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A novel strategy for the synthesis of uracil derivatives using bis(pentafluorophenyl)imidodicarbonate

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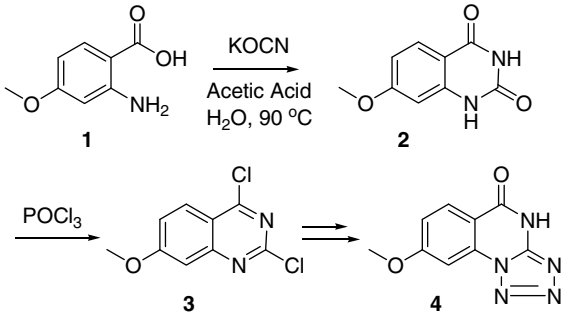
ABSTRACT

The disclosure herein describes a novel strategy for the synthesis of uracil derivatives via a solvent-free microwave cyclocondensation reaction using bis(pentafluorophenyl)imidodicarbonate.

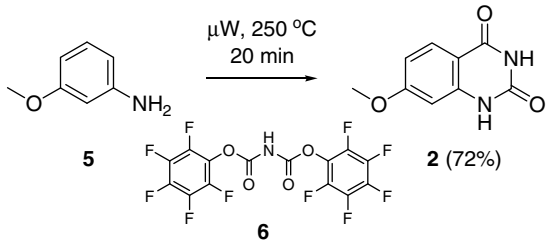
Uracil derivatives have been shown to be promising pharmaceutical agents for the treatment of viral diseases.[1] In addition, uracil derivatives have often served as precursors to 2,4-dichloropyrimidines, which have been used as intermediates in the synthesis of a variety of pharmaceutical agents (e.g., **2** → **3** → **4**).[2] The combination of pharmacological application and synthetic utility has generated interest in the development of methodology for the synthesis of uracil derivatives such as **2** (Scheme 1).[3]

Currently, there are several reported methods for the synthesis of substituted uracil derivatives.[3] However, these synthetic methods are limited because they often require highly toxic reagents or the use of harsh conditions.[4]

In an ongoing medicinal chemistry program, we required the synthesis of 2,4-dichloropyrimidines such as **3**. During the course of these studies, we discovered that 3-methoxyaniline (**5**) reacted efficiently with bis(pentafluorophenyl)imidodicarbonate (**6**), under solvent-free microwave conditions, to provide **2** in 72% yield (Eq. 1). This discovery was in large part due to our recent work in the development of the rapid synthesis of 3-aryl-4-hydroxyquinolin-2(1*H*)-one analogs via a solvent-free microwave cyclocondensation reaction using di-(2,4,6-trichlorophenyl)-2-phenylmalonate.[5]



Scheme 1.



(1)

The synthesis of **2** via our microwave method proved to be practical, and we therefore sought to explore the reaction scope further. To date, the synthesis of uracil derivatives using this type of cyclocondensation reaction has not been reported. Herein, we report the scope of the microwave cyclocondensation to prepare uracil derivatives using bis(pentafluorophenyl)imidodicarbonate.

The results from Table 1 show that bis(pentafluorophenyl)imidodicarbonate reacted efficiently with a variety of commercially available substrates to provide **7–20** in good yields. Reaction of meta-substituted anilines provided exclusively the regioisomers **7–10**. A variety of heterocyclic amines reacted efficiently to provide **12–14**. The broad scope of the reaction is highlighted by the reaction of (2*E*)-3-amino-3-(4-bromophenyl)acrylonitrile and 3-methoxyphenol to provide the corresponding **15** and **16** in high yield. N-Alkylated anilines **17** and **18** were shown to be well tolerated in the reaction and provided exclusively the single regioisomer. It is worth noting that the reactive functional groups, such as the methyl ester in **12** and nitrile in **15**, were tolerated in the reaction scope.

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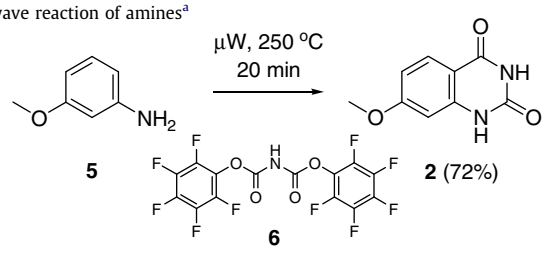
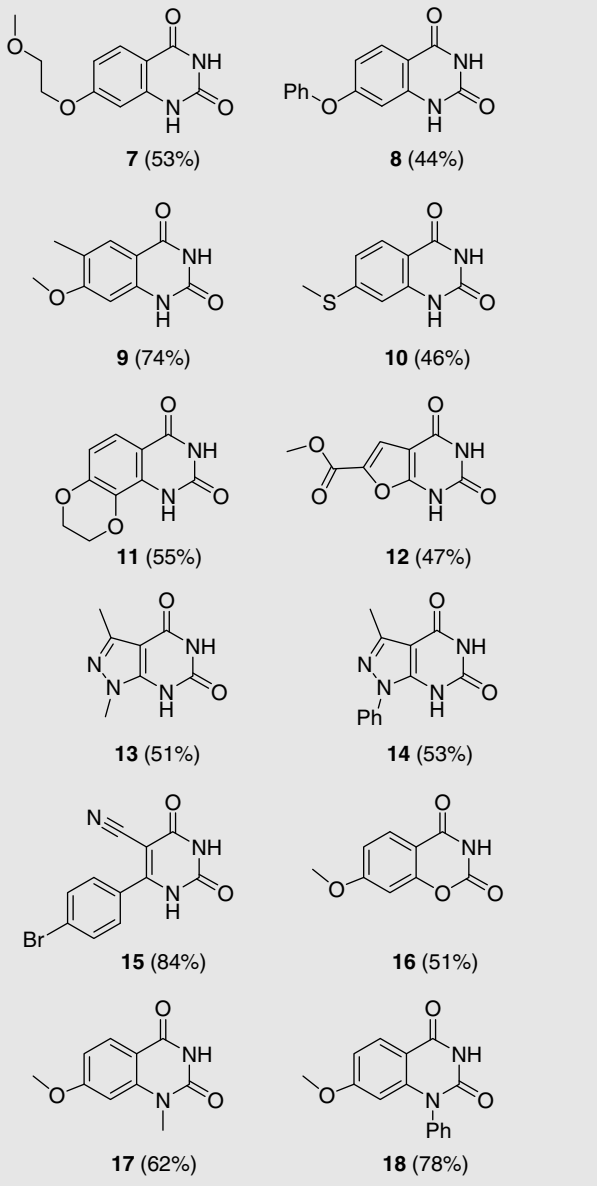
Table 1
Microwave reaction of amines[a]

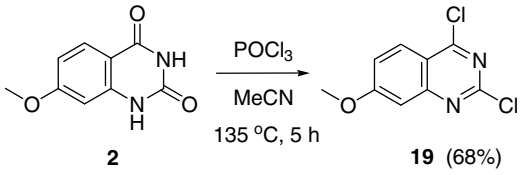


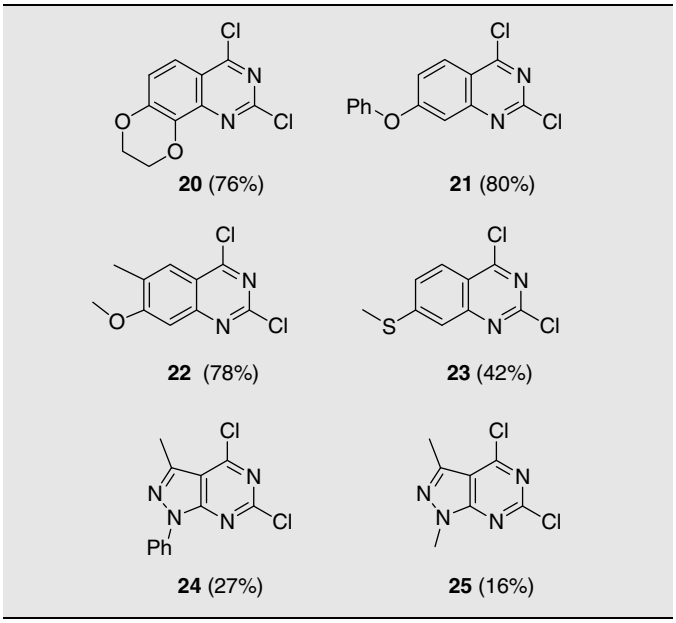


[a] Isolated yields of compounds, which were characterized by ^{1}H NMR, ^{13}C NMR, and LCMS.

In a typical solvent-free microwave cyclocondensation, a mixture of the substrate and bis(pentafluorophenyl)imidodicarbonate in a 1:2 ratio, respectively, was heated at 250 °C for 20 min. Upon completion, the reaction was allowed to reach room temperature and diluted with diethyl ether and the product, which precipitated out, was collected by filtration and washed with acetone to remove trace impurities. The purity of products **7–18**, as determined by LCMS and NMR, was 95–99% requiring no additional purification.

Table 2
Chlorination reaction of uracil derivatives[a]





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

Bis(pentafluorophenyl)imidodicarbonate is easily prepared in one step by the reaction of commercially available pentafluorophenol and *N*-(chlorocarbonyl)isocyanate.[6]

The conversion of uracil derivatives to their corresponding 2,4-dichloropyrimidines is typically accomplished using $POCl_3$.[3a] This reaction is highly sensitive, and may fail if the starting material is not of high purity. The results in Table 2 show that the products from the microwave cyclocondensations can be successfully converted to the corresponding 2,4-dichloropyrimidines **19–25** without further purification requiring column chromatography.

In summary, we have developed a novel method for the synthesis of uracil derivatives using bis(pentafluorophenyl)imidodicarbonate. This is the first example of this type of cyclocondensation for the synthesis of uracil derivatives. The combination of high yields, short reaction times, and minimal purification required makes this microwave method highly efficient. Further application of bis(pentafluorophenyl)imidodicarbonate in cyclocondensation reactions is currently under investigation.

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