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Solvent-free microwave synthesis of novel 6-hydroxypyrimidin-4(1*H*)-one derivatives using arylmalonates

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Abstract—The disclosure herein describes the rapid synthesis of novel 6-hydroxypyrimidin-4(1*H*)-one derivatives via a solvent-free microwave cyclocondensation reaction using di-(2,4,6-trichlorophenyl)malonates and a variety of heterocyclic amines.
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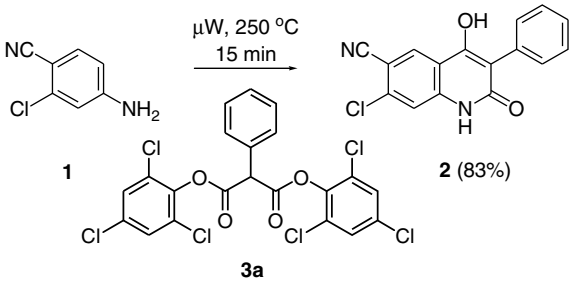
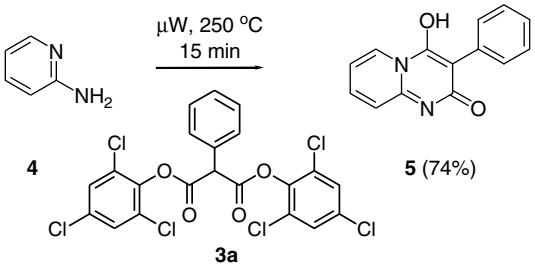
Derivatives of 4-hydroxypyridin-2(1*H*)-one have been shown to be promising pharmaceutical agents for the treatment of cancer,[1] central nervous system disorders,[2] sex hormone-related conditions,[3] the stimulation of bone formation,[4] and the suppression of allergy associated inflammations.[5] As a result of these therapeutic properties, interest has grown in the development of methodology for the rapid synthesis of 4-hydroxypyridin-2(1*H*)-one derivatives.[3a,6]

We recently reported the synthesis and SAR studies of 3-aryl-4-hydroxyquinolin-2(1*H*)-one analogues as a novel class of fatty acid synthase inhibitors (e.g., **2**, $IC_{50} = 136$ nM).[1] In order to expedite these SAR studies we developed a rapid synthesis of 3-phenyl-4-hydroxyquinolin-2(1*H*)-ones via a solvent-free microwave cyclocondensation reaction using di-(2,4,6-trichlorophenyl)-2-phenylmalonate (e.g., **1** → **2**, Eq. 1).[7]

During the course of these studies we discovered that 2-aminopyridine (**4**) reacted efficiently with di-(2,4,6-trichlorophenyl)-2-phenylmalonate (**3a**), under our microwave conditions, to provide 4-hydroxy-3-phenyl-2*H*-pyrido[1,2-*a*]pyrimidin-2-one (**5**) in 74% yield (Eq. 2).[8] This microwave reaction proved to be very practical and we therefore sought to explore the reaction scope further. To date, the scope of this type of cyclocondensation reaction has not been reported. Herein, we report the scope and the yields of the microwave cyclocondensation reaction to prepare derivatives of 6-hydroxypyrimidin-4(1*H*)-one by using di-(2,4,6-trichlorophenyl)malonates and a variety of heterocyclic amines.



(1)



(2)

The results from Table 1 show that di-(2,4,6-trichlorophenyl)-2-phenylmalonate reacted efficiently with a variety of commercially available heterocyclic amines and 2-methylpropionamidine to provide the desired products (**4**–**17**) in good yields. In a typical solvent-free microwave reaction, a mixture of the heterocyclic amines and di-(2,4,6-trichlorophenyl)-2-phenylmalonate in a 1:2 ratio, respectively, was heated at 250 °C for 15 min. The internal pressure of the reaction vessel never surpassed 1 bar. Upon completion, the reaction was

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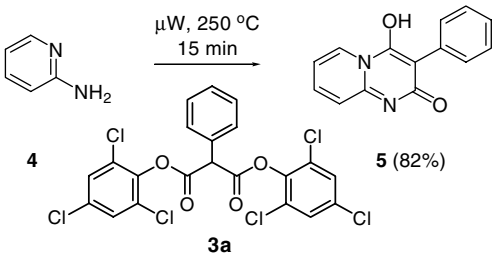
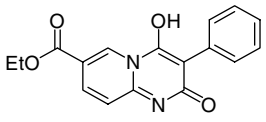
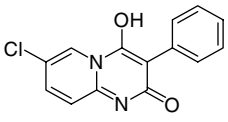
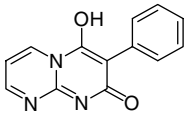
allowed to reach room temperature and diluted with diethyl ether and the precipitate, which was the product, collected by filtration. The purity of products **5**–**16**, as determined by LCMS and NMR, was 95–99% and no additional purification was required. The only exception was product **17**, which required purification via chromatography.

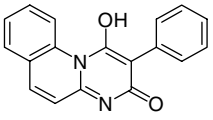
Table 1. Microwave reaction of heterocyclic amines[a]

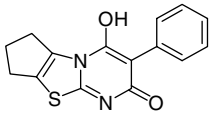


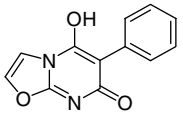

6 (87%)

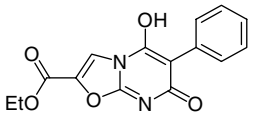

7 (74%)

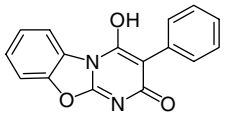

8 (89%)

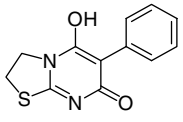

9 (79%)

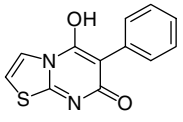

10 (74%)

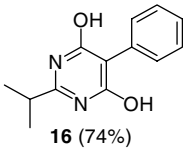

11 (89%)

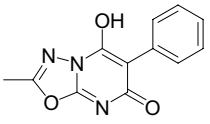

12 (78%)


13a (90%)


14 (82%)


15 (81%)

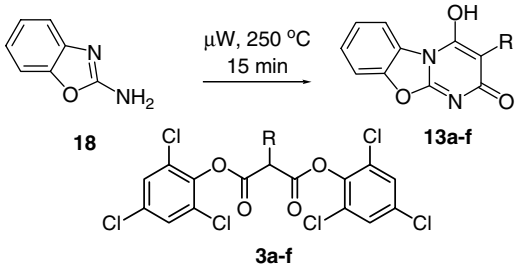

16 (74%)

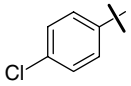
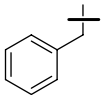

17 (79%)

[a] Isolated yields of compounds, which were characterized by ^{1}H NMR, ^{13}C NMR, and LCMS.

To further demonstrate the simplicity and potential generality of this microwave reaction, we conducted the microwave reaction with a variety of di-(2,4,6-trichlorophenyl)malonates (Table 2, **3a**–**f**).[9] The results show that a variety of di-(2,4,6-trichlorophenyl)malonates reacted efficiently with 1,3-benzoxazol-2-amine to provide the desired corresponding products **13a**–**f** in high yields. These products were purified via precipitation with diethyl ether and filtration.

Table 2. Microwave reaction with various malonates[a]



Malonate	R	Product (yield)
3a		**13a** (90%)
3b		**13b** (84%)
3c		**13c** (88%)
3d		**13d** (87%)
3e		**13e** (75%)
3f		**13f** (67%)

[a] Isolated yields of compounds, which were characterized by ^{1}H NMR, ^{13}C NMR, and LCMS.

In summary, we have shown that the short reaction time, in combination with the high yields and minimal purification of the products, makes this microwave reaction with di-(2,4,6-trichlorophenyl)malonates ideal for the rapid preparation of 6-hydroxypyrimidin-4(1*H*)-one derivatives. The key to the success of these microwave reactions is the use of di-(2,4,6-trichlorophenyl)malonates. The advantage of using di-(2,4,6-trichlorophenyl)malonates is that they form the intermediate anilide and undergo electrophilic aromatic cyclization more efficiently than less reactive malonates, such as diethyl-2-phenylmalonate. Furthermore, the by-product from the microwave reaction is 2,4,6-trichlorophenol, which reduces, relative to ethanol, the internal pressure in a closed microwave reaction vessel and allows the reaction to proceed efficiently. Further application of di-(2,4,6-trichlorophenyl)malonates in cyclocondensation reactions is currently under investigation.

Acknowledgments

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