Tetrahedron Letters 54 (2013) 4892–4895

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Microwave-assisted cyclocondensation: a rapid and solvent-free synthesis of 3-benzyl-2*H*-pyrido[1,2-*a*]pyrimidin-2-one derivatives

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ARTICLE INFO

Article history:
Received 22 February 2013
Revised 26 June 2013
Accepted 27 June 2013
Available online 4 July 2013

Keywords:
Microwave
Cyclocondensation
Methyl 2-(acetoxy(phenyl)methyl)acrylates
2-Aminopyridines
Solvent-free
2*H*-Pyrido[1,2-*a*]pyrimidin-2-ones

ABSTRACT

Microwave-induced cyclocondensation of methyl 2-(acetoxy(phenyl)methyl)acrylate with 2-aminopyridines under catalyst and solvent-free conditions has been achieved for a rapid synthesis of 3-substituted-2*H*-pyrido[1,2-*a*]pyrimidin-2-ones in good yields with high selectivity in short reaction times.

Pyrimidine core is often present in various natural products and synthetic molecules such as cytosine, uracil and thymine.[1] In particular, pyridopyrimidines display a diverse range of biological activities and are well-known pharmacophores[2] such as PDE-inhibitors,[3a] analgesic,[3b] antiinflammatory,[3c] antiallergic or antipsychotic agents[3d] and inhibitors of tyrosine kinase activity in the epidermal growth factor receptor.[4] Pyrido[1,2-*a*]pyrimidine derivatives are also most useful building blocks for the synthesis of biologically active molecules like fused azinopyrimidinone derivative (I),[5a] antiasthmatic agent (pemirolast (II)),[5b] antiulcerative agent (III),[5c] tranquilizer (pirenperone (IV)),[5d] and antiallergic agent (barmastine (V)) (Fig. 1).[5]

The densely functionalized Baylis–Hillman adducts allow numerous transformations and have made these adducts valuable synthetic intermediates.[6,7] 2-Aminopyridine is a versatile synthetic intermediate in pharmaceutical chemistry.

Consequently, several methods have been reported for the synthesis of substituted pyrido[1,2-*a*]pyrimidin-4-one derivatives.[8] A few processes have been reported for the synthesis of 3-substituted-2*H*-pyrido[1,2-*a*]pyrimidin-2-ones using different starting materials (Fig. 2).[9,10]

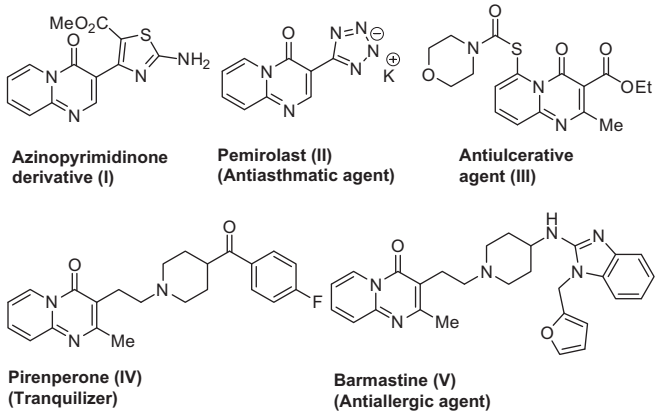

Figure 1. Examples of biologically active pyrido[1,2-*a*]pyrimidin-4-ones.

However, many of these methods often suffer from long reaction time, drastic reaction conditions as well as a narrow scope of the substrates. Thus, there is a need to develop a rapid process for the synthesis of 2*H*-pyrido[1,2-*a*]pyrimidin-2-one derivatives. In the past decades, microwave (MW) irradiation has become a powerful tool for rapid synthesis of several organic molecules because it provides enhanced reaction rates, good selectivity, improved yields, ease of manipulation and rapid optimization of the reaction.[11,12] However, there have been no reports on the effect

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http://dx.doi.org/10.1016/j.tetlet.2013.06.138

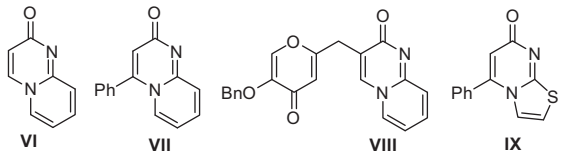
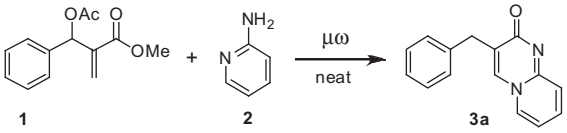


Figure 2. Biologically active pyrido[1,2-*a*]pyrimidin-2-ones and 5-phenylthiazolo[3,2-*a*]pyrimidin-7-one.



Scheme 1. Reaction of Baylis–Hillman acetate with 2-aminopyridine.

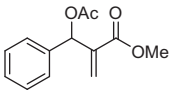
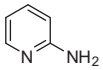
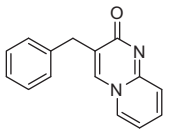
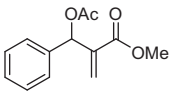
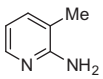
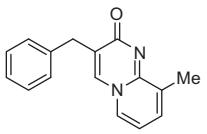
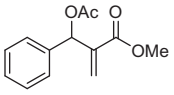
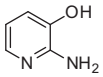
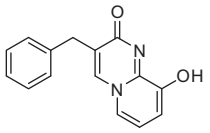
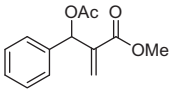
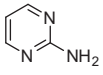
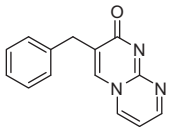
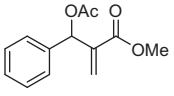
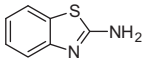
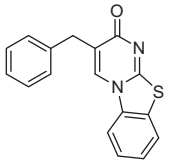
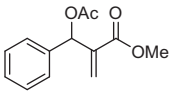
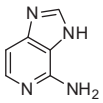
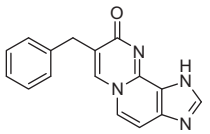
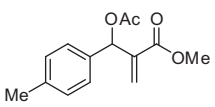
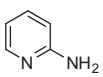
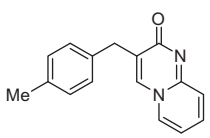
of microwave irradiation for the synthesis of 3-substituted-2*H*-pyrido[1,2-*a*]pyrimidin-2-ones.

Following our interest on the microwave irradiation,[13] we herein report for the first time, a simple and efficient method for the synthesis of 3-substituted-2*H*-pyrido[1,2-*a*]pyrimidin-2-ones from 2-heteroaryl amines and alkyl-2-(acetoxy(phenyl)methyl)acrylates using microwave (MW, 150 W). Initially, we attempted the reaction of methyl 2-(acetoxy(phenyl)methyl)acrylate (**1**) with 2-aminopyridine (**2**) under MW without any catalyst. Interestingly, the reaction proceeded smoothly at 95 °C under solvent-free conditions and the desired product **3a** was obtained in 90% yield (Scheme 1, Table 1).

Interestingly, substituted 2-aminopyridines such as 3-methyl-, and 3-hydroxy-derivatives participated well in this reaction (entries b, c, k and l Table 1). Other substrates such as 2-aminopyrimidine, 2-aminobenzothiazole and 3*H*-imidazo[4,5-*c*]pyridin-4-amine also underwent smooth coupling with different 2-(acetoxy(aryl)methyl)acrylates to afford the corresponding 3-substituted-2*H*-pyrido[1,2-*a*]pyrimidin-2-one derivatives in good yields (entries d–f and m, Table 1). The structure of the products was assigned by ^{1}H, ^{13}C NMR and mass spectral data and also by comparison with authentic samples.[10] The scope and generality of this process is illustrated with respect to various 2-aminopyridines and 2-(acetoxy(aryl)methyl)acrylates and the results are presented in Table 1.[14]

As depicted in Table 1, there was no significant effect of the substituent present on the aromatic ring of 2-(acetoxy(aryl)methyl)acrylates. *ortho*-Substituted 2-(acetoxy(aryl)methyl)acrylates also gave 3-substituted-2*H*-pyrido[1,2-*a*]pyrimidin-2-one derivatives in good yields (Table 1). This method works not only with 2-aminopyridines but also with 3*H*-imidazo[4,5-*c*]pyridin-4-amine, 2-aminopyrimidine and 2-aminobenzothiazoles. Indeed,

Table 1
Microwave-assisted synthesis of 3-substituted-2*H*-pyrido[1,2-*a*]pyrimidin-2-ones

Entry	Substrate (**1**)	Amine (2)	Product (3)[a]	Time (min)	Yield[b] (%)
a				4	90
b				3	86
c				5	87
d				5	74
e				4	90
f				5	70
g				5	87

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