80%. Thus acetonitrile is a better solvent for the preparation of pyrimidinecarbaldehydes from α-formylaroylketene dithioacetals.

The 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehyde **1** was mixed with guanidine hydrochloride in DMF or acetonitrile and the mixture was heated in a boiling water bath for 20 h. The reaction afforded 2-amino-6-aryl-4-(methylsulfanyl)-5-pyrimidinecarbaldehyde **2** in good yields (Scheme 3, Table 1).



Scheme 3. Synthesis of 2-amino-6-aryl-4-(methylsulfanyl)-5-pyrimidinecarbaldehydes (**2**).

In order to try the reaction of benzamidine and **1**, we treated 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes with benzamidine hydrochloride in DMF and the reaction mixture was heated in a boiling water bath for 20 h. The reaction afforded 4-(methylsulfanyl)-2,6-diphenyl-5-pyrimidinecarbaldehydes **3** in 35–50% yield (Scheme 4, Table 2).



Scheme 4. Synthesis of 4-(methylsulfanyl)-2,6-diphenyl-5-pyrimidinecarbaldehydes (**3**).

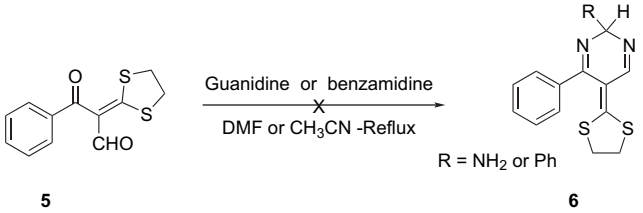
Table 1. Synthesis of 2-amino-6-aryl-4-(methylsulfanyl)-5-pyrimidinecarbaldehydes (**2**)

Compounds **1** and **2**	Ar	Yield (%)	
		DMF	CH_3CN
a	C_6H_5	40	70
b	4-$CH_3C_6H_4$	45	75
c	4-ClC_6H_4	43	76
d	4-BrC_6H_4	45	78
e	4-$CH_3OC_6H_4$	50	80
f	3-$CH_3OC_6H_4$	54	82
g	2,3-$(CH_3O)_2C_6H_3$	55	70
h	4-$NO_2C_6H_4$	40	—
i	2-Naphthyl	40	—

Table 2. Synthesis of 4-(methylsulfanyl)-2,6-diphenyl-5-pyrimidinecarbaldehydes (**3**)

Compounds **1** and **3**	Ar	Yield (%)
a	C_6H_5	41
b	4-$CH_3C_6H_4$	46
c	4-ClC_6H_4	48
d	4-BrC_6H_4	48
e	4-$CH_3OC_6H_4$	50
f	2-Naphthyl	35

The reaction was also extended with cyclic formylketene dithioacetals **5** produced from cyclic ketene dithioacetals (Scheme 5). The reaction failed to produce the expected product **6** due to the lower reactivity of these molecules in the presence of a weak base like potassium carbonate. However, the deformylation of α-formylketene dithioacetals **5** in the presence of strong bases like sodium hydride, potassium tertiary butoxide, sodium hydroxide, etc., limited our attempts to synthesize pyrimidines from these molecules.



Scheme 5. Reaction between cyclic formylketene dithioacetals and amidines (no pyrimidines).

The formation of **2** and **3** from **1** using amidines can be rationalized according to the mechanism proposed by Gompper and Topfl.[12] Initially a sequential conjugated addition–elimination of amidine to afford an acyclic *N,S*-acetal, followed by the intramolecular 1,2-nucleophilic addition to the carbonyl group of the intermediate, which eliminates a water molecule to produce the required pyrimidine-5-carbaldehyde. Among the carbonyl groups, the one adjacent to the aromatic ring system is more susceptible to the 1,2 intramolecular addition reaction. Therefore, the aldehyde remains unreacted generating a pyrimidine with a highly useful functional group. The presence of the formyl moiety in these compounds is further confirmed in our laboratory by the Knoevenagel reaction of them with malononitrile. The results will be discussed later.